ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN ADOLESCENTS: AN INVESTIGATIVE STUDY OF DOPAMINE NAD NOREPINEPHRINE SYSTEMS

By

Katherine Ellis Knight, MA

A Dissertation Submitted to the Faculty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College of

THE UNIVERSITY OF ARIZONA

2012

THE UNIVERSITY OF ARIZONA
GRADUATE COLLEGE

As members of the Dissertation Committee, we certify that we have read the dissertation

prepared by Katherine Ellis Knight

entitled Attention Deficit Hyperactivity Disorder (ADHD) in Adolescents: An investigative study of dopamine and norepinephrine systems

and recommend that it be accepted as fulfilling the dissertation requirement for the

Degree of Doctor of Philosophy

_____ Date: (7/9/12)
(Anouk Schere, PhD)

_____ Date: (7/9/12)
(John Allen, PhD)

_____ Date: (7/9/12)
(Richard Bootzin, PhD)

_____ Date: (9/7/12)
(Dave Sbarra, PhD)

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copies of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

_____ Date: (7/9/12)

Dissertation Director: (Anouk Scheres, PhD)

STATEMENT BY AUTHOR

This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

SIGNED: Katherine Ellis Knight

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

A better understanding of the neural mechanisms associated with Attention Deficit Hyperactivity Disorder (ADHD) and related cognitive deficits can potentially clarify the neural circuits involved in ADHD symptoms, help define neurobiologically informed subtypes and aid in developing more refined treatments. Two neurotransmitter (NT) systems have been implicated in ADHD: Dopamine (DA), and Norepinephrine (NE), and the primary cognitive deficits associated with ADHD are in working memory, response inhibition, reaction time variability, and reward processing. Frank et al. (2007a) proposes, based on computational models, that DA is associated with deficits in reward-based learning and updating of working memory, while NE is associated with deficits in response inhibition and greater response variability. Therefore, it might be possible to learn more about the NT systems' specific roles in ADHD by studying the associated cognitive deficits. The primary goal of this study was to assess performance in adolescents with and without ADHD on a number of cognitive tasks. We expected that the Attention Deficit Hyperactivity Disorder – Inattentive Subtype (ADHD-I) group would perform the worst on NE tasks and that the Attention Deficit Hyperactivity Disorder – Combined Subtype (ADHD-C) group would perform the worst on DA tasks, and that both groups would perform worse than controls on all tasks. Instead, we found that the ADHD-I group performed the most poorly on updating of working memory, while the ADHD-C group performed the best on this variable. However, the ADHD-C group performed worst on overall working memory. Dimensional analyses revealed that hyperactivity/impulsivity is positively correlated with updating of working memory,

while inattention is negatively correlated with updating of working memory. In addition, hyperactivity/impulsivity was positively correlated with reaction time variability. In conclusion, it is likely that the roles of these NT systems are not as mutually exclusive as initially expected. It is also possible that our ADHD group was performing more like control groups in other studies, which might be due to a more 'pure' ADHD sample with less comorbid Oppositional Defiant Disorder (ODD) and Conduct disorder (CD), or could be due to a less symptomatic ADHD group.

INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a heterogeneous childhood-onset psychiatric disorder that is characterized by a persistent pattern of age-inappropriate and impairing levels of inattention and/or hyperactivity and impulsivity (American Psychiatric Association [APA], 2000). The current *DSM IV* (American Psychiatric Association [APA], 1994) lists three subtypes of ADHD: primarily inattentive, primarily hyperactive and impulsive, and combined subtype. Because the purely hyperactive/impulsive subtype rarely occurrs in children older than age 6, this study primarily considers the hyperactive-impulsive and the combined subtypes together. Children with the hyperactive-impulsive and combined subtypes are overactive, restless, talkative, fidgety, impulsive, and have difficulty sitting still. Children with the inattentive subtype are disorganized, forgetful, inattentive, and frequently side-tracked (Diamond, 2005; *DSM IV*; APA, 2004).

The brain mechanisms associated with the primary symptoms and the cognitive deficits seen in ADHD are still poorly understood. Gaining insight into the brain mechanisms associated with ADHD and related cognitive deficits will not only help clarify the neural circuits involved in ADHD symptoms, but will also help in refining diagnostic criteria by defining neurobiologically informed subtypes and in developing more refined treatments.

This study attempts to do this by learning about the neurotransmitters involved. Recent theoretical and computational models suggest that both dopamine (DA) and norepinephrine (NE) play a major role in the symptoms of ADHD. These models are

mainly based on and supported by the fact that both dopaminergic and noradrenergic medications have been successfully used to treat ADHD symptoms in both children and adults (Swanson et al., 2006; Barkley, DuPaul & McMurray 1991). However, although both types of drugs have been proven to be effective in alleviating ADHD-related behaviors, very little research has been done thus far to test whether these neurotransmitters uniquely contribute to specific symptom domains, namely inattention, and hyperactivity-impulsivity. Therefore, more research is needed to clarify the specific roles of these neurotransmitters in the symptom domains of ADHD.

Dopamine's Role

Though dopamine's association with specific ADHD symptoms (inattention versus hyperactivity-impulsivity) has not yet been clearly defined, there is strong empirical support for dopamine's role in the etiology of ADHD. Several studies now support the notion that individuals with ADHD have low levels of both tonic and phasic DA in the striatum (Sagvolden et al., 2005; Solanto, 2002). Both children and adults with ADHD have an excessive quantity of dopamine transporters (DAT's) in the striatum, thus decreasing the synaptic domapine level (see for review: Spencer et al., 2005). Furthermore, candidate gene studies of ADHD have shown that the DAT gene is associated with ADHD, with a modest effect size (Farone et al., 2005; see for review: Mick & Faraone, 2008). The most profound evidence comes from studies in which the effects of Methylphenidate (MPH) on cognitive functioning and symptoms of ADHD are assessed. MPH increases extracellular DA in the striatum and prefrontal cortex (PFC) by

blocking DAT (Madras, Miller & Fischman, 2005). Because DA transporter density is highest in striatum (Madras et al., 2005), it has been supposed that the theraputic manipulation of DA effects takes place primarily in striatum. MPH has consistently been shown to reduce ADHD symptoms (e.g., MTA cooperative group, 1999) and to improve performance on a number of cognitive skills such as response inhibition, response variability, and working memory (e.g., Langleben et al., 2006; Rubia et al., 2003; Scheres et al., 2003; Tannock et al., 1995).

Norepinephrine's role

It is clear, however, that DA is not the only neurotransmitter underlying the behavioral symptoms and the cognitive deficits in ADHD. There is now mounting evidence for the role of Norepinephrine (NE) in the disorder, although it has not yet been studied as extensively as DA with regards to ADHD (eg: Frank et al., 2007b). A primary testaments to NE's role in ADHD is the effectiveness of Atomoxetine (ATX) in alleviating ADHD symptoms. ATX is a medication that blocks the NE transporter in the cortex, creating higher cortical levels of extracellular NE (Swanson et al., 2006). Because NE transporter density is highest in the prefrontal cortex (PFC) (Madras, Miller & Fischman, 2005), it has been supposed that the theraputic manipulation of NE effects takes place primarily in the PFC (Frank et al., 2007a). Further, Sengupta et al. (2012) found a relationship between ADHD and an NE transporter gene. There has been little research on ATX effects on cognitive functioning. However, two studies have shown

that it improves performance, as measured by a form of response inhibition, on the Stroop Color-Word Test (Faraone et al., 2005; Spencer et al., 1998).

The dynamic DA/NE Interaction

Given the support for both DA and NE contributing to the underlying cognitive deficits seen in ADHD, the next logical question is how do these systems interact and/or how do they differentially contribute to ADHD's core symptoms and cognitive deficits. Aston-Jones and Cohen (2005) have attempted to explain the dynamic interplay of DA and NE in exploration, attention, and performance. Their model, the adaptive gain theory, details the role of the Locus Coeruleus-Norepinephrine System (LC-NE) in task performance. This NE system is a neuromodulatory nucleus in the brainstem that projects to the neocortex (Aston-Jones, 2004). The adaptive gain theory is based on the idea that reinforcement learning relies on a process that promotes exploration in novel or unknown situations, but focuses on reward-producing actions when a reliable reward source is found. Aston-Jones and Cohen propose that the LC is primarily in a tonic state of activation, which promotes exploration. However, when reward sources are encountered, and reward-based behaviors are reinforced by the DA-dependent reinforcement learning system, the LC is prompted into a phasic state of activity, further promoting the reward-based behaviors. This increases performance by fostering task appropriate behaviors. As the reward or relevance of the behavior declines, the LC falls back into the tonic state to again promote learning and exploration. Theoretically, this exploration is an attempt to ultimately find another reward source. Though the authors

have not proposed this theory to adress ADHD specifically, they describe the LC-NE as an "attentional filter" in the sense that it fosters task relevant behaviors to the exclusion of distractions. Further, the dynamic interplay of NE and DA in the adaptive gain theory is especially relevant to the study of attention, and ADHD, as both DA and NE are thought to play a primary role.

Unique Contributions of DA and NE to Cognitive Functions

In addition to the interactions among DA and NE, it is possible that each of them also provides a unique contribution to the symptoms and cognitive deficits seen in ADHD. Frank et al. (2007a) assessed medicated and non-medicated ADHD participants and found that stimulant medications, which increase extracellular DA and NE, improved working memory, positive reinforcement learning, erratic behavior, and reaction time variability. The authors believe the effects on working memory and reinforcement learning were associated with each other, and independent from the effects on erratic behavior and reaction time variability, which were associated with each other. The authors suggest that the working memory and reinforcement learning improvements could be associated with the dopaminergic action of the medication, whereas the improved reaction time variability and erratic behavior could be associated with the noradrenergic action of the medication. The results are consistent with the notion of divergent DA and NE pathways underlying the symptoms of ADHD.

The computational brain models proposed by Frank and collegues attempts to explain the differential effects that the authors believe DA and NE have on specific

cognitive deficits of ADHD. These brain models suggest that low DA levels in striatum lead to disruption in reinforcement learning, deficient updating of working memory, and deficient long-term reward value maintenace. These models also predict that disruption in NE functioning is associated with increased reaction time variability and response inhibition deficits; it is expected that these NE related deficits are associated with decreased functioning in the PFC, and projections from the Locus Coeruleus to the PFC. This brain model is potentially very informative, but it is still theoretical and additional research is needed to determine whether it is accurate. Several other studies suggest that NE is primarily associated with response variability, reaction time variability, and response inhibition (Frank et al, 2007b; Llorente et al, 2006; Michelson et al, 2001; Overtoom et al, 2003; Chamberlain et al, 2006).

Unique Contributions of DA and NE to Behavioral Symptoms

Although clinicians commonly believe that ATX works better for the inattentive subtype whereas methylphenidate may be more effective for the combined subtype (Ghuman, personal communication), there is very little empirical research to test this hypothesis. One recent study compared the effects of ATX and MPH on inattention and hyperactivity-imulsivity, and found that both drugs were effective for both symptom domains, as compared with placebo, with MPH having a slight advantage over ATX (Newcorn et al., 2008). However, there is some initial, indirect evidence suggesting a unique relationship between DA and hyperactivity-impulsivity. A study using fMRI technology found that reduced ventral striatal activation during reward anticipation was

selectively associated with impulsivity-hyperactivity (Scheres et al., 2007). This reduced activation may be due to reduced DA in the ventral striatum, potentially implicating DA specifically in symptoms of impulsivity-hyperactivity (Frank et al., 2007b).

Additional indirect evidence for the hypothesized unique relationship between DA and NE and specific symptom domains comes from studies comparing ADHD symptoms with cognitive tasks that are expected to rely more or less heavily on either DA or NE (Frank et al., 2007a). DA is expected to be associated with working memory and reinforcement learning, while NE is expected to be related to reaction time variability, and inhibition control. Huang-Pollack et al. (2007) found evidence that both inattentive and combined subtypes have deficient inhibition control. However, the two subtypes differed in their ability to improve inhibition control in response to reward-based motivation in the Stop Task. The combined type improved inhibition control in the second reward condition, especially if a lower reward condition came first, whereas the inattentive subtype only improved in the second reward condition when it was a high reward condition preceeded by a low reward condition. Because response inhibition has been indirectly linked to NE, and reward-based learning has been indirectly linked to DA, this might suggest that the DA dependent reward system might act as a moderating factor in response inhibition. Further, it appears there might be differences between the subtypes in how this process takes place.

There is also some evidence that inattentive symptoms are more stongly associated with deficits in certain working memory components (Martinussen & Tannock, 2006; Willcutt et al., 2005; Diamond, 2005). Martinusen and Tannock (2006)

examined working memory performance in ADHD subtypes. A dimensional analysis revealed that working memory components were associated with the innatentive symptom dimension, but not with the hyperactive/impulsive symptom dimension. Further, Rogers et al. (2011) found an association between inattention and auditory and visual working memory in adolescents with ADHD. Based on the Frank et al. (2007a) model, which posits that DA is primarily associated with working memory, this could imply that DA is more strongly associated with symptoms of inattention, although this is a rather indirect link. This notion conflicts with the practicing clinicians' perspective, that ATX is more effective for individuals with the inattentive subtype (Ghuman, personal communication). However, the Frank et al. (2007a) model specifically expects updating of working memory to be associated with DA, and the Martinussen and Tannok article assessed "storage," and "manipulation" of working memoy, which both appear to fit best into Frank's "maintenance" of working memory. Therefore, it is possible that while updating of working memory is primarily associated with DA, some other components of working memory, such as maintenance, are more strongly associated with NE.

Although more research is needed to identify the specific underlying mechanisms, there is mounting support for the notion that the two subtypes, or symptom domains posess uniqe patterns of cognitive impairment. Following that reasoning, it is possible that DA and NE each primarily contribute specifically to either the innatentive, or the hyperactive/combined symptom dimensions, however, the research thus far has been rather indirect and inconclusive about whether this is the case.

THE PRESENT STUDY

There is converging evidence that DA and NE might be uniquely associated with specific cognitive deficits of ADHD, but it is unlikely that their roles in the disorder are mutually exclusive (eg. Aston-Jones & Cohen, 2005). Thus far, however, the existing research is not consistent regarding which symptoms are associated with which neurotransmitter (e.g. Frank et al., 2007a; Diamond, 2005). There is indirect evidence that there could be distinct neural pathways leading to the different subtypes of ADHD (i.e., the idea that DA and NE are differentially associated with the different subtypes, each contributing specifically to either the inattentive, or the hyperactive-combined subtypes) (eg. Diamond, 2005; Frank et al., 2007a). Most of the studies connect working memory function primarily with the inattentive symptoms (e.g. Martinussen & Tannock, 2006; Willcutt et al., 2005; Diamond, 2005), and some evidence has been found for a primary deficit in response inhibition/impulse control in the hyperactive/impulsive or combined subtypes (eg. Diamond, 2005). Frank et al. (2007a) has proposed an association between DA and updating of working memory and deficits in reward-based learning, and an association between NE and deficits in response inhibition and greater response variability. In addition, Atomoxetine studies have implicated NE in response inhibition (Farone et al., 2005; Spencer et al., 1998). However, the pieces of this complicated puzzle are still connected rather loosely, and more research is needed to concretely determine what behavioral symptoms are primarily associated with what

cognitive deficits, and if the neurotransmitter systems uniquely associated with the behavioral symptoms and associated cognitive deficits.

The present study aimed to assess how each neurotransmitter system is associated with the symptoms and cognitive deficits related to ADHD. To do this, the researchers examined performance on DA and NE tasks (i.e., tasks that are expected to rely specifically on either the DA system or the NE system for task performance) in individuals both with and without ADHD, including an ADHD-Inattentive Type (ADHD-I) group, an ADHD-Combined Type (ADHD-C) group, and a typical control group. We also included participants who fall within a 'gray area' diagnostically who do not clearly fit into any of the three categories. Those participants were excluded from categorical analyses because they could not be clearly classified, but included in dimensional analyses. These participants were included in order to look at the entire range of symptoms. Tasks that are expected to rely on the DA system include the Probabilistic Learning Task (Frank et al., 2004), the Updating of Working Memory Task (Westerberg et al., 2004), and the Temporal Reward Discounting task (Scheres et al., 2006; 2010). Tasks that are expected to rely on the NE system include the Stop Paradigm (Logan, 1994), and Probibilistic Learning Task (Frank et al., 2004). Note that the Probabilistic Learning task is expected to rely on both the NE and DA systems, depending on which variable we look at. For detailed information, see computer task descriptions below.

Hypotheses:

1) The ADHD-C and ADHD-I groups will perform more poorly than the control group on the DA and NE cognitive tasks

2) Group differences in computer task performance may depend on which neurotransmitter the task is expected to rely on.

3) Within the sample as a whole (including all subtypes and particiapnts who cannot clearly be classified into a specific group), the inattentive symptom dimension vs. the hyperactivity/impulsivity symptom dimension may correlate differentially with DA and NE measures.

Preliminary Studies

A preliminary study with well-functioning young adults (first year U of A students) was conducted to assess whether the DA tasks correlate with each other more than with the NE tasks, and the NE tasks correlate with each other more than with the DA tasks. A principal component analysis was preformed on dependent variables from all of the computer tasks. We expected that reward sensitivity and working memory would load on one factor ("DA"), while response inhibition and reaction time variability would load on a separate factor ("NE"). We found a clear "DA factor," onto which the expected "DA measures" loaded, but we did not find the expected "NE factor." Instead we found that reward processing and reaction time variability loaded onto the second factor, which was interpreted as a "reward maximization factor". It is possible that the roles of these NT systems are not as mutually exclusive as initially expected. However, it is also

possible that our “NE measures” were not as sound as our “DA measures,” or that the tasks used were not entirely appropriate for differentiating between DA and NE function.

Methods

Participants

This study included sixty-nine participants (39 male, 30 female) who were recruited through leaflets, fliers, newspaper ads, and a participant pool that the investigators of the Developmental Cognitive Neuroscience Lab at the Psychology Department of the University of Arizona have built over the past several years. They ranged in age from 12 – 17 (M = 13.95 years, SD = 1.54). Nine had comorbid Oppositional Defiant Disorder (ODD), and none had comorbid Conduct Disorder (CD). Their estimated intelligence scores, based on the WASI, ranged from 85 – 132 (M = 106.78, SD = 11.35). Forty-three of the participants identified as Caucasian, one identified as African American, 20 identified as Hispanic/Latino, 2 identified as Asian, 1 identified as Native American, and 2 identified as Native Hawaiian or other Pacific Islander.

Three groups were included: adolescents with ADHD-Combined Type (ADHD-C); adolescents with ADHD-Inattentive Type (ADHD-I); and a group of typically developing adolescents. None of our participants fell into the purely hyperactive/impulsive subtype (ADHD-H). One-way ANOVAs showed the group did not differ significantly with respect to age [$F(2, 68) = .13$, $p = .88$] or IQ [$F(2, 68) = 2.18$, $p = .12$] and Chi Square analysis showed the group did not differ significantly with respect to gender [$c^2(2, N = 69) = .40$, $p = .82$]. The ADHD-C group included 17 participants (10 male, 7 female). Five had comorbid ODD. They ranged in age from 12 – 17 (M = 13.88, SD = 1.83), and their estimated intelligence scores ranged from 86 –

118 (M = 102.41, SD = 9.66). The ADHD-I group included 25 participants (15 male, 10 female). Four had comorbid ODD. They ranged in age from 12 – 17 (M = 14.00, SD = 1.56), and their estimated intelligence scores ranged from 85 – 130 (M = 106.68, SD = 12.04). The typical control group included 27 participants (14 male, 13 female). They ranged in age from 12 – 16 (M = 13.94, SD = 1.38), and their estimated intelligence scores ranged from 88 – 132 (M = 109.63, SD = 11.17). See tables 1 and 2 for a breakdown of age, IQ, comorbidity, gender and LD. See table 3 for group means on the scales as obtained by the K-SADS, CPRS, CTRS, CBCL and DBD, parent and teacher questionnaires.

Table 1

	All Participants	Controls	ADHD-I	ADHD-C
	N = 69	N = 27	N = 25	N = 17
Meds[a]	7	0	0	6
ODD[b]	9	0	4	5
CD[c]	0	0	0	0
AD[d]	30	6	8	10
Males	39	14	15	10

Note: ADHD-I, Attention deficit Disorder, Inattentive subtype; ADHD-C, Attention deficit Disorder, Combined Subtype; Meds, Medication; ODD, Oppositional Defiant Disorder; CD, Conduct Disorder; AD, Academic Achievement Deficit

[a] Number on stimulant medication, discontinued for testing
[b] Number with ODD, based on the K-SADS
[c] Number with CD, based on the K-SADS
[d] Number with Academic Achievement Deficit as indicated by a difference score of 15 points or more between the Weschler Abbreviated Scale of Intelligence full scale IQ and any of the WIAT subscales (reading, spelling, numerical operations).

Table 2

	All Participants		Controls		ADHD-I		ADHD-C	
	N = 69		N = 27		N = 25		N = 17	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	13.95	1.54	13.94	1.38	14.00	1.56	13.88	1.83
IQ	106.75	11.35	109.63	11.17	106.68	12.04	102.41	9.66

Note: ADHD-I, Attention deficit Disorder, Inattentive subtype; ADHD-C, Attention deficit Disorder, Combined Subtype; Meds, Medication; ODD, Oppositional Defiant Disorder; CD, Conduct Disorder; AD, Academic Achievement Deficit; IQ, estimated IQ based on the Weschler Abbreviated Scale of Intelligence

Table 3

	All Participants		Controls		ADHD-I		ADHD-C		Group Comparison[a]
	N = 58[d]		N = 22		N = 19		N = 17		
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
K-SADS									
Inattentive Symptoms[b]	8.98	6.69	1.78	2.58	12.78	3.95	14.82	3.15	ADC,ADI>C
Hyp/imp Symptoms[b]	4.87	5.13	1.42	2.53	3.56	2.96	12.06	3.15	ADC>ADI>C
Parent									
CPRS T-scores[e]									
Anxiety	56.11	14.23	47.91	7.76	61.83	14.47	60.65	16.00	ADC, ADI>C
Social Problems	57.65	14.67	46.95	3.54	61.00	15.56	67.94	14.05	ADC, ADI>C
Psychosomatic	60.40	16.97	46.23	6.36	69.00	15.15	69.65	16.15	ADC, ADI, >C
Oppositional	59.28	15.10	44.95	4.57	64.83	11.85	71.94	11.58	ADC, ADI>C

Inattentive Symptoms	63.05	15.69	49.59	9.45	69.88	13.13	76.65	9.55	ADC,ADI>C
Hyperactive Symptoms	62.27	17.58	50.19	11.60	63.33	14.89	79.88	13.12	ADC>ADI>C
ADHD Problems	63.71	16.10	50.04	9.88	69.63	12.95	78.59	9.40	ADC,ADI>C
CBCL T-scores[f]									
Aggressive Behavior	58.54	8.26	51.23	2.27	61.00	7.25	66.13	6.20	ADC>ADI>C
Rule Breaking	58.73	8.34	52.41	4.18	63.00	7.92	62.60	7.91	ACD, ADI>C
Thought Problems	59.27	8.92	51.50	2.74	63.05	7.47	65.87	8.28	ADC, ADI>C
Social Problems	59.18	9.57	51.59	3.05	61.59	9.80	66.80	7.69	ADC, ADI>C
Somatic Complaints	62.50	10.46	53.36	4.20	68.37	9.92	68.47	7.81	ACD, ADI>C
Withdrawn	58.91	9.52	52.55	3.36	62.89	9.81	63.20	10.50	ADC, ADI>C
Anxious/ Depressed	58.88	11.71	51.32	2.46	62.95	11.61	64.80	12.57	ADC, ADI>C
Attention Problems	63.57	12.24	52.09	2.62	70.74	10.84	71.33	9.26	ADC, ADI>C
DSM-IV ADHD	60.88	9.14	51.59	2.22	64.58	6.23	69.80	5.52	ADC>ADI>C
DSM-IV ODD	58.82	8.31	51.59	2.28	61.11	7.35	66.53	6.40	ADC>ADI>C
DSM-IV CD	58.66	8.33	52.32	4.69	62.37	7.68	63.27	7.69	ADC,ADI>C
DBD[g]									
Inattentive Average	1.37	1.02	.45	.65	1.84	.80	2.14	.60	ADC, ADI>C
Hyperactive Average	.72	.73	.29	.46	.60	.47	1.6	.67	ADC>ADI, C
ODD Average	.82	.70	.29	.36	.96	.67	1.48	.47	ADC>ADI>C
CD Average	.15	.23	.05	.10	.18	.23	.29	.31	ADC>C; ADI=ADC; ADI=C
Teacher[c]									
CTRS T-scores[h]									
Inattentive Symptoms	59.21	14.34	50.10	10.86	64.57	13.29	64.09	14.63	ns

Hyperactive Symptoms	58.21	15.92	54.00	15.76	54.57	13.95	64.36	16.60	ns
ADHD Problems	60.75	14.83	52.90	13.96	62.71	16.83	66.64	12.09	ns
DBD[i]									
Inattention Average	.85	.91	.43	.64	1.36	1.12	1.10	.85	ADI>C; ADC=ADI; ADC=C
Hyperactivity Average	.47	.56	.27	.43	.49	.63	.77	.60	ns
ODD Average	.28	.48	.16	.27	.23	.30	.53	.78	ns
CD Average	.06	.15	.05	.17	.05	.09	.10	.18	ns
TRF[j]									
ADHD Problems	56.03	6.62	52.54	3.28	58.50	9.12	58.63	4.84	ns
ODD Problems	54.10	3.53	52.31	4.63	54.50	5.72	56.50	8.21	ns
CD Problems	54.58	5.53	53.15	4.36	54.00	5.72	57.63	6.46	ns

Note: ADHD, Attention Deficit Disorder; ADHD-I and ADI, Attention deficit Disorder, Inattentive subtype; ADHD-C and ADC, Attention deficit Disorder, Combined Subtype; DSM-IV Diagnostic and Statistical Manual of Mental Disorders-IV: Hyp/Imp, Hyperactive/Impulsive; K-SADS, Kiddie-Schedule for Affective Disorders; CPRS, Conners' Parent Rating Scale; CBCL, Child Behavior Checklist; DBD, Disruptive Behavior Parent/Teacher Rating Scale; CTRS, Conners Teacher Rating Scale; TRF, Teacher Report Form; ODD, Oppositional Defiant Disorder; CD, Conduct Disorder.

[a] Analyses of variance were performed. If the group effect was significant ($p < .05$), post hoc Tukey tests were performed to clarify the main effect.

[b] Participants received 1 point for mild symptoms and 2 points for moderate to severe symptoms.

[c] Teacher questionnaires were received for 34 participants (15 controls, 10 ADHD-I, 9 ADHD-C).

[d] Total number included in categorical analyses. Ten participants were excluded from categorical analyses due to a mismatch between K-SADS and questionnaire data and one was excluded due to meeting the K-SADS criteria for ODD but not ADHD so this person could not be considered a control.

[e] N = 57

[f] N = 56

[g] N = 56

[h]N = 28
[i]N = 28
[j]N = 27

Screening Procedure

All participants were administered the same set of screening instruments, including parent and teacher questionnaires, and the K-SADS. We used the following questionnaires for parents: the Conners' Parent Rating Scale (CPRS), the Child Behavior Checklist (CBCL), and a Demographics form for parents, Disruptive Behavior Parent/Teacher Rating Scale. We also made every effort possible to obtain the Conners' Teacher Rating Scale (CTRS), Disruptive Behavior Parent/Teacher Rating Scale, and the Teacher Report Form (TRF). However, we only received 34 teacher packets back from the teachers. Additionally, we administered the parent version of the Schedule for Affective Disorders and Schizophrenia for School-age Children – Present and Lifetime Version (K-SADS-PL). The K-SADS-PL includes sections on disruptive behavioral disorders (ADHD, Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD)), substance abuse, alcohol abuse, cigarette use, Affective Disorders, Psychotic Disorders, and Anxiety Disorders. Intelligence level was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI), and achievement levels were assessed using the Wechsler Individual Achievement Test (WIAT).

In order to be assigned to either ADHD group, participants were required to have a score higher than 1.5 SD above the mean on at least one of the ADHD-related scales of the CPRS. Additionally, they were required to meet DSM-IV criteria for ADHD-

C/ADHD-H or ADHD-I based on the K-SADS-PL, administered by the PI or a trained research assistant. The typically developing control group was required to have scores within the normal range (not higher than 1.5 SD above the mean) on all scales of the CBCL and the CPRS, and not meet the DSM-IV diagnostic criteria for ADHD or other behavioral disorders. We allowed participants in the control group if they had sub-threshold symptoms of ADHD to create an inclusive sample that most closely resembles the general population, and in order to increase variability in the sample for dimensional analyses. We aimed to have as homogenous an ADHD group as possible without excluding the most common comorbid conditions such as Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), depression/anxiety, and high-functioning autism spectrum disorders.

The exclusionary criteria included: major medical conditions that would interfere with task performance or interpretation of results (such as blindness or deafness), estimated full scale IQ below 70 (based on the WASI), inability or unwillingness to provide assent, absence of signed consent by parent or legal guardian, inability to read or speak English, use of psychoactive drugs that cannot be temporarily discontinued on the day of participation. Although we screened for ODD and CD in the interview (see above), individuals with ADHD and comorbid ODD or CD were not excluded. Participants who used psychoactive medication for ADHD were asked to discontinue medication 24 hours prior to testing (WASI and WIAT), and computer task performance.

Measures

Screening instruments.

K-SADS-PL (Kiddie-Schedule for Affective Disorders and Schizophrenia for School aged children) (Kaufman, et al., 1996; 1997): The K-SADS-PL is a semi-structured interview designed to assess and diagnose present and lifetime episodes of psychological disorders in children and adolescents, ages 12-17. This instrument assesses individual symptoms, which are based on the diagnostic criteria provided by the DSM-III-R, and the DSM-IV. Primary diagnoses included in the K-SADS-PL cover the major affective disorders, psychotic disorders, anxiety disorders, childhood behavioral disorders, and a number of other common childhood disorders.

The K-SADS-PL is designed to be administered to the parent, child, and a teacher or school official in order to provide a comprehensive view of the child's symptoms. It is ideal for research settings as it can be administered by properly trained research assistants. In addition, it is structured so that it can be administered very consistently, and consistent results should be obtained by different administrators. For the present study, researchers administered the screening portion of the KSADS-PL, plus the behavioral disorders supplement for all participants.

For categorical analyses, the K-SADS was used to group participants into categories (i.e. ADHD-I, ADHD-C or control), based on the DSM IV diagnostic criteria. For dimensional analyses, participants received a sum score for inattentive and hyperactive/impulsive based on the symptoms they endorsed; they received 1 point for mild symptoms and 2 points for moderate to severe symptoms, and these were summed

to form a total score for inattentive symptoms and a total score for hyperactive/impulsive symptoms.

WASI (Wechsler Abbreviated Scale of Intelligence) (Wechsler, 1999): The WASI was designed to reliably measure intelligence in individuals from 6 to 89 years of age. The test is nationally standardized and the results produce the familiar, and traditionally used Verbal, Performance, and Full Scale IQ scores. The assessment includes four subtests: Vocabulary, Block Design, Similarities, and Matrix Reasoning. These four subtests can be administered in approximately 30 minutes. There is a high correlation (r = .90) between the 4 subtests and the full intelligence test (Groth-Marnat, 1997). Full scale IQ score from the WASI was used to estimate IQ for this study.

WIAT-II-A (Wechsler Individual Achievement Test – Second Edition - Abbreviated) (Wechsler, 2001): The WIAT-II-A is a nationally standardized achievement test that can be administered in approximately 15 – 30 minutes. The test is designed for individuals aged 6 – 85 years. It contains three subtests: Numerical Operations, Spelling, and Word Reading. The WAIT-II-A is co-normed with the Wechsler intelligence scales, so combined use of the WASI and the WIAT-II-A can effectively estimate meaningful ability-achievement discrepancies. To determine whether students have an academic achievement discrepancy (AD), we used a difference score of 15 points or more between the WASI full scale IQ and any of the WIAT subscales (reading, spelling, numerical operations) (Barkely, DuPaul & McMurry, 1990).

Demographics form: This is a brief questionnaire that was filled out by the parents about their child's age, family/living situation, presence or absence of parental figures, medication use, disabilities, and parents' occupation and educational background.

Conners' Parent Rating Scale (CPRS) (Conners et al., 1998a): This is a comprehensive questionnaire to obtain information from parents regarding their children's behavior in the following domains: cognitive problems, oppositional, hyperactivity-impulsivity, anxious-shy, perfectionism, social problems, and psychosomatic. The instrument demonstrates good internal reliability, high test-retest reliability, and effective discriminatory power at distinguishing between children with and without ADHD.

Conners' Teacher Rating Scale (CTRS) (Conners et al., 1998b): This teacher rating scale includes the following six domains: hyperactivity-impulsivity, perfectionism, inattention/cognitive problems, social problems, oppositionality, anxious/shy factors. This questionnaire is well established, commonly used, and considered to have good test-retest and internal consistency, and excellent discriminatory power in differentiating between children with and without ADHD.

Child Behavior Checklist (CBCL) (Achenbach & Rescorla, 2001): This questionnaire was designed to be completed by parents regarding their child's functioning. It provides nationally norm-referenced T-scores and percentile scores in addition to raw scores for the following scales: aggressive behavior, anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, and withdrawn/depressed, activities competence, social competence, school

competence, total competence, internalizing, externalizing, and total problems. In addition, there are six scales designed to reflect the DSM diagnostic categorization: affective problems, anxiety problems, somatic problems, attention deficit/hyperactivity problems, oppositional defiant problems, and conduct problems.

Teacher Report Form (TRF) (Achenbach & Rescorla, 2001): This was filled out by teachers, and includes questions about the adolescent regarding the following domains: academic performance, adaptive functioning, and behavioral/emotional problems. It provides nationally norm-referenced T-scores and percentile scores in addition to raw scores for the following scales: academic performance, total adaptive functioning, aggressive behavior; anxious/depressed, attention problems, rule-breaking behavior, social problems, somatic complaints, thought problems, withdrawn/depressed, affective problems, anxiety problems, somatic problems, attention deficit/hyperactivity problems, oppositional defiant problems, conduct problems, internalizing, externalizing, and total problems.

Disruptive Behavior Parent/Teacher Rating Scale (DBD) (Pelham, Gnagy, Greenslade, & Milich, 1992): This scale was designed to help diagnose disruptive behaviors based on the DSM diagnostic criteria, and is considered especially useful in the diagnosis of ADHD and ODD in children and adolescents, when completed by their parents and/or teachers.

Computerized Tasks.

Probabilistic Learning Task (PL) (Frank et al., 2004; Frank et al., 2007a) (DA): Participants were presented with abstract stimuli pairs (ex: AB, CD), and instructed to learn to choose one of the stimuli based on either positive or negative feedback. The actual stimuli were Japanese characters. There were two pairs of abstract stimuli, each with a different probability of positive versus negative feedback during the training phase. For example, in the AB pair, the selection of stimulus A results in positive feedback on 80% of trials, and it results in negative feedback on 20% of trials. Selection of stimulus B results in negative feedback on 80% of trials, and it results in positive feedback on 20% of trials. For CD pairs, the probability is .7/.3. The participant was then presented with novel pairs of the same stimuli and asked to choose between them during the test phase. If the individual learned more from positive feedback, their performance on A-pairs is higher; if they learn more from negative feedback, their performance on B-pairs is higher. The dependent variable expected to be associated with DA for this task is accuracy on A-pairs vs. B-pairs.

Updating of Working Memory Task (WM) (Westerberg et al., 2004) (DA): Circles (memory stimuli) were presented one at a time in a 4 x 4 grid on the computer screen. After a series of memory stimuli, participants were provided with an empty grid, and asked to point to the boxes in the grid in the same locations, and in the same order as the circles just presented. Working memory load varied from a series of 2-9 memory stimuli followed by an empty grid. At each difficulty level, there were two trials without distracters, and two trials with distracters. In one of the distracter trials for each difficulty level, there was a delay before the empty grid was presented. The distracter and delay

trials are intended to distinguish between updating vs. maintenance of working memory. The dependent variables for this task are the highest number of correct responses in each condition (i.e.: no delay, no distracter; delay, no distracter; distracter, no delay; delay and distracter). In addition, an updating of working memory variable was created by subtracting the average of the two non-distracter variables from the average of the two distracter variables (i.e.: (distracter, delay + distracter, no delay)/2 – (no distracter, delay + no distracter, no delay)/2).

Temporal Discounting Task (TD) (DA): In order to measure temporal discounting of rewards, subjects were presented with a computer choice task. This task was an adjusted version of the temporal discounting task that was used in previous research with children and adolescents with ADHD (Scheres et al., 2006; 2010). Participants were presented with a series of choices between a smaller reward that was available immediately and a larger reward that was available after a delay period. Rewards consisted of monetary amounts presented on a computer screen. At the end of the task, participants received the amount that they won.

The large reward was always 5 cents and the delay preceding this reward varied across trials from 5, 10, 20, 30, to 60 seconds. Small immediate rewards varied in amount, and were either1, 2, 3, or 4 cents. Each immediate reward was paired four times with the large reward at every delay, resulting in a total of 80 choice trials.

The primary dependent variable for this task is the Area Under the discounting Curve (AUC) (see Scheres et al., 2006).

Stop Paradigm (Logan, 1994; Logan & Cowan, 1984; Scheres et al., 2003; 2004) (NE): Participants responded to a stimulus on the computer screen by pushing a button on the key board. The task involved two types of trials: go trials and stop trials. Go trials consisted of cartoon airplanes presented for a period of 1000 ms in the center of the computer screen. A fixation point appeared on the screen for 500 ms immediately before the go stimulus onset. If the plane points to the right, subjects were to press the response key on the right, and if the plane points to the left, subjects were instructed to press the key on the left.

The inter-stimulus-interval (ISI) is 1,500 ms. The inter-trial interval is 3000 ms. Stop trials consisted of a go trial and a stop signal (a 1000 Hz tone, 50 ms in duration). The stop signal was usually presented shortly after the plane, but might be presented concurrently with or shortly before the plane, depending on the child's performance (see below). Children were instructed not to press either of the two buttons, when they heard the tone. Seventy-five percent of the trials were go trials, and 25% were stop trials.

The Stop Paradigm allowed measurement of both response execution (go trials) and response inhibition (stop trials). Within a block, the plane pointed to the right or left with equal frequency, and stop signals were balanced for right and left go trials. Stop trials were presented randomly within each block. A stop trial was always followed by a go trial. However, to prevent the expectation that a stop trial is always be followed by a go trial, two stop trials were presented in succession once per block.

The stop task began with two practice bocks to ensure the participant understood the paradigm. In the first practice block only go trials were presented, and participants

were encouraged to respond as quickly and as accurately as possible. In the second practice block, 25% of the trials are stop trials, and participants were instructed to work as quickly and accurately as possible while suppressing their response when they hear the stop signal. After practice, participants were administered four experimental blocks of 64 trials each.

The dependent variable that reflects latency of the inhibitory process is stop signal reaction time (SSRT). Because SSRT cannot be directly observed, it has to be estimated. This can be done using the race model (Logan & Cowan, 1984). This model assumes that the go process and the stop process are independent. The go stimulus triggers the go process and the stop signal initiates the stop process. If the go process wins the race, the response is executed. If the stop process finishes first, the response is inhibited. The outcome of the race depends on the speed and the variability of the go process, the delay between go stimulus and stop signal, and the speed and the variability of the stop process. In the current study, the delay between the onset of the go signal and the stop signal varies dynamically, based on the subject's performance. The initial delay between go signal and stop signal is 250 ms. If the participant succeeds in inhibiting his or her response, the delay on the next stop trial is increased by 50 ms. If the participant does not succeed in inhibiting, the delay on the next stop trial is decreased by 50 ms. The computer program is set to establish a delay that allows individuals to inhibit 50% of the time. This means that on average, the go and the stop process finish at the same time. In this way, the finishing time of the go process becomes an estimate of the finishing time of

the stop process. SSRT can then be calculated by subtracting the mean delay from the mean go signal reaction time.

SSRT is the primary dependent variable, reflecting the latency of the inhibition process.

The stop task used in this study included both reward conditions where the participants were rewarded for correct answers and neutral conditions where they did not receive any feedback. In the analyses for this study, we only focused on the neutral condition. However, because there were also reward conditions in the task, this could affect the results of the neutral condition in an undetermined way.

Probabilistic Learning Task (NE): The Probabilistic Learning Task, described, was also used as an NE task. Reaction time variability (RT) in this task was expected to be associated with NE functioning.

Procedure

This experiment took place in the Psychology Department. The experiment involved two visits. The consent form and screening questionnaires were mailed to the parents prior to the first meeting so that participants could arrive at their first visit already having completed the self-report questionnaires. When they arrived, the researchers discussed the informed consent and assent with the participants before proceeding with the rest of the experiment. During visit 1, the parent version of the Schedule for Affective Disorders and Schizophrenia for School-age Children – Present and Lifetime Version (K-SADS-PL) was administered to the parents, and the WASI and WIAT was administered to the participant if they did not already have results on record at the DCNL lab from participation in a previous study, or if the previous results were more than 2 years old. During visit 1, two experimenters were present, allowing one experimenter to administer the K-SADS-PL to the parent/guardian, while the other administers the WASI and WIAT to the child/adolescent participant. The collaboration of two administrators allowed for visit 1 to be completed within two hours. However, in rare cases when it was not be possible to have two administrators present at visit 1, this visit was broken up into two separate visits: one for K-SADS-PL administration to the parent, and one for WASI/WIAT administration to the adolescent, or the K-SADS-PL was given over the phone. If participants had already undergone the procedures of visit 1 in a previous study in the Developmental Cognitive Neuroscience Lab, and if these data were not older than 2 years, participants were asked to give permission to the researchers to use this information for the current study. In that case, participants could skip visit 1.

During visit 2, participants performed the computer tasks designed to measure response inhibition, working memory, probabilistic learning, reward processing, and response time variability (see Measures for a description of the tasks). The computer tasks were administered in two orders (order 1: TD, PL, WM, Stop; order 2: WM, Stop, TD, PL) to counterbalance fatigue effects. Standardized instructions were read to participants at the beginning of each task. Each task included practice trials before the experimental trials started. The experimenter observed the participant during task performance, taking note of any behavior that might be relevant to data interpretation, such as distractibility or random responding. Participants responded to visual stimuli on the screen by pressing buttons on the keyboard. A video camera was used during the Working Memory task to record responses so that the experimenter could score accurately. The video camera was focused on the computer screen, and recorded the participants' finger pointing at the screen where visual stimuli appeared. The participants' faces and other identifying information were not recorded. The tapes were erased after scoring was complete. Participants were compensated $15 for each visit. It was also possible for participants to win monetary rewards on the computer tasks, not to exceed $22 per individual.

Missing Data and Outliers

Sixty-nine participants completed the study. PL data for one participant, and Stop data for one participant could not be used due to computer malfunction. Connors' Parent Rating Scale information was missing and could not be used for one participant. Two

participants were excluded from analyses of the Stop task because they inhibited more than 80% of the time, which indicates the tracking mechanism did not work effectively. One participant was excluded from analyses of the Probabilistic Learning Task data for having accuracy less than 50% on both A and B pairs in the training phase, which indicates they were not learning from positive or negative feedback. Ten participants were excluded from categorical analyses due to a mismatch between K-SADS and questionnaire data and one was excluded due to meeting the K-SADS criteria for ODD but not ADHD so this person could not be considered a control.

In order to assess for outliers, a box and whisker plot was created for each of the dependent variables [area under the discounting curve (TD), stop signal reaction time (Stop Task), reaction time variability (PL task), accuracy on A pairs over B pairs (PL task), and working memory difference score (WM task)] to assess for outliers. If a participant was an extreme outlier (i.e., 3 quartile ranges [IQR's] outside of the inter-quartile range) on at least one dependent variable, (s)he was excluded from the statistical analyses. Based on this rule, one participant was excluded from all analyses involving the PL task for being an outlier on reaction time variability, one participant was excluded from all analyses involving the Stop task for being an outlier on SSRT, and three participants were excluded from analyses with the stop task for being outliers on the proportion inhibit variable.

Statistical Analyses

ANOVAs with group as the between-subject factor (3 levels: ADHD-C, ADHD-I, and typically developing adolescents) were performed for the dependent variables on the DA tasks and the NE tasks. ANCOVAs were used to minimize unexplained variance in the dependent variables due to confounding factors (Field, 2009). In the case of significant results, a post hoc Tukey test was performed to determine the main effect.

Regression analyses were used to examine the unique contribution of the symptom dimensions inattention and hyperactivity/impulsivity to performance on the DA/NE measures. The advantage to this analysis is that it includes more participants, including those who fall in the "gray area" between ADHD and typical. In the first model, inattention as measured in the K-SADS was entered as a predictor in step 1, and hyperactivity/impulsivity was entered in step 2. In the second model, the order of the two predictors was reversed.

Results

Categorical Analyses

Age, IQ, ODD, CD and AD were all considered as potential covariates. None of the participants had CD so this was not considered further. Chi square analysis revealed that ODD [$c^2(2, N = 69) = 5.63, p = .06$] differed as a function of group assignment. Therefore, ODD was not further considered as a covariate (Miller and Chapman, 2001). However, ANOVAs revealed that IQ [$F(2, 66) = 2.18, p = .12$] and age [$F(2, 66) = .13, p = .88$] did not significantly differ based on ADHD group assignment and Chi square

analysis revealed that AD [$c^2(2, N = 58) = 3.94, p = .14$] did not significantly differ based on group assignment so it was appropriate to use them as covariates if they were significantly associated with the dependent variable. Age in months was significantly correlated with reaction time variability ($r = -.29, p < .05$) and therefore it was used as a covariate in the analyses of reaction time variability. IQ was significantly correlated with updating of working memory ($r = .37, p < .01$) and therefore it was used as a covariate in the analysis for the updating of working memory. For correlations between the dependent variables and the potential covariates, see Appendix 1, Table 1.

ANOVAs

ANOVAs with group as the between-subject factor (3 levels: ADHD-C, ADHD-I, and typically developing adolescents) were performed for the dependent variables on the DA tasks and the NE tasks (updating of WM, AUC, SSRT, reaction time variability and accuracy on A vs. B pairs). No significant group differences were found for AUC [$F(2, 57) = .18, p = .84$], SSRT [$F(2, 50) = .38, p = .69$], reaction time variability [$F(2, 54) = .45, p = .64$] and accuracy on A vs. B pairs [$F(2, 53) = .45, p = .88$]. The analysis for updating of WM revealed a significant difference as a result of group assignment [$F(2, 57) = 3.44, p = .04$}. Tukey's post hoc analysis revealed that ADHD-C was significantly different from ADHD-I, but the control group was not significantly different from ADHD-C or ADHD-I. The ADHD-C group had the highest score on updating of WM, the ADHD-I group had the lowest score, and the control group fell in between and was not significantly different from either ADHD group. See Table 3 for group means.

Because updating of WM is a difference score, please refer to Figure 1 for group performance on the four raw WM scores used to obtain the updating variable. Figure 1 indicates that the ADHD-C group performed worse overall on WM, compared to the other conditions, but had the highest score on updating of WM because there was very little difference in their performance on distracter trials compared to non-distracter trials. ADHD-I had the highest updating score because they did relatively well on the non-distracter trials, but poorly on the distracter trials. Thus, the lower updating score indicates that this group is the most sensitive to distracters, which is also indicated in Figure 1 as their performance drops off notably on the distracter trials. The control group performed the best on all trial types, but their performance dropped when both a distracter and a delay were present.

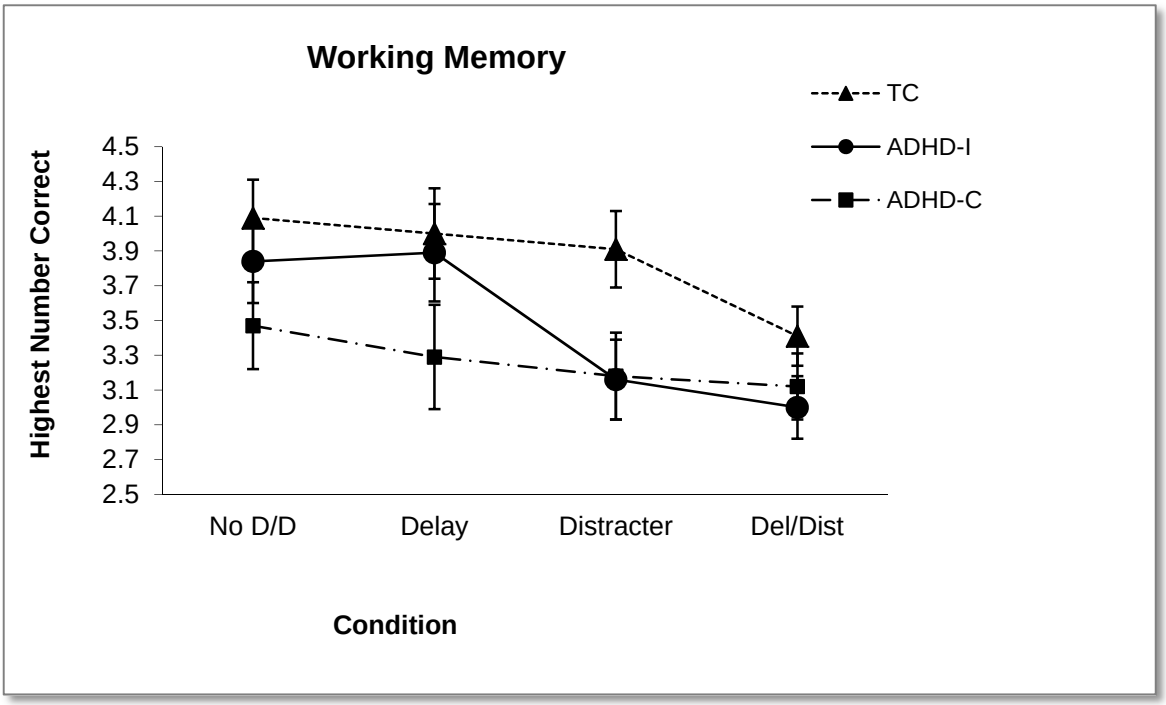

Figure 2: No D/D, no distracter and no delay condition; Delay, delay only condition; Distracter, Distracter only condition; Del/Dist, distracter plus delay condition; TC, typically developing controls; ADHD-I, Attention Deficit Hyperactivity Disorder – Inattentive Subtype; ADHD-C, Attention Deficit Hyperactivity Disorder – Combined Subtype

ANCOVAs

An ANCOVA was run with group as the between-subject factor (3 levels: ADHD-C, ADHD-I, and typically developing adolescents) and updating of working memory as the dependent variable using IQ as a covariate and this analysis revealed a significant group difference [$F(2, 54) = 1.54$, $p = .04$], which is consistent with the ANOVA. An ANCOVA was run with group as the between-subject factor (3 levels: ADHD-C, ADHD-I, and typically developing adolescents) and reaction time variability as the dependent variable using age in months as a covariate and this analysis also did not reveal a significant group difference [$F(2, 51) = .37$, $p = .70$]. See Table 4 for group performance on the dependent variabls. See Figure 2 for the Temporal Discounting Curve for each group.

Table 4

	All Participants		Controls		ADHD-I		ADHD-C	
	M	SD	M	SD	M	SD	M	SD
% Correct A pairs PL	.74	.16	.76	.14	.73	.15	.74	.20

% Correct B pairs PL	.70	.19	.71	.17	.67	.18	.72	.23
Accuracy[a] A/B pairs	.04	.20	.04	.21	.05	.20	.05	.21
RT variability	.54	.18	.53	.20	.51	.16	.60	.20
SSRT[b]	167.48	51.26	166.68	59.41	172.11	55.04	162.79	31.52
AUC[c]	.49	.33	.47	.32	.46	.31	.55	.38
WM no del, no dist[d]	3.83	1.06	4.09	1.11	3.84	1.01	3.47	1.01
WM delay, no dist[e]	3.76	1.25	4.00	1.02	3.89	1.37	3.29	1.31
WM dist, no delay[f]	3.45	1.06	3.91	1.19	3.16	.69	3.18	1.07
WM dist + delay[g]	3.20	.78	3.41	.73	3.00	.88	3.12	.70
Updating of WM[h]	-.47	.69	-.38	.55	-.79	.71	-.24	.73

Note: % correct A pairs PL, Percent correct on A pairs in the Probabilistic Learning Task; % correct B pairs PL, Percent correct on B pairs in the Probabilistic Learning Task; Accuracy A/B pairs, Accuracy on A pairs minus accuracy on B pairs from PL task; RT variability, Reaction time variability; SSRT, Stop Signal Reaction Time in milliseconds, neutral condition; AUC, Area under the discounting curve from Temporal Discounting Task; WM no del, no dist, Working Memory total correct on no delay, no distracter trials; WM delay, no dist, Working Memory total correct on delay, no distracter trials; WM dist, no delay, Working Memory total correct on distracter, no delay trials; WM dist + delay, WM total correct on distracter + delay trials; Updating of Working Memory, Updating of Working Memory: (distracter, delay + distracter, no delay)/2 – (no distracter, delay + no distracter, no delay)/2.

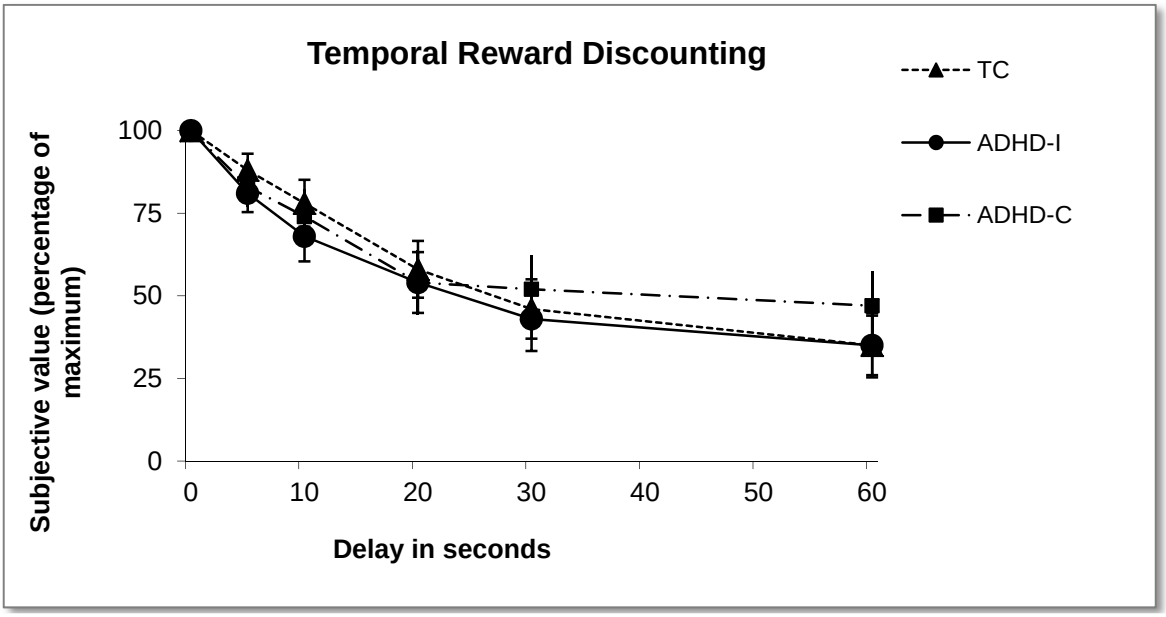

Figure 2: Delay in seconds, amount of time participant had to wait to receive large reward; TC, typically developing controls; ADHD-I, Attention Deficit Hyperactivity Disorder – Inattentive Subtype; ADHD-C, Attention Deficit Hyperactivity Disorder – Combined Subtype

Dimensional Analyses

Again, age, IQ, ODD, CD and AD were all considered as potential covariates. None of the participants had CD so this variable was not considered further. ODD and IQ were correlated with one or both of the predictive factors (inattention or hyperactivity/impulsivity) so they were not appropriate to use as covariates. Age and AD were not correlated with either so they were further analyzed as covariates. See Table 5, below, for correlations among the predictive factors and potential covariates. Age was significantly correlated with reaction time variability ($r = -.291$, $p < .05$) so age was used as a covariate for analyses involving RT variability. See Appendix 1, Table 2 for all correlations among dependent variables and potential covariates.

Table 5

Univariate Correlation Table for predictive factors (inattention and hyperactivity/impulsivity) with potential covariates.

		IQ	AD	Age	ODD	Hyperactivity/ Impulsivity [a]	Inattention [b]
IQ	r	1.00	-	-	-	-	-
AD	r	-.04	1.00	-	-	-	-
Age	r	.07	-.07	.1.00	-	-	-
ODD	r	.03	.02	.04	1.00	-	-
Hyperactivity/ Impulsivity [a]	r	-.32**	.20	-.11	.36**	1.00	-
Inattention [b]	r	-.22	.22	-.05	.36**	.66**	1.00

Note: IQ, estimated IQ based on the Weschler Abbreviated Scale of Intelligence; AD, Academic Achievement Deficit; ODD, Oppositional Defiant Disorder

[a]Hyperactivity/Impulsivity as measured by the K-SADS; Participants received 1 point for mild symptoms and 2 points for moderate to severe symptoms.

[b]Inattention as measured by the K-SADS; Participants received 1 point for mild symptoms and 2 points for moderate to severe symptoms.

Pearson Correlation Sig. = .05 (2-tailed).
* $p < .05$. ** $p < .01$.

Regressions

The regression analyses revealed that hyperactivity/impulsivity is positively correlated with updating of WM [b = .06, SE = .02, t(65) = 3.05, p < .01] but only after variance due to inattention has been accounted for and that inattention is negatively correlated with updating of WM [b = -.04, SE = .02, t(65) = -2.69, p < .01] but only after variance due to hyperactivity/impulsivity has been accounted for. They also revealed that hyperactivity/impulsivity is positively correlated with reaction time variability both before [b = .01, SE < .01, t(63) = 2.11, p = .02] and after [b = .02, SE = .01, t(62) = 2.10, p = .04] variance from inattention has been accounted for. When age was used as a covariate, hyperactivity/impulsivity was still positively correlated with reaction time variability [b = .01, SE < .01, t(62) = 2.11, p = .04], but only before the variance due to inattention has been accounted for. The regression analyses did not reveal any other significant results.

The results of the regression analyses are reported in Tables 6 - 11.

Table 6

Stepwise Regression Analyses with Inattention and Hyperactivity/Impulsivity as Predictors and Updating of Working Memory as the Dependent Variable

	Updating of Working Memory			
	β	R^2	ΔR^2	sign
Analysis 1				
Model 1 inattention	-11	.01	.01	.39
Model 2 hyp/imp[a]	.47	.14	.12	<.01
Analysis 2				
Model 1 hyp/imp[a]	.20	.04	.04	ns
Model 2 inattention	-.41	.14	.10	.01

Inattention, hyperactivity/impulsivity as measured with the K-SADS.
[a]*hyp/imp* hyperactivity/impulsivity.

Table 7

Stepwise Regression Analyses with Inattention and Hyperactivity/Impulsivity as Predictors and AUC as the Dependent Variable

	AUC			
	β	R^2	ΔR^2	sign
Analysis 1				
Model 1 inattention	.00	.00	.00	ns
Model 2 hyp/imp[a]	.14	.01	.01	ns
Analysis 2				
Model 1 hyp/imp[a]	.08	.01	.01	ns
Model 2 inattention	-.10	.01	.01	ns

Inattention, hyperactivity/impulsivity as measured with the K-SADS.
[a]*hyp/imp* hyperactivity/impulsivity.

Table 8

Stepwise Regression Analyses with Inattention and Hyperactivity/Impulsivity as Predictors and SSRT as the Dependent Variable

	SSRT			
	β	R^2	ΔR^2	sign
Analysis 1				
Model 1 inattention	.02	.00	.00	ns
Model 2 hyp/imp[a]	.03	.00	.00	ns
Analysis 2				
Model 1 hyp/imp[a]	.03	.00	.00	ns
Model 2 inattention	-.01	.00	.00	ns

Inattention, hyperactivity/impulsivity as measured with the K-SADS.
[a]*hyp/imp* hyperactivity/impulsivity.

Table 9

Stepwise Regression Analyses with Inattention and Hyperactivity/Impulsivity as Predictors and Reaction Time Variability as the Dependent Variable

	Reaction Time Variability			
	β	R^2	ΔR^2	sign
Analysis 1				
Model 1 inattention	.15	.02	.02	ns
Model 2 hyp/imp[a]	.34	.08	.07	.04
Analysis 2				
Model 1 hyp/imp[a]	.29	.08	.08	.02
Model 2 inattention	-.08	.09	.00	ns

Inattention, hyperactivity/impulsivity as measured with the K-SADS.
[a]*hyp/imp* hyperactivity/impulsivity.

Table 10

Stepwise Regression Analyses with Inattention and Hyperactivity/Impulsivity as Predictors and Accuracy on A pairs vs. B pairs as the Dependent Variable

	Accuracy A pairs vs. B pairs			
	β	R^2	ΔR^2	sign
Analysis 1				
Model 1 inattention	.01	.00	.00	ns
Model 2 hyp/imp[a]	.08	.00	.00	ns
Analysis 2				
Model 1 hyp/imp[a]	.05	.00	.00	ns
Model 2 inattention	-.05	.00	.00	ns

Inattention, hyperactivity/impulsivity as measured with the K-SADS.
[a]*hyp/imp* hyperactivity/impulsivity.

Table 11

Stepwise Regression Analyses with Inattention and Hyperactivity/Impulsivity as Predictors, Reaction Time Variability as the Dependent Variable, and Age as a Covariate

	Reaction Time Variability			
	β	R^2	ΔR^2	sign
Analysis 1				
Model 1 age	-.36	.13	.13	<.01
Model 2 inattention	.13	.14	.02	ns
Model 3 hyp/imp[a]	.28	.19	.04	ns
Analysis 2				
Model 1 age	-.36	.13	.13	<.01
Model 2 hyp/imp[a]	.24	.19	.06	.04
Model 3 inattention	-.06	.19	.00	ns

Inattention, hyperactivity/impulsivity as measured with the K-SADS.
[a]*hyp-imp* hyperactivity/impulsivity.

Discussion

This study investigated the relationship between symptoms of inattention and hyperactivity/impulsivity as observed in adolescents with ADHD and cognitive functions which, based on theoretical models (e.g.: Frank et al, 2007a), are expected to be primarily associated with either DA or NE. To assess this, we used the following "DA measures": probabilistic learning from positive feedback versus probabilistic learning from negative feedback, updating of WM and AUC on a temporal reward discounting task; and the following "NE measures": SSRT on the Stop Task and RT variability in the probabilistic learning task. We hypothesized that: 1) The ADHD-C and ADHD-I groups would perform more poorly than the control group on the DA and NE cognitive tasks; 2) Group differences in computer task performance may depend on which neurotransmitter the task is expected to rely on; 3) Within the sample as a whole (including all subtypes and participants that could not clearly be classified into a specific group), the inattentive symptom dimension vs. the hyperactivity/impulsivity symptom dimension may correlate differentially with DA and NE measures.

General Findings

Categorical Analyses.

The ADHD-C group had significantly *higher* updating of WM scores than the ADHD-I group, and the control group did not differ significantly from either ADHD

group. Interestingly, the difference was not in the direction we expected based on the Frank et al. (2007a) brain model. No other significant group differences were found on task performance. Thus, the first hypothesis, that the ADHD-C and ADHD-I groups would perform more poorly than the control group on the DA and NE cognitive tasks, was not supported because we did not find a group difference for most of the DVs. The second hypothesis, that the extent to which performance differs between the ADHD-C group and the control group, and between the ADHD-I group and the control group may depend on which neurotransmitter the task relies on, was only partially supported because we did find differential performance between the ADHD-I and ADHD-C groups on updating of WM and this difference could be due to differential NT involvement in the two subtypes. However, the difference was not in the direction we expected, and the difference between each ADHD subtype and the control group did not reach statistical significance. Thus, it is unclear if this is because the NTs are not associated with either the subtypes or updating of WM in the expected way or if another factor is responsible for this result.

Frank et al. (2007a) found that stimulant medication, which increases extracellular DA, improved updating of WM. Scheres et al. (2007) found reduced activation in the ventral striatum was associated with symtpoms of hyperactivity/impulsivity and not inattention, and this reduced activation could indicate reduced DA levels. Thus, we would expect the ADHD-C group to be the most impaired on updating of working memory, which is not consistent with the present results. However, updating of WM was

computed here as the difference between distracter trials and non-distracter trials and it is imporant to also look at the individual WM variables. A higher score on the updating of WM variable indicated poor performance on distracter trials compared to performance on non-distracter trials. The ADHD-I group had the greatest drop off in performance on distracter trials compared to non-distracter trials. While they did relatively well on non-distracter trials, they did notably more poorly on distracter trials. The control group did the best, overall, on the four WM trial types, and their performance dropped off only when both a distracter and a delay were introduced in the same trial. The ADHD-C group did most poorly overall, and did not show a notable drop-off in their performance when distracters were introduced. Thus, although the ADHD-C group had the highest updating of WM score, they had the poorest overall performance on WM. Another way to look at this would be to say that the ADHD-C group had reduced overall vigilance leading to poor performance on all trial types, and the ADHD-I group had a more specific difficulty ignoring the distracter.

It is possible that the present updating of WM task was not appropriate to test the Frank et al. (2007a) model. The updating of WM variable was created to emulate the updating of WM task that Frank and colleagues used to test his 2007 brain model, however, it was not exactly the same. Frank used a similar difference variable to calculate a score of updating and not maintenance, but he used a variation of the AX-CPT (continuous performance task) working memory task (Servan-Schreiber e al, 1997; Barch et al, 1997, 2001), whereas we used a visuospatial WM task (described in detail above)

that was based on a visuospatial WM task by Westerberg et al. (2005) that has been found to discriminate well between ADHD and control participants. Although the difference variable was calculated in the same way, it is possible the two tasks are different enough that we did not measure the same construct. It is also possible that both updating and other aspects of WM are associated with DA. Bedard et al. (2004) found that MPH improved both updating and maintenance of visuospacial working memory in children with ADHD, which supports the idea that the DA and NE effect on updating vs. maintenance might not be mutually exclusive.

There is very little existing literature on updating of WM and ADHD, but recent studies that looked at overall WM have not found a difference in performance between subtypes. Cockcroft (2011) found that both hyperactive and inattentive subtypes of ADHD performed more poorly than controls on verbal and visuospacial WM, but the two ADHD groups did not perform significantly differently from each other. Alloway et al. (2010) also did not find a difference on overall WM performance between subtypes in a group of 9-year olds. Schweitzer et al. (2006) found gender differences on WM in adults and also found that the ADHD groups did worse than the control group, but no subtype differences were found on WM performance. It is interesting that the present study did find a difference between subtypes on WM performance when a great deal of the more current literature is not in line with this finding. It is possible that the present WM test was more sensitive to differences between the ADHD subtypes and additional research with this task is warranted to test whether that is the case. This is consistent with the

notion that the Westerberg et al. (2005) task, that the present WM task was modeled after, discriminates well between ADHD and control participants.

Dimensional Analyses.

Finally, we predicted that within the sample as a whole (including all subtypes), the inattentive symptom dimension vs. the hyperactive/impulsive symptom dimension may correlate differentially with DA and NE measures. We found a significant result for two of the dependent variables; these were WM and RT variability.

Updating of WM. The regression analysis for WM revealed that hyperactivity/impulsivity is positively correlated with updating of WM after entering inattention into the model, and inattention is negatively correlated with WM after entering hyperactivity/impulsivity into the model. This is consisted with the categorical analysis findings, discussed above. It is important to keep in mind that this is not a measure of WM overall, but a measure of how participants performed on distracter trials compared to non-distracter trials. Thus, it means that participants with more hyperactive/impulsive symptoms performed more similarly on distracter trials and non-distracter trials, whereas participants with more inattentive symptoms showed poorer performance on distracter trials compared to non-distracter trials. In general, hyperactive/impulsive symptoms are associated with poorer performance overall on WM trials, whereas inattentive symptoms are associated with relatively good performance on non-distracter trials and a notable decrease in performance on distracter trials. Again, the direction of these correlations is not what we would expect, based on Frank et al. (2007a;

Scheres, 2007). However, the research up to this point has been very inconsistent about which neurotransmitter is associated with which cognitive task (eg., Cummins et al., 2011; Nandam et al., 2011; Frank et al. 2007a; Bedard et al., 2007). Thus, one can wonder how useful it is to try to link symptom domains to neurotransmitters based on task performance. Additionally, it seems that the roles of NE and DA in contributing to symptom domains of ADHD might not be as specific as we once thought and perhaps they both play an important role in each symptom domain. For example, we proposed that SSRT would be related to NE, but a recent study found that polymorphisms in a dopamine transporter gene predicted outcome on SSRT (Cummins et al., 2011). Further, Nandam et al. (2011) found that Methylphenidate improved SSRT, but Atomoxetine did not, which also indicates that SSRT might be modulated by DA, rather than NE. This supports the notion that the roles of NE and DA might not be as mutually exclusive as we once expected and this idea is consistent with the results of the preliminary study conducted by the present researchers (Knight, unpublished), described above.

RT Variability. Hyperacitivity/impulsivity, but not inattention, predicted a significant amount of variance in performance on RT variability. This result was present when no covariates were used and also when age was entered as a covariate. However, a stronger effect was seen when no covariate was used. In that case, hyperactivity/impulsivity predicted reaction time variability in both models of the regression analysis, (i.e., when hyperactivity/impulsivity was entered first, before accounting for variance due to inattention, and also when it was entered second so that

variance due to inattention had already been accounted for). When age was used as a covariate, hyperactivity/impulsivity only predicted reaction time variability when variance due to inattention was not already accounted for. Further, age accounted for more variance in reaction time variability than hyperactivity/impulsivity did. Thus, there does seem to be an association between hyperactivity/impulsivity and reaction time variability, but that association is relatively small, based on these findings. This is consistent with the direction of the mean differences we saw in the categorical analyses, indicating that the ADHD-C group had greater reaciton time variability than the other two groups, but that difference did not approach significance.

Castellanos and Tannock (2002) note that large response variability is likely the most consistent finding in those with ADHD. Individuals with ADHD tend to show greater variability in responding in the majority of studies. It was unexpected, however, to find that hyperactivity/impulsivity predicted reaction time variability and inattention did not. Frank (2007a) predicts that reaction time variability is primarily associated with NE and Scheres et al. (2007) has found initial evidence suggesting a possible link between hyperactivity/impulsivity and DA. However, this is a weak and rather indirect link between DA and hyperactivity/impulsivity and the research has thus far been relatively inconsistent regarding some of these findings. Furthermore, just because hyperactivity/impulsivity is associated with DA, that does not mean it cannot also be associated with NE. A more recent study found an association between the DAT1 gene (a dopamine transporter gene) both the inattentive subtype as well as severity of

inattentive symptoms (Shang et al., 2011) so perhaps the differential associated between NE and DA and the subtypes is not as specific as once expected. Moreover, Kratz et al. (2012) found that MPH led to a greater decrease in RT variability than ATX, which further supports the role of DA in RT variability.

Sample Comparison

The results for WM and RT variability indicate an association between ADHD symptoms and cognitive functioning, but it is somewhat surprising that we did not find an association between ADHD symptoms and the other three dependent variables (AUC, SSRT and Accuracy on A vs. B pairs). To investigate why we did not find the same results as previous studies in this area, we compared the present sample to those in previous studies on a number of potentially relevant factors. ADHD is a very heterogeneous disorder (i.e., Steinhausen, 2009) and there is a lot of variety in samples and recruitment methods. A study on temporal discounting by Scheres et al. (2010) used a similar recruitment method as the present study and described their sample in detail. Both studies include slightly more boys than girls, and the present study has a slightly older average age, compared to the study by Scheres and colleagues. All three groups from the Scheres et al. study had slightly higher estimated IQs, based on the WASI, but only by 3 to 6 points. Because the WASI is an estimated IQ and the scores are not exact, this difference is quite small. However, it is notable since the same trend for slightly higher IQ than the present sample was seen across all three groups. The ADHD-C group in the present study had a higher level of overall ADHD symptoms and inattentive

symptoms, based on the CPRS, compared to the Scheres et al. study, but otherwise the two samples were similar with regards to ADHD symptoms. The present study had substantially fewer participants on medication in both the ADHD-I and ADHD-C groups and this could be an important difference. Although participants in both studies discontinued their medication on testing day, this might indicate that the two samples differ on some underlying characteristics that are relevant to study outcome. The present study also had fewer participants with both ODD and CD, compared to the Scheres and colleagues study. Twenty-nine percent of participants in the ADHD-C group and 16% of participants in the ADHD-I group in the present study had ODD, compared to 40% in the ADHD-C group and 30% in the ADHD-I group in the Scheres et al., 2010 study.

In general, it appears the participants in the present study had a notably lower rate of ODD and CD than is typically seen in ADHD samples (e.g. Ollenick et al., 2008; Scheres et al., 2010; Martinusen and Tannock, 2006). Ollenick et al. (2008) reported that 40% of their participants with ADHD also had ODD and 11% had CD. In the present study, the numbers were again much lower as only 21.4% of ADHD participants had a comorbid ODD diagnosis and none had a comorbid CD diagnosis. Perhaps the present study was a more pure sampling of ADHD with fewer comorbidities and some of the links between ADHD and cognitive functions may actually be due to common comorbid conditions such as conduct disorder more than they are directly related to ADHD. In support of this idea, Di Trani et al., (2011) found that comorbidity pattern (i.e., internalizing vs. externalizing comorbid conditions) predicted performance on executive

functions in children and adolescents with ADHD, whereas subtype did not. This is an important area for additional research. Regardless, the lower rate of comorbidity in the present sample could indicate that we have a unique sampling of the ADHD population and this could account for the present study's predictions not being supported.

We also had a somewhat high rate of AD in the control group. We found that 22.2% of the control participants had a deficit in academic achievement, compared to approximately 8% of children and adolescents in the general population according to a 2010 National Health Survey (Bloom, Cohen & Freeman, 2011). When recruiting participants, we advertised the fact that a summary report would be provided to parents about how their children performed on the questionnaires, and the intelligence/achievement tests so it is possible that many parents were motivated by this factor and that we attracted a control group with underlying problems we are unable to fully identify. The high percentage of controls with potential AD could indicate the control group was not as pure as those in other studies, and that they were performing relatively poorly on the cognitive tasks due to the higher rate of AD. However, there are a variety of different ways to detect AD and this can result in a huge variation in the percentage of kids who are found to have an AD (Barkely, DuPaul & McMurry, 1990). A comparison showed that controls with AD did not perform significantly differently on the computer tasks than controls without AD. Because of the small N, significance would be difficult to achieve, but the group means on all 5 DVs are very similar for participants with and without AD. Further, an exploratory analysis was run where all

controls with AD were excluded and this did not change the results. Thus, it is not highly likely that the presence of AD in the control group effected outcome.

Task Comparisons

We also compared task performance of the present participants on AUC and SSRT with performance in other studies, as data for these tasks was available in the existing research.

SSRT.

A meta-analysis by Willcutt et al. (2005) found that SSRT consistently discriminates between ADHD and control groups, and typically also discriminates between subtypes. Thus, we wanted to investigate why the present study did not find any group differences on this measure. Bitsakou et al. (2008) reported mean SSRT scores for adolescents in the same age range as the present study. The controls had slightly slower SSRTs (M = 201ms, SD = 57) compared to the present study (M = 166.68ms, SD = 59.41), but the ADHD participants had significantly slower SSRTs (M = 300ms, SD = 153) compared to the ADHD-I (M = 172.11ms, SD = 55.04) or ADHD-C (M = 162.79ms, SD = 31.52) groups in the present study. Bitsakou and colleagues' control participants also had a slightly slower mean reaction time on the stop task of 559ms (SD = 133) compared to the controls in the present study (M = 490.09ms, SD = 169.19), and their ADHD group had more similar mean reaction times (M = 546ms, SD = 138) compared to those in the present study as the ADHD-I group had a mean reaction time of

547.52 (SD = 223.57) and the ADHD-C group had a mean reaction time of 539.83 (SD = 234.12. Williams et al. (1999) conducted a developmental study where they looked at SSRT in various different age groups in the general (non-clinical) population. For adolescents, they found a mean SSRT of 197.7ms (SD = 75.9). This is similar to the scores Bitsakou and colleagues (2008) reported for their control group and also similar to the present study's control group. Based on these comparisons, it seems the controls in the Bitsakou and colleagues study reacted to the go signal a bit more slowly than the present controls did, but both ADHD groups reacted similarly to the go signal. The place where there is a very notable difference is that the present ADHD groups both had much faster SSRT scores than the Bitsakou and colleagues ADHD group, and the present ADHD group looked more like their control group when it comes to SSRT performance. Both control groups performed somewhat similarly to the normal adolescents in the Williams et al. study. Thus, it is possible that the reason we did not see a significant difference between the controls and ADHD group is because the ADHD group was performing more like a control group on this measure while the control group was performing as we would expect.

AUC.

In general, individuals with ADHD show a strong preference for a smaller, immediate reward over a larger, delayed reward (see for a review: Luman et al., 2005). Gupta et al. (2011) conducted a study on children where they found that performance on a Choice Delay Task (very similar to the TD tasks used in this study, where participants

had to choose between a large, delayed reward and a smaller, immediate reward) distinguished between ADHD participants and control participants most accurately out of a number of neuropsychological measures assessed in the study. Scheres et al. (2010) reported AUC scores for adolescents for the same Temporal Discounting Task that was used in the present study. The means for their study were as follows: controls: .55, ADHD-I: .55, ADHC-C .33. Scheres and colleagues found that the ADHD-C group had a much smaller AUC, indicating a greater preference for the smaller, immediate reward. These findings contrast with those of the present study (AUC means: Controls 47, ADHD-I 46, ADHD-C 55) where the three groups did not differ significantly, indicating that the ADHD groups did not demonstrate a preference for the smaller, immediate reward, as we had expected. If we compare the scores, it seems that the ADHD groups, and particularly the ADHD-C group in the present study, were again performing more like the control group from the Scheres et al. study. Another study by Scheres (2006) used a slightly different Temporal Discounting Task where the longest delay was 30s, versus 60s in the present study, and that study also did not find a significant group difference on AUC, but it is difficult to make a comparison here because a different task was used.

Group Assignment Validity

We categorized participants and measured inattention and hyperactivity/impulsivity based on parent report, which might be a weakness of this study. For an ADHD diagnosis to be accurate, it is important to be sure that the

behaviors are present in at least two environments (e.g., home and school). Thus, we sent out questionnaire packets to teachers of each participant in the study and made every effort to get the packets back so we would have information about how the participants behave in school. The research team followed up with teachers by phoning them and explaining the importance of receiving the packets back every couple of months until we finished collecting data and began analyzing it. In many cases, we asked participants if an alternative teacher would be able to fill out the packets when we did not hear back from the original teacher, but another teacher was often not suitable because it is important that the information come from a teacher who knows the participant well and was working with them at the time we did their testing. Even when we were given an alternative teacher to contact, we often did not receive the packet back from the new teacher. Unfortunately, despite our efforts, we only received 49% of the packets back from the teachers. This was not entirely unexpected, as it has proven difficult, in the past, to receive teacher packets back from participants in middle school and high school. Nonetheless, it made it harder to assess whether participants were also acting out in school and if anyone other than the participants' parents noticed or were bothered by the symptoms.

In an attempt to do that, we compared the results from the teacher questionnaires with the results from the parent questionnaires, but it is important to keep in mind the low number of teacher packets when considering this comparison. There was a significant difference based on group assignment (i.e., ADHD-C, ADHD-I, control) on all of the

ADHD scales on parent questionnaires, but we found a significant difference based on group assignment on only one scale (DBD inattention) on the teacher questionnaires. See Table 3 for details. This raises the question of whether the ADHD group was not as symptomatic as their parents' reports indicate. If the teacher reports are accurate, it is possible that we did not find some of the results we expected to find because the ADHD lacks a certain level of symptom pervasiveness. This is consistent with the conclusion that the ADHD groups appeared to be performing more like controls in other studies on the SSRT and AUC variables. Nonetheless, no firm conclusions can be drawn based on the teacher packets because we had so few of them. In the future, we recommend researchers offer teachers compensation in exchange for the packets to ensure they receive a higher number back.

Another way to validate the categorization of participants is to look at how many have had a previous diagnosis of ADHD from a clinician in the community. Eight out of 25 participants in the ADHD-I group had a previous ADHD diagnosis and 8 out of 17 participants in the ADHD-C group had a previous diagnosis. Five participants in the ADHD-I group and 4 participants in the ADHD-C group had never seen a mental health professional or been evaluated for ADHD before participating in this study. Twelve people in the ADHD-I group and 4 people in the ADHD-C group had seen a mental health professional in the past, but never received a diagnosis. Unfortunately, it was still unclear how many of these remaining participants should have received a formal ADHD diagnosis. In many cases, they received counseling for something unrelated, such as a

divorce or trauma and their ADHD symptoms might not have received attention because they were not the focus of treatment. Furthermore, they might have seen a counselor who is not qualified to make an ADHD diagnosis. Thus, it is hard to infer if these individuals would have received a diagnosis had they been appropriately evaluated. In conclusion, the severity or pervasiveness of the ADHD symptoms might be somewhat questionable for some individuals in the ADHD group and it is possible that some of them had relatively mild or situation specific symptoms that occurred only at home.

Conclusions and Recommendations for Future Research

The present study findings indicate a positive correlation between hyperactivity/impulsivity (more hyperactivity/impulsivity is associated with greater reaction time variability), a positive correlation between hyperactivity/impulsivity and updating of WM, and a negative correlation between inattention and updating of WM. In general, the findings were not consistent with the Frank et al. (2007a) model, as that would have predicted an association between RT variability and inattention, rather than hyperactivity/impulsivity. It also would have predicted a negative correlation between hyperactivity/impulsivity and updating of WM, and that the ADHD-C group would perform worst on updating of WM while the ADHD-C group did not have a specific updating of WM memory problem according to the present results, and instead, the ADHD-I performed most poorly on updating of WM. Thus, we have found some group differences on these tasks, but they were not the differences we expected. The present

findings do not support the Frank et al. (2007a) brain model but more research is needed to determine whether the present study is replicable or if, indeed, there is some accuracy to the theoretical brain models.

Our predictions were based primarily on the Frank et al. (2007a) model, however, as mentioned above, the links between specific neurotransmitters and symptom domains have been inconsistent. It also appears that the roles of NE and DA in these computer tasks might not be as mutually exclusive as we once expected. Further, the method the present study used to learn about neurotransmitter function is rather indirect so it is hard to tell how much the present results are truly inconsistent with the expectations and how much it might be due to due to incorrect inferences about the expected links between the neurotransmitters and symptom domains. Thus, we suggest that future research assess these questions using a more direct method such as medication studies.

Another reason we might not have found the results we expected, mainly in reference to the lack of findings for the SSRT, AUC and accuracy on A vs. B pairs variables, is that we seem to have a slightly unusual sample in some ways. To the extent it was possible to make direct comparisons with other studies, the present sample appears to have a lower number of ADHD participants who were taking stimulant medication and a lower number of comorbid ODD and CD. It is possible that the lower rate of ODD and CD in the present sample could indicate a more pure ADHD sample, suggesting that some of the differences found in other studies could be due to the presence of ODD and CD, rather than being directly linked to ADHD. This is, however, speculation and would

need to be tested in future studies by comparing samples with and without comorbid ODD and CD, although this would preclude random assignment to groups, which would bring up another study concern. Alternatively, future studies could run all of their analyses once including the ODD and CD participants and once excluding them to see if this affects the results. This could be a useful approach but would require a relatively large sample size.

It is also possible that some of the ADHD group participants lack the symptom pervasiveness necessary for a formal diagnosis. Based on the fact that the teacher reports did not show significant differences among groups in ADHD symptoms and the fact that the ADHD groups appeared to be performing more like the control group in other studies on the SSRT and AUC variable, it is possible that some of the participants were misclassified and that their symptoms were overestimated based on their parents' reports. It is impossible to know if this is accurate without the rest of the teacher reports so it is very important for future researchers to obtain a significantly higher number of teacher reports. If possible, it is recommended that future studies offer teachers compensation for completing these reports and returning them to the researchers.

APPENDIX A: TABLES FOR DEPENDENT VARIABALES AND POTENTIAL CONFOUNDS

Table 1

Univariate Correlation Table for Dependent Variables and Potential Confounds in categorical analyses

		ODD	Age	IQ	AD	Accuracy A vs. B	RT variability	SSRT	AUC	WM
ODD	R N	1.00 58	-	-	-	-	-	-	-	-
Age	r N	.02 58	1.00 58	-	-	-	-	-	-	-
IQ	r N	.03 58	-.06 58	1.00 58	-	-	-	-	-	-
AD	r N	.03 58	.02 58	-.11 58	1.00 58	-	-	-		-
Accuracy A vs. B	r N	.24 57	.62 57	-.15 57	-.22 57	1.00 57	-	-	-	-
RT variability	r N	-.12 57	- .28* 57	-.21 57	.11 57	.02 56	1.00 57	-	-	-
SSRT	r N	.02 57	-.06 57	.26* 57	.12 57	.01 56	2.5 56	1.00 57	-	-
AUC	r N	.04 58	-.05 58	.11 58	.05 58	.06 57	-.08 57	.10 57	1.00 58	-
WM	r N	.05 58	.19 58	.37** 58	.13 58	-.08 57	.19 57	.24 57	.08 58	1.00 58

Note: ODD, Oppositional Defiant Disorder; AD, Academic Achievement Deficit; IQ, estimated IQ based on the Weschler Abbreviated Scale of Intelligence; Accuracy A/B pairs, Accuracy on A pairs minus accuracy on B pairs from PL task; RT variability, Reaction time variability; SSRT, Stop Signal Reaction Time in milliseconds, neutral

condition; AUC, Area under the discounting curve from Temporal Discounting Task; WM, Updating of Working Memory: (distracter, delay + distracter, no delay)/2 – (no distracter, delay + no distracter, no delay)/2.

Pearson Correlation Sig. = .05 (2-tailed).
* $p < .05$. ** $p < .01$.

Table 2

Univariate Correlation Table for Dependent Variables and Potential Confounds in dimensional analyses

		ODD[a]	Age	IQ[b]	AD[c]	Accuracy A vs. B[d]	RT variability	SSRT[e]	AUC[f]	WM[g]
ODD[a]	R N	1.00 69								
Age	r N	.04 69	1.00 70	-	-	-	-	-	-	-
IQ[b]	r N	.03 69	.07 69	1.00 69	-	-	-	-	-	-
AD[c]	R N	.02 69	-.07 69	-.04 69	-	-	-	-	-	-
Accuracy A vs. B[d]	r N	.19 68	-.03 68	-.06 68	-.19 68	.1.00 69	-	-	-	-
RT variability	r N	-.10 68	- .29* 68	-.18 68	.08 68	.17 69	1.00 69	-	-	-
SSRT[e]	r N	.05 68	-.02 68	.11 68	.04 68	.07 69	.23 69	1.00 69	-	-
AUC[f]	r N	-.02 69	-.03 70	.03 69	.04 68	-.07 69	-.11 69	.11 69	1.00 69	-
WM[g]	r N	.10 69	.22 69	.37** 69	.14 69	-.05 69	.15 69	.16 69	.06 69	1.00 69

Note: ODD, Oppositional Defiant Disorder; AD, Academic Achievement Deficit; IQ, estimated IQ based on the Weschler Abbreviated Scale of Intelligence; Accuracy A/B pairs, Accuracy on A pairs minus accuracy on B pairs from PL task; RT variability, Reaction time variability; SSRT, Stop Signal Reaction Time in milliseconds, neutral condition; AUC, Area under the discounting curve from Temporal Discounting Task; WM, Updating of Working Memory: (distracter, delay + distracter, no delay)/2 – (no distracter, delay + no distracter, no delay)/2.

Pearson Correlation Sig. = .05 (2-tailed).
* $p < .05$. ** $p < .01$.

REFERENCES

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for ASEBA School-Age Forms & Profiles*.

Alloway, T., Elliot, J., Place, M. (2010). Investigating the relationship between attention and working memory in clinical and community samples. *Child Neuropsychology, 16,* 242-254.

American Psychiatric Association (2000). Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision). Washington DC: Author.

Aston-Jones G. 2004. Locus coeruleus, A5 and A7 noradrenergic cell groups. In: Paxinos G, editor. The rat nervous system, 3rd ed. San Diego: Elsevier Academic Press. p. 259–294.

Aston-Jones, G, Cohen, J (2005). Adaptive Gain and the Role of the Locus Coeruleus–Norepinephrine System in Optimal Performance. *The Journal of Comparative Neurology, 493*, 99–110

Barkley R. A., DuPaul G. J., McMurray M.B. (1990). Comprehensive evaluation of attention deficit disorder with and without hyperactivity as defined by research criteria. *Journal of Consulting and Clinical Psychology, 58*, 775-89.

Bedard, A., Martinussen, R., Ickowicz, A., Tannock, R. (2004). Methylphenidate improves visual-spatial **memory** in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 43*, 260-268.

Barch DM, Braver TS, Nystom LE, Forman SD, Noll DC, Cohen JD (1997). Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia*, *35*, 1373–1380.

Barch DM, Carter CS, Braver TS, Ans Sabb FW, MacDonald AR, Noll DC *et al* (2001). Selective deficits in prefrontal cortex function in medication-naive patients with schizophrenia. *Arch Gen Psychiatry*, *58*, 280–288.

Barkley, R., DuPaul, G. & McMurray, M. (1991). Attention deficit disorder with and without hyperactivity: Clinical response to three dose levels of methylphenidate. *Pediatrics, 87*, 4 519-523.

Bitsakou, P., Psychogiou, L., Thompson, M., Sonuga-Barke, E. (2009). Delay Aversion in Attention Deficit/Hyperactivity Disorder: An empirical investigation of the broader phenotype.

Neuropsychologia, 4, 446-456.

Bitsakou, P., Psychogiou, L., Thompson, M., Sonuga-Barke, E. J. S. (2008). Inhibitory deficits in attention-deficit/hyperactivity disorder are independent of basic processing efficiency and IQ. *Journal of Neural Transmition, 115,* 261 – 268.

Bloom, B., Cohen, R.A., Freeman, G. (2011). Summary health statistics for U.S. children: national health interview survey, 2010. *Vital Health Stat 10*, 1 – 80.

Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Castellanos FX, Tannock R (2002) Neuroscience of attention deficit/hyperactivity disorder: the search for endophenotypes*. National Review of Neuroscience, 3*: 617–628.

Carver, C, White, T (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology*, 67, 319-333.

Chamberlain SR, Muller U, Blackwell AD, Clark L, Robbins TW, Sahakian BJ (2006). Neurochemical Modulation of Response Inhibition and Probabilistic Learning in Humans. *Science, 311,* 861–863.

Cockcroft, K. (2011). Working memory functioning in children with attention-deficit/hyperactivity disorder ADHD): A comparison between subtypes and normal controls. *Journal of Child and Adolescent Mental Health, 23*, 107-118.

Conners, K, Sitarenios, G, Parker, J, Epstein, J (1998a). The Revised Conners' Parent Rating Scale (CPRS-R): Factor Structure, Reliability, and Criterion Validity. *Journal of Abnormal Child Psychology, 26*, 4, 257-268.

Conners, K, Sitarenios, G, Parker, J, Epstein, J (1998b). Revision and restandardization of the conner's teacher rating scale (CTRS-R): Factor structure, reliability, and criterion validity. Journal *of Abnormal Child Psychology, 26*, 4, 279-291.

Conners, K, Wells, K, Parker, J, Sitarenios, G, Diamond, J, Powell, J (1997). A new self-report scale for assessment of adolescent psychopathology: Factor structure, reliability, validity, and diagnostic sensitivity. *Journal of Abnormal Child Psychology, 6*, 487-497.

Cummins, T. D., Hawi, Z., Hocking, J., Strudwick, M., Hester, R., Garavan, H., Wagner, J., Chambers, C. D., Bellgrove, M. A. (2011). Dopamine transporter genotype predicts behavioural and neural measures of response inhibition. *Molecular Psychiatry, 1038*, 104.

Di Trani, M., Casini, M., Capuzzo, F., Gentile, S., Bianco, G., Menghini, D., Vicari, S. (2011). Executive and intellectual functions in attention-deficit/hyperactivity disorder with and without comorbidity. *Brain & Development, 33,* 462-469.

Diamond A (2005). Attention-deficit disorder (attention-deficit/hyperactivity disorder without hyperactivity): a neurobiologically and behaviorally distinct disorder from attention-deficit/hyperactivity disorder (with hyperactivity). *Developmental Psychopathology, 17*, 807–825.

Faraone, SV, Biederman, J, Spencer, T, Michelson, D, Adler, L, Reimer, F, Seidman, L (2005). Atomoxetine and stroop task performance in adult attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology, 15*, 664-670.

Field, A. P., Discovering statistics using SPSS: and sex and drugs and rock 'n' rolee (3rd Edition). Londong: Sage.

Frank, M.J., Santamaria, A., O'Reilly, R. & Willcutt, E. (2007a). Testing computational models of dopamine and noradrenalin dysfunction in Attention Deficit/Hyperactivity Disorder. *Neuropsychopharmacology, 32,* 1583-99. (Frank et al., 2007a)

Frank, M.J., Scheres, A. & Sherman, S.J. (2007b). Understanding decision making deficits in neurological conditions: Insights from models of natural action selection. *Philosophical Transactions of the Royal Society - B, 362,* 1641-1654. (Frank et al., 2007b)

Frank, MJ, Seeberger, L & o'Reilly, RC (2004). By carrot or by stick: Cognitive reinforcement learning in Parkinsonism. *Science, 306*, 1940 – 1943.

Groth-Marnat, G. (1997). *Handbook of psychological assess- ment* (3rd ed.). New York: John Wiley & Sons.

Huang-Pollack, C, Mikami, A, Pfiffner, L, McBurnett, K (2007). ADHD subtype difference in motivational responsivity but not inhibitory control: Evidence from a reward-based variation of the stop signal paradigm. *Journal of Clinical Child and Adolescent Psychology, 36*, 2, 127-136.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. (2006). Schedule for Affective Disorders and Schizophrenia for School-Aged Children - Present and Lifetime (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry, 36*, 980-988.

Kaufman J, Birmaher B, Brent D, Rao U, Ryan N. Kiddie SADS - Present and Lifetime Version (K-SADS-PL) [unpublished instrument]. Pittsburgh, Penn: University of Pittsburgh School of Medicine, Western Psychiatric Institute and Clinics; 1996.

Kelly, A.M.C., Scheres, A., Sonuga-Barke, E.S.J., & Castellanos, F.X. (2007). Functional neuroimaging of reward and motivational pathways in ADHD. In M. Bellgrove (Ed.), Handbook of ADHD (pp. 209-235). New Jersey: Wiley.

Kratz, O. Studer, P., Baack, J., Malcherek, S., Erbe, K., Moll, G. H., Heinrich, H. (2012). Differential effects of methylphenidate and atomoxetine on attentional processes in children with ADHD: An event-related potential study using the Attention Network Test. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 37*, 81-89.

Langleben, DD, Monteroso, J, Elman, I, Ash, B, Krikorian, G, Austin, G (2006). Effect of methylphenidate on Stroop Color-Word task performance in children with attention deficit hyperactivity disorder. *Psychiatry Research, 141,* 315-320.

Llorente AM, Voigt RG, Jensen CL, Berretta MC, Fraley JK, Heird WC (2006). Performance on a visual sustained attention and discrimination task is associated with urinary excretion of norepineprhine metabolite in children with attention-deficit/ hyperactivity disorder (AD/HD). *Clinical Neuropsychology, 20,* 133–144.

Logan, GD (1994). On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In D. Dagenbach & T. H. Carr (Eds.), *Inhibitory processes in attention, memory, and language* (pp. 189-239). San Diego: Academic Press.

Logan, GD, & Cowan, WB (1984). On the ability to inhibit thought and action: A theory of an act of control. *Psychological Review, 91*, 295-327.

Luman, M., Oosterlaan, J., Sergeant, J. (2004). The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. Clinical Psychology Review, 25, 183 – 213.

Madras, BK, Miller, GM, Fischman, AJ (2005). The dopamine transporter and attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57,* 1397-1409.

Martinussen, R & Tannock, R (2006). Working memory impairmens in children with attention-deficit hyperactivity disorder with and without comorbid language learning disorders. *Journal of Clinical and Experimental Neuropsychology, 28*, 1073 – 1094.

Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR (2001). Atomoxetine in the treatment of children and adolescents with attention-

deficit/hyperactivity disorder: a randomized, placebo-controlled, dose–response study. *Pediatrics 108*, E83.

Mick, E, Faraone, S (2008). Genetics of attention deficit hyperactivity disorder. *Child and Adolescent Psychiatric Clinics of North America, 17*, 261-284.

Miller, G. A, Chapman, J. P. (2001). *Misunderstanding Analysis of covariance. Journal of Abnormal Psychology, 110*, 40 -48.

MTA cooperative group (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. The MTA Cooperative Group. Multimodal Treatment Study of Children with ADHD. *Archives of General Psychiatry and Adolescent Psychiatry, 44*, 240-248.

Nandam, L. S, Hester R., Wagner, J., Cummins, T. D., Garner, K., Dean, A.J., Kim B. N., Nathan, P. J., Mattingley, J. B., Bellgrove M. A. (2011). Methylphenidate but not atomoxetine or citalopram modulates inhibitory control and response time variability. *Biological Psychiatry, 69*, 902-904.

Newcorn, J, Kratochvil, C, Allen, A, Casat, C, Ruff, D, Moore, R, Michelson, D (2008). Atomoxetine and Osmotically Released Methylphenidate for the Treatment of Attention Deficit Hyperactivity Disorder: Acute Comparison and Differential Response. *American Journal of Psychiatry, 165*, 721-730.

Ollendick, T. H., Jarrett, M. A., Grills-Taquechel, A. E., Hovey, L. D., Wolff J. C. (2008). Comorbidity as a predictor and moderator of treatment outcome in yourht with anxiety, affective, attention deficit/hyperactivity disorder, and oppositional/conduct disorders. *Clinical Psychology Review, 28*, 1447-1471.

Overtoom CC, Verbaten MN, Kenemans JL, van Engeland H, Buitelaar JK, & van der Molen MW (2003). Effects of methylphenidate, desipramine, and L-dopa on attention and inhibition in children with attention deficit hyperactivity disorder. *Behavior and Brain Reserve*, 145, 7–15.

Pelham, W. E., Gnagy, E. M., Greenslade, K. E., & Milich, R. (1992). Teacher ratings of DSM-IIIR symptoms for the disruptive behavior disorders. *Journal of American Academy of Child and Adolescent Psychiatry, 31*, 210-218.

Gupta, R., Kar, B. Srinivasan, N. (2011). Cognitive-motivational deficits in ADHD: Development of a classification system. *Child Neuropsychology, 17*, 67-81.

Rogers, M., Hwang, H., Toplak, M., Weiss, M., Tannock, R. (2011). Inattention,

working memory, and academic achievement in adolescents referred for attention deficit/hyperactivity disorder (ADHD). *Child Neuropsychology, 17*, 444-458.

Rubia, K, Noorloos, J, Smith, A, Gunning, B, Sergeant, J (2003). Motor timing deficits in community and clinical boys with hyperactive behavior: the effect of methylphenidate on motor timing. *Journal of Abnormal Child Psychology, 31,* 301-313.

Sagvolden, T, Johansen, E. B., Aase, H & Russel, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences, 28*, 397-468.

Scheres, A., Dijkstra, M., Ainslie, E., Balkan, J., Reynolds, B., Sonuga-Barke, E., & Castellanos, F. X. (2006). Temporal and probabilistic discounting of rewards in children and adolescents: Effects of age and ADHD symptoms. *Neuropsychologia, 44(11),* 2092-2103.

Scheres, A., Milham, M. P., Knutson, B., Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward prediction in Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry, 61(5),* 720-724.

Scheres, A, Oosterlaan, J, Geurts, H, Morein-Zamir, S Meiran, N, Schut, H, Vlasbeld, L & Sergeant, JA (2004). Executive functioning in boys with ADHD: primarily an inhibition deficit? *Archives of Clinical Neuropsychology, 19*, 569-594.

Scheres, A, Oosterlaan, J, Swanson, J, Morein-Zamir, S Meiran, N, Schut, H, Vlasbeld, L & Sergeant, JA (2003). The effect of methylphenidate on three forms of response inhibition in boys with AD/HD. *Journal of Abnormal Child Psychology, 31*, 105-120.

Scheres, A., Tontsch, C., Thoeny, A.L., & Kaczkurkin, A. (2010). Temporal Reward Discounting in Attention-Deficit/Hyperactivity Disorder: The Contribution of Symptom Domains, Reward Magnitude, and Session Length. *Biological Psychiatry, 67*, 641 – 648.

Schweitzer, J., Hanford, R., Medoff, D. (2006). Working memory deficits in adults with ADHD: Is there evidence for subtype differences? *Behavioral and Brain Functions, 2*, ArtID 43.

Seidman, L (1998). Effectiveness and tolerability of Atomoxetine in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 155,* 693-695.

Sengupta, S. M., Grizenko, N., Thakur, G. A., Bellingham, J., DeGuzman, R., Robinson, S., TerStepanian, M., Poloskia, A., Shaheen, S. M., Fortier, M., Choudhry, Z., Joober, R.

(2012). Differential association between the norepinephrine transporter gene and ADHD: Role of sex and subtype. *Journal of Psychiatry & Neuroscience, 37*, 129-137.

Servan-Schreiber D, Cohen JD, Steingard S (1997). Schizophrenic deficits in the processing of context: A test of a theoretical model. *Arch Gen Psychiatry, 53*, 1105–1113

Shang, C., Gau, S., Liu, C., Hwu, H. (2011). Association between the dopamine transporter gene and the inattentive subtype of attention deficit **hyperactivity** disorder in Taiwan. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 35*(2), 421-428.

Solanto, MV (2002). Dopamine dysfunction in AD/HD: integrating clinical and basic neuroscience research. *Behavioral Brain Research, 130*, 655-71.

Sonuga-Barke, EJS, Taylor, E, Sembi, S & Smith, J (1992). Hyperactivity and delay aversion – I. the effect of delay on choice. *Journal of Child Psychology and Psychiatry, 33*, 387-398.

Spencer, T, Biederman, J, Wilens, T, Prince, J, Hatch, M Jones, J, Harding, M, Farone, SV, Dougherty, D, Bonab, A, Fischman, A (2005). In vivo neuroreceptor imaging in attention-deficit/hyperactivity disorder: A focus on the dopamine transporter. *Biological Psychiatry, 57*, 1293, 1300.

Steinhausen, H.C. (2009). The heterogeneity of causes and courses of attention-deficit/hyperactivity disorder. *Acta Psychiatrica Scandanavia, 120*, 392 – 399.

Swanson CJ, Perry KW, Koch-Krueger S, Katner J, Svensson KA, Bymaster FP (2006). Effect of the attention deficit/hyperactivity disorder drug atomoxetine on extracellular concentrations of norepinephrine and dopamine in several brain regions of the rat. *Neuropharmacology, 50*, 755–760.

Tannock, R, Schachar, R, Logan, G (1995). Methylphenidate and cognitive flexibility: Dissociated dose effects in hyperactive children. *Journal of Abnormal Child Psychology, 23*, 235-266.

Westerberg, H, Hirvikoski, T, Forssberg, H & Klingberg, T (2004). Visuospacial working memory span: a sensitive measure of cognitive deficits I children with ADHD. *Child Neuropsychology, 10*, 155-161.

Willcutt, E.G., Pennington, B.F., Olson, R.K., Chhabildas, N., & Hulslander, J. (2005). Neuropsychological analysis of comorbidity between reading disability and attention-

deficit hyperactivity disorder: In search of the common deficit. *Developmental Neuropsychology*, *27*, 1, 35–71.

Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biological Psychiatry, 57,* 1336 - 46.

Williams, B. R. Ponesse, J. S. Schachar, R., J., Logan, G., D.,Tannock, R. (1999). Development of inhibitory control across the life span. *Developmental Psychology, 35*, 205-213.