DOPAMINERGIC FUNCTION IN ADHD IN RELATION TO SYMPTOMATOLOGY, NEUROCOGNITION AND CORTICAL STRUCTURE

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Submitted December 15, 2011

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Doctor of Philosophy

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To my grandfather E. P. Krupnik who introduced me to psychology.

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ACKNOWLEDGMENTS AND FUNDING

I would like to thank the people whose contributions, help and support made this work and thesis possible. First and foremost, I would like to thank my advisor Dr. Gillian O'Driscoll for guiding me through my graduate studies, teaching me so much about research, and giving me exceptionally thorough and careful feedback on my work.

I also sincerely thank Dr. Chawki Benkelfat and Dr. Marco Leyton for giving me the opportunity to carry out my research on their research team, for making me feel welcome and part of the team, for being supportive of my work, for their ideas and feedback regarding the data and the dissertation, and for giving me opportunities to present the data.

I would like to thank Dr. Nazlie Faridi, who started this research as part of her MSc, for the work she has done on the project and for sharing her knowledge, experience and ideas with me. Many thanks to the two research assistants, Jennifer Palmer and Andrea Perna, whose hard work on this research was so critical to its completion. I would also like to thank Dr. Lily Hechtman and Dr. Ridha Joober for their help with recruitment and assessment of research participants, and to thank Dr. Ridha Joober for his help with genotyping and the interpretation of the genetic data. I also very much appreciate Dr. Alain Dagher's input on the imaging data.

I am tremendously grateful to the colleagues who helped me with my imaging data analyses: Kevin F. Casey, Kevin Larcher, Krzysztof Welfeld, Boris Bernhardt, Paul Gravel, Elaine Setiawan, and Dr. Sylvia Cox. I cannot overstate the contribution of their knowledge, experience, ideas, and discussion. I thank the technicians at the PET unit and the cyclotron for more than 60 successful scans and the research nurse, Kathleen Auclaire, for blood draws, vitals, and being so accommodating with her schedule. I also thank Dr. Glenn Baker for plasma amphetamine analyses. And I especially thank my research participants, without whom this work would not have been possible!

A very special thanks goes to my friends and family who supported and encouraged me through this lengthy process! I thank Lana and Ava for the fun times at the lab and for so often boosting my morale. I thank my friends, in particular, Alek, Irene, Joannie, Stéphanie, Katherine, and Nico for their friendship and support. I thank my parents, my grandparents, and Lena for being patiently encouraging and unconditionally supportive throughout! In particular, I thank my dad for research discussions and for being so helpful every step of the way. Last but not least, a big thanks to Dave for gentle encouragement, understanding, being there for me in difficult times!

Funding

The research presented in this dissertation was supported by an operating grant from the Canadian Institutes of Health Research awarded to Drs. Chawki Benkelfat and Marco Leyton, and by a William Dawson Scholarship awarded to Dr. Gillian O'Driscoll

I was fortunate to have been sponsored by the Richard H. Tomlinson Doctoral Fellowship, the Lloyd Carr-Harris McGill Major Fellowship, and a Graduate Student Fellowship awarded by McGill University.

CONTRIBUTIONS

In accordance with McGill University's requirement, an explicit statement of contributions to this dissertation is provided below.

The research reported here was initiated by Dr. Nazlie Faridi before I became involved. Dr. Faridi participated in study design, obtained ethics approval for the protocol and collected data from the initial nine participants in the sample; four additional participants were tested by my colleague Mr. Kevin Casey. When I took over this research, I revised the protocol, particularly the neurocognitive component, and recruited and tested the remaining participants. I also obtained some additional data from the previously tested participants as per my protocol revision. I processed, analyzed and interpreted all the data, reviewed the literature, wrote the first draft of the dissertation, and made subsequent revisions based on feedback. Dr. Benekelfat and Dr. Leyton were involved in every aspect of study design and data interpretation, as well as provided feedback on the dissertation. Dr. O'Driscoll was involved in design of the neurocognitive battery, data analysis and interpretation, and in dissertation revision. Mr. Kevin Casey and Mr. Kevin Larcher contributed to the neuroimaging data analysis. Dr. Lily Hechtman's clinic and Dr. Ridha Joober helped with clinical assessment of ADHD participants. Dr. Ridha Joober's laboratory performed the genotyping, and Dr. Glen Baker's laboratory determined plasma amphetamine levels during scans. Ms. Jennifer Palmer and Ms. Andrea Perna assisted with participant recruitment and screening, participant testing, and behavioral data preprocessing.

ORIGINAL SCHOLARSHIP AND CONTRIBUTION TO KNOWLEDGE

The research in this dissertation makes a unique contribution to our understanding of dopaminergic function in ADHD in relation to symptomatology, neurocognition, and cortical structure. Although converging evidence had implicated the dopamine system in the pathophysiology of ADHD, direct *in vivo* evidence pertaining to dopaminergic alterations in ADHD has been inconclusive. This is the first *in vivo* investigation to demonstrate an augmented amphetamine-induced striatal dopamine response in treatment-naïve adults with ADHD relative to healthy Controls.

This research also makes a unique contribution to the literature by showing a quadratic association between the reactivity of the dopamine system to the amphetamine challenge and symptoms of hyperactivity. A linear association was found between dopamine responsivity and a measure of motor impulsivity – anticipatory saccades on the antisaccade task -- suggesting that dopaminergic transmission may be differentially related to different behavioral characteristics of ADHD. Finally, this research is the first to examine the relationship between dopamine neurotransmission and frontal cortical structure in ADHD. Our investigation shows that: 1) thickness of certain frontal cortical regions is related to striatal dopaminergic transmission and 2) the nature of this relationship is different in adults with ADHD versus healthy Controls.

ABSTRACT

Converging evidence suggests a dysfunction in dopamine (DA) neurotransmission in attention deficit/hyperactivity disorder (ADHD). For example, DA genes are implicated in the etiology of ADHD, and DA augmenting agents, such as methylphenidate (MPH) and dextroamphetamine (*d*-AMPH) produce significant symptom improvement. In this dissertation, I examined the response of striatal DA to a *d*-AMPH challenge in treatment-naïve adults with ADHD and control participants, using positron emission tomography (PET) and the radioligand [^{11}C]raclopride. I also examined the relationship between DA response and symptomatology, neurocognitive function, and neuroanatomy.

The ADHD group showed greater *d*-AMPH induced striatal DA responses than controls. A quadratic U-shaped relationship was observed between the *d*-AMPH induced DA responses and self-reported hyperactivity across both groups, with the largest DA response in individuals reporting moderate levels of activity and smaller responses in both non-hyperactive and highly hyperactive individuals. Compared to Controls, ADHD participants performed more poorly on tests of response inhibition, showing longer inhibitory reaction times on the stop signal reaction time task, a higher error rate on the antisaccade task, and a higher error rate on a version of the go/ no-go task. Inhibitory performance on one measure of the antisaccade task, anticipatory saccades, was linearly related to DA release. Frontal cortical thickness did not differ significantly between ADHD and control participants. Cortical thickness was linearly related to striatal DA response but the direction of the association was opposite in the two groups. In the control group, thicker cortex was associated with smaller *d*-AMPH-induced DA increases while in the ADHD group thicker cortex was associated with larger *d*-AMPH-induced DA increases.

The findings are consistent with a model of ADHD proposing abnormally low striatal DA tone coupled with an exaggerated phasic DA release (Grace, 2001). The greater *d*-AMPH induced increases in extracellular DA in the ADHD group likely reflect the exaggerated phasic component. Stimulant medications might acutely increase DA

tone and diminish phasic reactivity. Since the most severely hyperactive patients had lower DA responses, the quadratic association may reflect a more rapid increase in DA tone accompanied by a down-modulation of phasic reactivity, effects that would be consistent with reports of the greatest clinical response to stimulants in the most symptomatic patients (Robbins & Sahakian, 1979; Buitelaar et al, 1995). The performance on neuropsychological tests is consistent with previous reports (Nigg, 2005) suggesting an important neurocognitive deficit in the area of inhibitory function. The divergent associations of frontal cortical thickness and *d*-AMPH induced DA release in the two groups may reflect differences in cortical developmental trajectories in Controls and ADHD participants (Shaw et al. 2007) or differences in cortico-striatal connectivity between the two groups.

RÉSUMÉ

Plusieurs données semblent suggérer qu'un dérèglement du système dopaminergique pourrait être présent dans le trouble déficitaire d'attention avec hyperactivité (TDAH). Par exemple, les gènes liés au système dopaminergique sont impliqués dans l'étiologie du TDAH et des agents qui augmentent la neurotransmission dopaminergique, tels que le méthylphénidate (MPH) et la dextroamphétamine (*d*-AMPH), améliorent les symptômes du trouble. Dans la présente thèse, j'ai examiné la réactivité du système dopaminergique à une dose de *d*-AMPH chez des adultes présentant un TDAH et n'ayant jamais reçu de traitement comparé à un groupe témoin. J'ai également examiné la relation entre la réactivité du système dopaminergique et la symptomatologie, la fonction neurocognitive et la neuroanatomie.

Le groupe TDAH a montré une plus grande augmentation de la réactivité du système de neurotransmission dopaminergique que le groupe témoin après une dose de *d*-AMPH. Une relation quadratique a pu être observée entre les réponses dopaminergiques induites par *d*-AMPH et les symptômes d'hyperactivité auto-rapportés dans les deux groupes. Les sujets déclarant des niveaux modérés d'activité avaient la plus grande réponse dopaminergique, tandis que les sujets non hyperactifs et les sujets très hyperactifs avaient la réponse moins prononcée. Les participants présentant un TDAH ont obtenu des performances moindres que ceux du groupe témoin dans les taches d'inhibition d'une réponse motrice, y compris la tâche de "signal-arret" (stop-signal), la tâche « antisaccade », et la tâche «go/ no-go». Il y avait une relation linéaire entre un aspect de la performance au niveau de l'inhibition – saccades anticipatifs – et la réactivité dopaminergique à d-AMPH. L'épaisseur du cortex frontal ne différait pas significativement entre les participants TDAH et le groupe témoin. Il y avait une relation linéaire entre l'épaisseur du cortex frontal et la réactivité du système dopaminergique, mais la direction de cette association était opposée dans les deux groupes. Dans le groupe témoin, une plus grande épaisseur du cortex frontal était associée à une réponse dopaminergique moins prononcée, tandis que dans le groupe TDAH, une plus grande épaisseur du cortex frontal était associée à une réponse dopaminergique plus prononcée.

Les résultats sont cohérents avec le modèle proposant que le tonus dopaminergique dans le striatum soit diminué et que la libération phasique de la dopamine soit amplifiée chez les individus présentant un TDAH (Grace, 2001). L'administration aiguë des médicaments stimulants pourrait augmenter le tonus dopaminergique et diminuer la libération phasique de la dopamine. Étant donné que les patients les plus hyperactifs avaient la réponse dopaminergique moins prononcée à *d*-AMPH, la relation quadratique peut refléter une amplification plus rapide du tonus dopaminergique accompagnée par une diminution de réactivité phasique du système. Ces effets sont concordants avec les études ayant démontré une meilleure réponse clinique aux stimulants chez des patients les plus symptomatiques (Robbins & Sahakian, 1979; Buitelaar *et al*, 1995). De plus, les résultats des tests neuropsychologiques sont compatibles avec les études précédentes (Nigg, 2005), suggérant un déficit neurocognitif important au niveau de l'inhibition. Le fait que l'association entre l'épaisseur du cortex frontal et la réactivité du système dopaminergique soit inverse dans les deux groupes pourrait indiquer des différences dans les trajectoires de développement cortical chez les participants présentant un TDAH comparé aux participants témoins ou des différences dans la connectivité cortico-striatale entre les deux groupes.

PREFACE

Attention Deficit Hyperactivity Disorder (ADHD) is a common childhood psychiatric disorder that often persists into adolescence and adulthood (Cherkasova, Ponde, & Hechtman, In Press). It is characterized by age-inappropriate symptoms of inattention, hyperactivity and impulsivity and is believed to have both genetic and environmental causes (Faraone & Biederman, 1998). Converging evidence from both clinical and preclinical research has implicated the dopamine system in the pathophysiology of ADHD. However, the nature of the putative dopaminergic dysfunction remains poorly understood.

The present dissertation examines dopaminergic function in ADHD in relation to symptomatology, personality, neurocognitive function, cortical structure, and genotypic variation. I begin this dissertation by providing an overview of ADHD and of the dopamine system, and by reviewing the various lines of evidence suggesting dopamine system involvement in the pathophysiology of ADHD and underlying the hypotheses of the present research (Chapter 1). In Chapter 2, I describe the methodology of the present research. In Chapter 3, I present the findings of this research mainly pertaining to symptomatology, personality, neurocognitive function, striatal dopaminergic function, cortical structure, and genotypic variation (Chapter 3). I also explore the relationship between striatal dopaminergic function and symptomatology, personality, neurocognitive performance, cortical structure and genotypic variation. In Chapter 4, I interpret and discuss the findings in the in the context of the available knowledge in the field. Finally, in Chapter 5, I discuss the limitations of the present research, and suggest future directions for further investigation.

CHAPTER 1:

INTRODUCTION

1.1 Attention Deficit Hyperactivity Disorder

1.1.1. Epidemiology and Clincal Presentation

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed disorder of childhood with a worldwide prevalence of 3-10% depending on the criteria used (Burd, Klug, Coumbe, & Kerbeshian, 2003; Faraone, Sergeant, Gillberg, & Biederman, 2003; Ford, Goodman, & Meltzer, 2003). It is characterized by age-inappropriate symptoms of inattention, hyperactivity, impulsivity, and motor restlessness (APA, 1994) and is highly heritable with approximately 76% of the phenotypic variance accounted for by genetic factors (Faraone et al., 2005a). The Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) recognizes three ADHD subtypes: the predominantly inattentive subtype requires at least 6/9 inattention symptoms; the predominantly hyperactive-impulsive subtype requires 6/9 hyperactivity-impulsivity symptoms; and the combined subtype requires both the inattentive and the hyperactive-impulsive criteria to be met. The predominantly hyperactive-impulsive subtype without inattention rarely presents in clinical practice.

Although ADHD is a disorder with a childhood onset, symptoms often persist into adolescence and adulthood (Weiss, Hechtman, Milroy, & Perlman, 1985), with about 4% of the adult population meeting the DSM-IV diagnostic criteria (Faraone, Biederman, & Mick, 2006; Kessler et al., 2006; Murphy & Barkley, 1996). While symptoms of hyperactivity tend to decline with age, symptoms of inattention show greater persistence (Biederman, Mick, & Faraone, 2000; Brown & Gammon, 1995; Hart, Lahey, Loeber, Applegate, & Frick, 1995; Millstein, Wilens, Biederman, & Spencer, 1997). The

diagnosis of ADHD in childhood is associated with academic underachievement, problems with discipline, repeated grades, placement in special classes, poor social relationships, and psychiatric comorbidities (Wender, 1987). In adulthood, ADHD is associated with lower rates of professional employment, more frequent job changes and more difficulties at work, lower socioeconomic status, higher rates of separation and divorce, more traffic violations and accidents, more convictions and incarcerations, and higher rates of psychiatric comorbidity, most notably with mood, anxiety, substance use, and conduct/ antisocial personality disorders (Barkley, Murphy, & Fischer, 2008; Biederman et al., 1993; Biederman et al.; Faraone et al., 2003; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998; Murphy, Barkley, & Bush, 2002; Weiss, 1993).

1.1.2 Neuropsychological Profile and Models

Neuropsychological studies suggest that ADHD is characterized by deficits in a wide range of neurocognitive domains, including executive functions, arousal, motivation and reward processing, temporal information processing, memory, motor control, language processing, and response distribution properties (Nigg; Nigg, 2005). Meta-analyses have suggested that the most pronounced deficits lie in the domains of working memory, response inhibition, arousal, interference suppression, set shifting, and planning (Nigg, 2005), while the domain of visuospatial functions appears to be relatively intact (Huang-Pollock, Nigg, & Carr, 2005; Pennington & Ozonoff). Although the majority of these studies have been conducted in children, the available data in adults concur with the above findings (Hervey, Epstein, & Curry, 2004). The major neuropsychological models

have emphasized disturbances in 1) executive functions; 2) motivation and reward processing; 3) self-regulation; and 4) interplay between state factors (*e.g.* activation and arousal), attention, and executive functions (Barkley, 1997; Douglas, 1983; Sergeant, Oosterlaan, & Van der Meere, 1999; Sonuga-Barke, 2003).

Models emphasizing executive functions, or higher order cognitive processes that bring behavior under volitional control (Logan, 2004), are supported by an extensive literature demonstrating performance deficits in ADHD on tasks that tap executive functions such as inhibition, working memory, set shifting, and planning (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). According to recent meta-analyses, performance on tasks of inhibition and spatial working memory is associated with the largest effect sizes (d = .61 – 1.14) (Nigg, 2005). Executive function deficits are believed to result from an underlying dysfunction of the fronto-striato-thalamic circuitry, linking the prefrontal cortex and the dorsal striatum (Alexander & Crutcher, 1990). This view is supported by the resemblance of ADHD symptomatology to symptoms observed in patients with frontal lobe lesions (Chudasama & Robbins, 2006; Mattes, 1980), as well as by an extensive body of structural and functional neuroimaging literature (reviewed below).

According to the model emphasizing a disruption of reward processing mechanisms (Sagvolden & Sergeant, 1998; Sonuga-Barke, 2005), the core dysfunction in ADHD is a reduced behavioral sensitivity to future rewards and faster decline in the subjective value of rewards as they become more distant. This framework is supported by reports of hypersensitivity to delays and difficulty waiting for desired outcomes: children with ADHD prefer smaller immediate gains over larger delayed ones (Kuntsi,

Oosterlaan, & Stevenson, 2001; Neef, Bicard, & Endo, 2001; Schweitzer & Sulzer-Azaroff, 1995; Sonuga-Barke, Williams, Hall, & Saxton, 1996; Tripp & Alsop, 2001). The reward processing disturbance in ADHD is believed to result from a dysfunction of the mesolimbic dopamine system and the associated circuitry linking the ventral striatum with ventromedial prefrontal and orbitofrontal regions (Sonuga-Barke, 2005).

The model postulating self-regulation as the central deficit in ADHD (Douglas, 1983; Douglas, 1988) is based on the observation that performance on a variety of tasks (*e.g.* monitoring and reaction time, search, perceptual-motor, and memory tasks) varies in children with ADHD depending on testing conditions, such as task duration, complexity, and the amount of feedback provided (Douglas, 1988). Deficits are most likely to be found under testing conditions where heavy demands are placed on self-regulation, with little external control, support, or motivation.

The Cognitive-Energetic-Model of ADHD emphasizes overall efficiency of information processing, which is determined by the interplay among attentional processes, state or energetic factors (i.e. arousal, activation, and effort), and executive functions (Sergeant, 2005; Sergeant, Oosterlaan, & Van der Meere, 1999). The model argues that deficits at all three levels can be found in ADHD, and that some of the most widely documented executive function deficits (*e.g.* inhibitory) could at least in part be secondary to energetic factors. The model is supported by findings that children with ADHD have higher overall activity levels and altered sleep parameters (Corkum, Moldofsky, Hogg-Johnson, Humphries, & Tannock, 1999; Gruber, Sadeh, & Raviv, 2000; Porrino et al., 1983), altered evoked potential parameters related to anticipation and preparation (Dimoska, Johnstone, Barry, & Clarke, 2003; Perchet, Revol, Fourneret,

Mauguiere, & Garcia-Larrea, 2001; Pliszka, Liotti, & Woldorff, 2000), performance deficits at slow rates of stimulus presentation (van der Meere, Vreeling, & Sergeant, 1992), and reduced P300 amplitudes to cues and distracters (Banaschewski et al., 2003). All of these are suggestive of alterations in the activation/ arousal and attentional systems. In addition to the frontro-striato-thalamic circuitry underlying the executive dysfunction, the cognitive-energetic model postulates involvement of the reticular formation, the amygdala, and the hippocampus.

1.1.3 Structural Neuroanatomy

Overall, structural imaging findings support a primary dysfunction of the frontostriatal circuitry in ADHD and point to the possibility of a delay in brain maturation, especially in the frontal regions. The majority of volumetric studies have demonstrated reductions in the total cerebral volumes, total gray and white matter volumes, and intracranial volumes in children and adolescents with ADHD, particularly in the right hemisphere (Castellanos et al., 2001; Castellanos et al., 1996b; Castellanos et al., 2002; Filipek et al., 1997; Hill et al., 2003; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). Structural abnormalities in the frontal lobes have been widely documented (Seidman, Valera, & Makris, 2005), with many volumetric studies reporting prefrontal volume and cortical thickness reductions in children (Almeida et al.; Batty et al., 2010; Castellanos et al., 2001; Castellanos et al., 1996b; Castellanos et al., 2002; Durston et al., 2004; Filipek et al., 1997; Hill et al., 2003; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Kates et al., 2002; Makris et al., 2007; McAlonan et al., 2007; Monuteaux et al., 2008; Mostofsky, Cooper, Kates, Denckla, & Kaufmann,

2002; Overmeyer et al., 2001; Shaw et al., 2007a; Shaw et al., 2007b; Shaw et al., 2006b; Sowell et al., 2003b; Wang, Jiang, Cao, & Wang, 2007), as well as adults (Makris et al., 2007; Seidman et al., 2006). Furthermore, a study examining developmental trajectories of cortical thickness in children and adolescents with ADHD reported a delay in cortical maturation in ADHD, with the most prominent delay in the frontal regions (Shaw et al., 2007a). In these regions, children with ADHD attained maximal cortical thickness several years later than controls.

Reductions in volumes of the caudate and the pallidum have also been reported by several labs and large scale studies (Aylward et al., 1996; Castellanos et al., 2001; Castellanos et al., 1994b; Castellanos et al., 1996b; Castellanos et al., 2002; Castellanos et al., 2003; Filipek et al., 1997; Hynd et al., 1993; Mataro, Garcia-Sanchez, Junque, Estevez-Gonzalez, & Pujol, 1997; Overmeyer et al., 2001; Semrud-Clikeman et al., 2000; Wang et al., 2007). A number have reported a lack or a reversal of the normative left > right caudate volume asymmetry in subjects with ADHD (Castellanos et al., 1994b; Hynd et al., 1993; Semrud-Clikeman et al., 2000), and one has suggested normalization of caudate volumes in late adolescence (Castellanos et al., 2002). A recent meta-analysis of the coordinates of gray matter differences between ADHD and controls identified the most consistent regional gray matter reduction in the right putamen/globus pallidus region (Ellison-Wright, Ellison-Wright, & Bullmore, 2008).

However, reports of alterations in structural neuroanatomy have not been limited to the frontostriatal circuitry. Volumetric reductions have also been reported in other brain regions, most commonly the cerebellum (Berquin et al., 1998; Bussing, Grudnik, Mason, Wasiak, & Leonard, 2002; Castellanos et al., 2001; Castellanos et al., 1996b;

Durston et al., 2004; Hill et al., 2003; Mostofsky, Reiss, Lockhart, & Denckla, 1998), parietal lobes (Carmona et al., 2005; Castellanos et al., 2002; Filipek et al., 1997; Makris et al., 2007; McAlonan et al., 2007; Overmeyer et al., 2001; Wang et al., 2007), and the corpus callosum (Baumgardner et al., 1996; Giedd et al., 1994; Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994).

1.1.4 Functional Neuroanatomy

Findings of functional imaging studies have also been consistent with a primary dysfunction of the frontostriatal circuitry. A number of studies looking at cerebral perfusion in the resting state have reported frontal (Amen & Carmichael, 1997; Kim, Lee, Shin, Cho, & Lee, 2002; Langleben, Austin, Krikorian, Ridlehuber, & Strauss, 2001; Lou, Henriksen, & Bruhn; Sieg, Gaffney, Preston, & Hellings, 1995) and / or striatal hypoperfusion (Lou et al., 1984; Lou, Henriksen, & Bruhn, 1990; Lou, Henriksen, Bruhn, Borner, & Bieber Nielson, 1989; Teicher et al., 2000) in ADHD participants. Administration of methylphenidate has been reported to increase perfusion in those regions (Kim, Lee, Cho, & Lee, 2001; Lou et al., 1984; Lou et al., 1989). Studies examining brain function in ADHD during task performance have also produced evidence of hypofrontality (Booth et al., 2005; Bush et al., 1999; Durston et al., 2007; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Epstein et al., 2007; Ernst et al., 1994; Mulder et al., 2008; Pliszka et al., 2006; Rubia et al., 2008; Rubia et al., 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Smith, Taylor, Brammer, Toone, & Rubia, 2006; Suskauer et al., 2008; Tamm, Menon, Ringel, & Reiss, 2004; Zametkin et al., 1993; Zametkin et al., 1990; Zang et al., 2005), with some also reporting evidence of

reduced striatal activity in ADHD relative to controls (Booth et al., 2005; Durston et al., 2003; Epstein et al., 2007; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Rubia et al., 1999; Scheres, Milham, Knutson, & Castellanos, 2007; Shafritz, Marchione, Gore, Shaywitz, & Shaywitz, 2004; Ströhle et al., 2008; Vaidya et al., 1998; Vaidya et al., 2005; Vance et al., 2007). It should be noted, however, that over 50% of these studies have used tasks tapping executive functions, such as response inhibition (e.g. the go/no-go task, the stop signal reaction time task), working memory (e.g. the n-back task), and set-shifting (e.g the Stroop task), which are putatively subserved by the frontostriatal circuitry (Alexander, DeLong, & Strick, 1986). Methylphenidate, the main treatment for ADHD, has been reported to increase task-related activation in fronto-striato-thalamic circuitry. Studies have reported significant increases in frontal (Bush et al., 2008; Epstein et al., 2007; Lee, Han, Lee, & Choi, 2010; Prehn-Kristensen et al., 2011; Rubia et al., 2011a; Rubia, Halari, Mohammad, Taylor, & Brammer, 2011b; Vaidya et al., 1998), anterior cingulate (Bush et al., 2008) and striatal (Epstein et al., 2007; Shafritz et al., 2004; Vaidya et al., 1998) activity in the context of tasks of response inhibition and attention in children and adults with ADHD. Thus, the therapeutic effects of methylphenidate could be mediated by increasing activity in the frontostriatal circuitry.

Functional abnormalities are not limited to the frontrostriatal circuitry, and there is now accumulating evidence of functional alterations in other brain regions, such as the cerebellum and parietal regions, as well as in functional connectivity among brain regions (reviewed in Cherkasova & Hechtman, 2009).

1.1.5 Molecular genetics

ADHD is a highly heritable disorder. Risk for ADHD is two- to eight-fold higher in first-degree relatives of ADHD probands than in the general population (Faraone, 2000). Biological relatives of children with ADHD or hyperactivity are more likely to present with hyperactivity compared to adoptive relatives (Cantwell, 1975; Morrison & Stewart, 1973; Sprich, Biederman, Crawford, Mundy, & Faraone, 2000). A review of 20 twin studies reported a mean heritability estimate of 76% (Faraone et al., 2005b), suggesting that ADHD is among the most heritable psychiatric disorders.

Genome-wide linkage scans have produced inconclusive results, perhaps reflecting a low likelihood that vulnerability to ADHD is conferred by genes of moderately large effect (Faraone & Mick, 2010). However, association studies have reported consistent associations with a number of candidate monoamine genes.

Genes encoding dopamine receptors and transporters have attracted most attention, and many studies have reported evidence of significant associations between ADHD and dopamine genes. Meta-analyses found significant associations of ADHD with the 7-repeat allele polymorphism of 48-base pairs (bp) variable number of tandem repeats (VNTR) on the exon III of the DA receptor 4 (DRD4) gene (Faraone, Doyle, Mick, & Biederman, 2001; Li, Sham, Owen, & He, 2006; Smith, 2010), with the most recent meta-analysis reporting the odds ratio (OR) of 1.33 (Smith, 2010). The larger effect sizes were associated with a larger proportion of ADHD combined type in the sample (Smith, 2010). In vitro studies have suggested that this allele produced blunted responses of the D4 receptor to DA (Asghari et al., 1995; Van Tol et al., 1992). Significant associations have also been reported in two meta-analyses between ADHD

and the 148-bp microsatellite marker of the DA receptor 5 (DRD5) gene (ORs 1.2 and1.3) (Li et al., 2006; Lowe et al., 2004, but see Mill et al., 2005), as well as with two other microsatellite markers and a single nucleotide polymorphism (SNP) in the 3' untranslated region (UTR) within the DRD5 gene (Faraone & Mick, 2010). Relevant to DA catabolism, some studies have found significant associations with the 10-repeat allele 3'untranslated region VNTR of the dopamine transporter (DAT) SLC6A3 gene, although meta-analyses report either a weak association or no association (Faraone & Mick, 2010; Li et al., 2006; Yang et al., 2007). The inconsistencies may indicate that this allele is in partial linkage disequilibrium with another marker of ADHD, rather than directly conferring vulnerability for the disorder. The VNTR occurs at a non-coding site and is thought to affect DAT expression, rather than the amino acid sequence: the density of DAT binding sites for the 10-repeat polymorphism was found elevated by about 50% over the 9-repeat polymorphism (VanNess, Owens, & Kilts, 2005), which would be expected to increase synaptic DA clearance. Allelic variation in the DAT SLC6A3 gene has also been linked with response to stimulants, with subjects homozygous for the 9-repeat allele showing a diminished response (Joober et al., 2006; Lott, Kim, Cook, & de Wit, 2004; Stein et al., 2005). Notably, elimination of the SLC6A3 gene in mice can produce hyperactive and impulsive behavior, which is reduced by stimulants (Gainetdinov et al., 1999b; Giros, Jaber, Jones, Wightman, & Caron, 1996).

Significant associations have also been reported between ADHD and serotonergic genes. An association with a SNP (861G>C) on the serotonin 1B receptor gene has been found, suggesting an over transmission of the G861C allele (OR = 1.35) in ADHD (Smoller et al., 2006). An association has also been reported with a 44-bp

insertion/deletion polymorphism in the promoter region of the serotonin transporter gene (SLC6A4), suggesting an over transmission of the long allele in ADHD (pooled OR = 1.31) (Cadoret et al., 2003; Kent et al., 2002; Manor et al., 2001; Retz, Thome, Blocher, Baader, & Rösler, 2002; Seeger, Schloss, & Schmidt, 2001), which leads to more transcription of the gene, resulting in higher 5HT uptake and therefore decreased 5HT neurotransmission (Lesch et al., 1996).

In addition to monoamine candidate genes, significant associations have been reported with polymorphisms of a gene on chromosome 20p12 encoding the synaptosomal associated protein (SNAP25) involved in regulation of neurotransmitter release. SNAP25 is known to be deficient in coloboma mice – an animal model of ADHD. A meta-analysis reported an OR of 1.19 (Faraone et al., 2005b).

However, despite the reported associations between ADHD and monoamine gene polymorphisms, the effects of these on monoamine function in vivo remain unknown.

1.2 Neurotransmission in ADHD

Converging evidence implicates dopamine neurotransmission in the pathophysiology of ADHD, although contributions of other neurotransmitter systems have also been proposed (see below). The DA system plays an important role in a range of behaviors relevant to the ADHD symptomatology and neurocognitive profile. These include initiation of motor activity which is dependent on the nigrostrial dopamine system (Barbeau, Murphy, & Sourkes, 1961; Carlsson, 2001; Lanska, 2010); sensitivity to reward and goal-directed behaviour, dependent on DA transmission in the mesolimbic system (Berridge & Robinson, 1998; Phillips, Pfaus, & Blaha, 1991; Stewart, 1983;

Wise, 2004); and executive functions, such as working memory, which have been linked to mesocortical DA transmission (Brozoski, Brown, Rosvold, & Goldman, 1979; Goldman-Rakic, 1995; Seamans & Yang, 2004). Although attention and arousal are usually considered to primarily depend on norepinephrine (NE) transmission (Aston-Jones, Rajkowski, & Cohen, 1999; Sara & Segal, 1991), DA in the cortex and striatum may play a significant role in the ability of environmental stimuli to sustain interest (Kapur, 2003; Seamans & Yang, 2004; Stewart, de Wit, & Eikelboom, 1984; Volkow et al., 2004). In addition, as reviewed above, molecular genetic studies have implicated DA genes in the aetiology of ADHD (Faraone & Mick, 2010).

Evidence that more directly implicates the DA system in the pathophysiology of ADHD and is reviewed below includes: the clinical efficacy of stimulant medications such as methylphenidate and amphetamine (Spencer et al., 1996), which increase the extracellular levels of monoamines, especially DA and NE (Solanto, 1998); animal models of ADHD implicating altered DAergic function; and, most informatively, in-vivo imaging findings in individuals with ADHD demonstrating DA system alterations.

1.2.1 Overview of the Dopamine System

1.2.1.1 Neuroanatomy of ascending DA pathways. There are three major ascending DA projection pathways in the mammalian brain, the nigrostriatal, the mesolimbic, and the mesocortical (Björklund & Dunnett, 2007). These arise from three cytoarchitectonic groups in the midbrain – A8 cells in the retrorubral area, A9 cells in the substantia nigra (SN) pars compacta, and A10 cells in the ventral tegmental area (VTA). Although the origin cells of these pathways are intermixed in the SN-VTA complex

(areas A8, A9, and A10) (Björklund & Dunnett, 2007), the three pathways are anatomically and functionally distinct, with their projections largely confined to their respective targets: striatum for the nigrostriatal pathway; ventromedial striatum (including the nucleus accumbens), limbic regions, and the prefrontal cortex for the mesolimbic pathway; and the cortical mantle for the mesocortical pathway (Bentivoglio & Morelli, 2005).

Based on their connectivity and morphological features, neurons in areas A8, A9, and A10 can be separated into dorsal and ventral tiers. The dorsal tier is composed of calbindin (calcium-binding protein) positive cells in the dorsal aspects of the SN and VTA, as well as cells in A8, innervating the ventral striatum, limbic, and cortical areas, as well as the matrix compartment of the dorsal striatum (Bentivoglio & Morelli, 2005; Gerfen, Herkenham, & Thibault, 1987; Lynd-Balta & Haber, 1994a). These cells express low levels of the dopamine transporter (DAT). The ventral tier contains calbindin negative cells in ventral aspects of SN and VTA, which innervate mostly the patch compartment of the dorsal striatum and have high expression levels for DAT and D2 receptor mRNA (Bentivoglio & Morelli, 2005; Gerfen et al., 1987; Lynd-Balta & Haber, 1994a; Prensa & Parent, 2001). Many of these cells also extend prominent dendrites ventrally to the SN pars reticulata (Gerfen et al., 1987).

In addition to the three major ascending pathways, the midbrain DA neurons also project to downstream targets containing basal ganglia output neurons. These include external and internal segments of the globus pallidus, parts of the ventral pallidum, the subthalamic nucleus, and the SN pars reticulata (Hassani, François, Yelnik, & Féger,

1997; Lavoie, Smith, & Parent, 1989; Lindvall & Björklund, 1979; Smith, Lavoie, Dumas, & Parent, 1989).

1.2.1.2 Functional topography of striatal projections. Striatal cortical and thalamic inputs and downstream outputs are topographically and functionally organized, forming cortico–basal ganglia–thalamo–cortical loops.

Striatal neurons receive topographically and functionally organized inputs from the cortex and thalamus, based on which the striatum has been subdivided into limbic, associative and sensorimotor subcompartments (Haber, 2010; Haber & McFarland, 1999; Middleton & Strick, 2002). Inputs from ventromedial cortical regions terminate in the ventromedial striatum, and inputs from dorsolateral cortical regions terminating in the dorsolateral striatum. Frontal regions mediating motivation, reward, and affect regulation, such as the orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (vmPFC) and the dorsal anterior cingulate cortex (dACC), project to the ventral striatum, including the nucleus accumbens (NAc) and the ventromedial aspects of caudate and putamen (Haber, 2010). Ventral striatum also receives prominent projections from the amygdala and the hippocampus (Friedman, Aggleton, & Saunders, 2002; Fudge, Kunishio, Walsh, Richard, & Haber, 2002). The dorsolateral prefrontal cortex (DLPFC) mediating executive functions projects to the head of the caudate and the precommissural dorsal putamen, with few terminals in the post-commissural putamen (Haber, 2010). Rostral premotor areas project to both caudate and putamen, bridging the two with a continuous projection, while motor and somatosensory cortical areas send somatotopically organized projections to the post-commissural putamen (Aldridge,

Anderson, & Murphy, 1980; Flaherty & Graybiel, 1994; Kimura, 1986). Thalamo-striatal projections are organized in a similar topographic manner, such that functionally associated thalamic and cortical areas terminate in the same striatal regions (Haber, Fudge, & McFarland, 2000).

Striatal projections to downstream output targets in the pallidal complex and the SN pars reticulata are also topographically organized reflecting functional organization of the striatum described above (Haber, Lynd, Klein, & Groenewegen, 1990; Hedreen & Delong, 1991; Lynd-Balta & Haber, 1994b). This topography continues to be evident in the projections from the pallidal complex and the SN pars reticulata to the thalamic output nuclei, and from the thalamic nuclei back to the limbic, associative control, and sensorimotor control cortical areas, completing the loops (Ilinsky, Jouandet, & Goldman-Rakic, 1985; Kuo & Carpenter, 1973; Middleton & Strick, 2002; Strick, 1976).

Despite their roughly parallel topographical organization, however, these functional loops are not segregated and have points of convergence, enabling information transfer across functional domains. In the striatum, there is convergence between inputs from limbic and cognitive control cortical areas rostrally, as well as between inputs from cognitive and motor areas more caudally, which has been proposed to enable learning and adaptation/ modification of behavioral responses (Haber, 2010).

Midbrain DA neurons' afferent inputs from and projections to the striatum also follow a similar, but reverse topographic organization, forming striato-nigro-striatal loops. Striatal projections terminate in both the dorsal and the ventral midbrain DA cell tiers with an inverse dorso-ventral topography, such that with ventral striatum (as well as the extended amygdala) projects to the dorsal tier and the dorsal aspect of the ventral tier,

the associative striatum projects to the dorsal aspect of the ventral tier (central and ventral parts of the densocellular region of SN pars compacta), and the sensorimotor striatum projects to the ventral aspect of the ventral tier (cell columns of SN pars compacta), as well as to SN pars reticulata (Haber, 2010). Projections from the limbic and associative aspects are widely distributed over their general projection areas, while projections from the sensorimotor sub-region have a more restricted field. The ascending nigrostriatal projections also exhibit an inverse dorso-ventral topography. However, the descending and ascending limbs of these loops are not completely reciprocal and differ in proportional distribution of projections to and from different functional domains of the striatum. While the ventral striatum projects widely to the SN-VTA complex, with terminal fields in both the dorsal tier and the dorsal aspect of the ventral tier, it receives relatively limited midbrain input. Conversely, the dorsolateral striatum projects to a limited region, but receives inputs from a wide range of dopamine cells (Haber et al., 2000). The proportional differences between inputs and outputs of the stiato-nigro-striatal projection system, coupled with their topography, result in an organization where, for each striatal sub-region there is a reciprocal connection with the midbrain (with overlapping inputs and outputs), which is flanked ventrally and dorsally by non-reciprocal connections (Haber, 2010). This system of both reciprocal and non-reciprocal connections creates a feedforward organization, which allows for information transfer from the limbic through the associative to the sensorimotor striatum, possibly providing a mechanism by which motivation and cognition can influence motor behavioral responses, enabling learning and adaptation of behavior (Haber, 2010; Haber et al., 2000) (Figure 1).

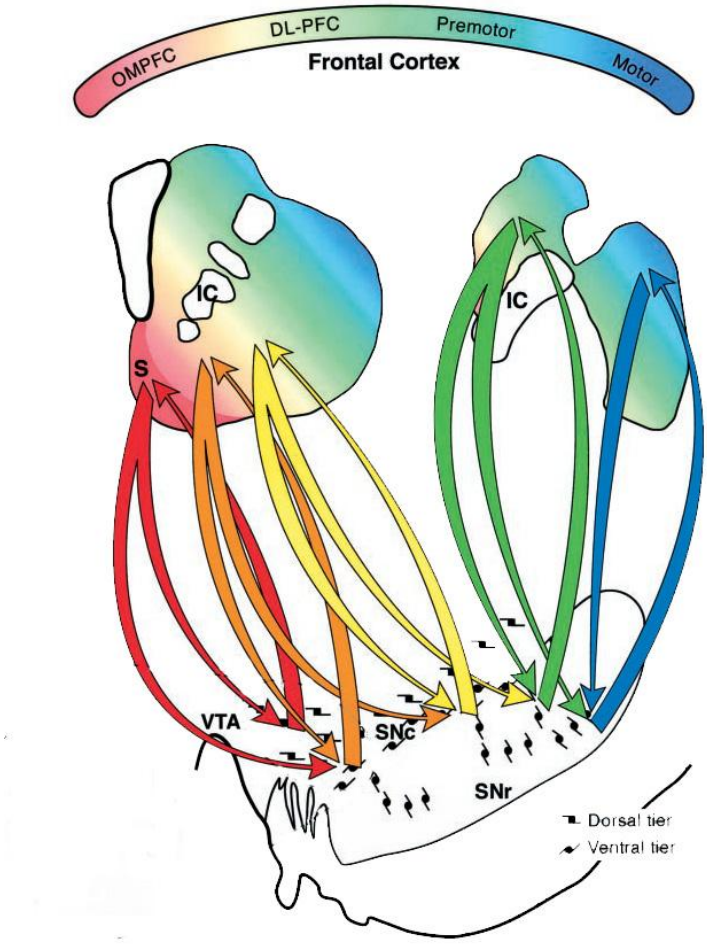


Figure 1-1. Schematic illustrating the organization of the midbrain dopamine cells and their projections to regions of the striatum: S = shell of the nucleus accumbens; VTA = ventral tegmental area; SNc= substantia nigra pars compacta; SNr = substantia nigra pars reticulata. Striatal regions are color coded to represent the cortical inputs they receive: red = limbic; green = associative; blue = motor; OMPFC = orbital and medial prefrontal cortex; DL=PFC = dorsolateral prefrontal cortex. (Adapted from Haber *et al* 2000, Figure 12).

1.2.1.3 Presynaptic DA function and firing modes. DA is a catecholamine synthesized both in the cytosol and the presynaptic terminals of DA neurons through conversion of *L*-tyrosine to L-3-(3, 4-dihydroxy-o-phenylalanine) (DOPA) by tyrosine hydroxylase (TH) and subsequent conversion of DOPA to DA by aromatic acid decarboxylase. Tyrosine hydroxylase is allosterically regulated by a number of influences, such as impulse flow, levels of cyclic AMP and intracellular calcium, and

non-vesicular DA concentrations, and is the rate limiting enzyme in DA synthesis. Following synthesis, vesicular DA is packaged into synaptic vesicles by the vesicular monoamine transporter. Local increases in calcium concentration can trigger fusion of the vesicle with the cell membrane and release of DA into the synaptic space.

DA neurons fire in two modes: tonic single spike firing mode and phasic burst firing mode. Tonic firing is slow (3-8 Hz) and irregular spontaneous baseline spike activity, driven by pacemaker-like membrane currents of the neuron (Grace & Bunney, 1984b). Tonic firing underlines the baseline tonic concentration of DA, which is 10-20 nM in the striatum (Keefe, Zigmond, & Abercrombie, 1992) and orders of magnitude lower in the prefrontal cortex and limbic regions (Garris & Wightman, 1994; Ihalainen, Riekkinen Jr, & Feenstra, 1999). Spontaneous DA neuron firing is under powerful GABAergic inhibition, with only about half of DA neurons showing spontaneous activity (Grace & Bunney, 1979). However, cortical glutamatergic inputs promote tonic firing by stimulating presynaptic glutamate receptors on the terminals of DA neurons (Grace, 1991). Burst spike firing that is associated with behaviorally relevant stimuli, such as presentation of unexpected rewards or sensory signals predicting such rewards, causes a transient phasic DA release bringing the synaptic DA concentration into 100 nM to μM range in the striatum (Grace & Bunney, 1984a). The rapid but transient increases in levels of synaptic DA occurring during phasic firing are believed to activate post-synaptic DA receptors (Grace, 1991).

In subcortical structures, extracellular DA is inactivated after release by a number of mechanisms. It can be metabolized within the synapse by catechol-O-methyl transferase (COMT), which produces the metabolite 3-methoxytyramine. It can also be

transported back into the presynaptic terminal by the dopamine transporter (DAT). Intracellular DA is then metabolized by monoamine oxidase (MAO) into 3,4-dihydroxy-O-phenylacetic acid (DOPAC) and can be further catabolized by COMT producing homovanillic acid (HVA). DA remaining in the extracellular space can stimulate presynaptic D2 autoreceptors, which can lead to homeostatic changes, such as decrease in DA synthesis by inhibition of TH and decrease of impulse flow and phasic firing by activation of K^+ channels. Presynaptic DA function is similar in the PFC, with the main difference being the lower density of DAT and its and extrasynaptic location (Sesack, Hawrylak, Matus, Guido, & Levey, 1998). Hence, reuptake by DAT can only be activated when extracellular DA levels are extremely high. Thus synaptic DA in the PFC is either metabolized by COMT or might also be taken up by the NE transporter (NET) (Carboni, Tanda, Frau, & Di Chiara, 1990; Yamamoto & Novotney, 1998).

1.2.1.4 Postsynaptic DA targets. DA receptors are G protein-coupled receptors categorized into two subgroups: D1-like and D2-like receptors. This classification is based on the receptors' differential response to agonists by either increasing or inhibiting the activity of the enzyme adenylate cyclase, which generates the intracellular second messenger cyclic adenosine monophosphate (cAMP) (Kebabian & Greengard, 1971). The D1-like receptors (D1 and D5) couple primarily to the G_s family of G proteins (G_s and G_{olf}) and activate adenylate cyclase and cAMP protein kinases. The D_2-like receptors (D_2, D_3, and D_4) couple primarily to $G_{i/o}$ family of G proteins and inhibit adenylate cyclase. D2 receptors activate K_+ channels and have both hetero and auto receptor functions.

D1 receptors are expressed in many brain regions receiving DAergic innervation, with the highest amount of D1 receptor mRNA found in the striatum, the olfactory tubercle, NAc, the medial prefrontal cortex, and limbic regions, including the piriform and entorhinal cortices, the amygdala, the anterior cingulate and the insula. D1 receptors are sparsely distributed in the SN on non-DA containing interneurons and on nerve terminals from other brain regions (Mansour et al., 1992). D5 receptors are also expressed in multiple brain regions, including the SN, NAc, hypothalamus, striatum, cerebral cortex, and olfactory tubercule (Khan et al., 2000). They are particularly abundant in the limbic regions.

D2 receptors are found throughout the brain and within all thee major DA signaling pathways, with the highest levels of D2 receptor mRNA found within the striatum, the nucleus accumbens, and the olfactory tubercle (Bouthenet et al., 1991). Somewhat lower levels of D2 mRNA have been found in the prefrontal and entorhinal cortices, amygdala, VTA, hippocampus, hypothalamus, and SN pars compacta (Bouthenet et al., 1991; Meador-Woodruff et al., 1989; Weiner et al., 1991). D2 receptors have been localized more specifically to the GABAergic medium spiny neurons in the striatum and dendrites and the soma in the SN pars compacta (Levey et al., 1993). D2 receptors are primarily localized intracellularly in the brain and may be trafficked to the plasma membrane if necessary (Prou et al., 2001).

D3 receptor expression is roughly 10-fold lower than D2 expression but has a 20 fold higher affinity for DA. The highest levels of expression of the D3 receptor are found in the islands of calleja and the olfactory bulb, and moderate levels are found in the NAc, vestibulocerebellum, and the SN, with relatively little D3 expression in the caudate and

putamen (Bancroft, Morgan, Flietstra, & Levant, 1998; Bouthenet et al., 1991; Levant, Grigoriadis, & DeSouza, 1992; Lévesque et al., 1992; Ricci, Vega, Mammola, & Amenta, 1995). At least some D3 receptors likely function as presynaptic autoreceptors (Shafer & Levant, 1998).

D4 receptors in the brain are most abundant in the prefrontal cortex, amygdala, hippocampus, hypothalamus and pituitary, and are sparse in the basal ganglia (Meador-Woodruff et al., 1996). D4 receptors are present in GABA-producing pyramidal and non-pyramidal neurons in the cortex (mainly layer V) and the hippocampus (Mrzljak et al., 1996). D4-receptor positive neurons in the thalamus, globus pallidus, and SN pars reticulata are also GABA-ergic.

In the human brain, postmortem studies and in-vivo binding studies with PET have reported high D1-type and D2-type receptor densities in caudate and putamen, with somewhat lower densities in the nucleus accumbens (Camus, Javoy-Agid, Dubois, & Scatton, 1986; Hall, Farde, & Sedvall, 1988). D1 and D2 receptors were found to be considerably less abundant in cortical and limbic regions, with D1 receptor density substantially higher than D2 receptor density in those regions (Camus et al., 1986; Hall et al., 1988; Hall et al., 1994) (Figure 2).

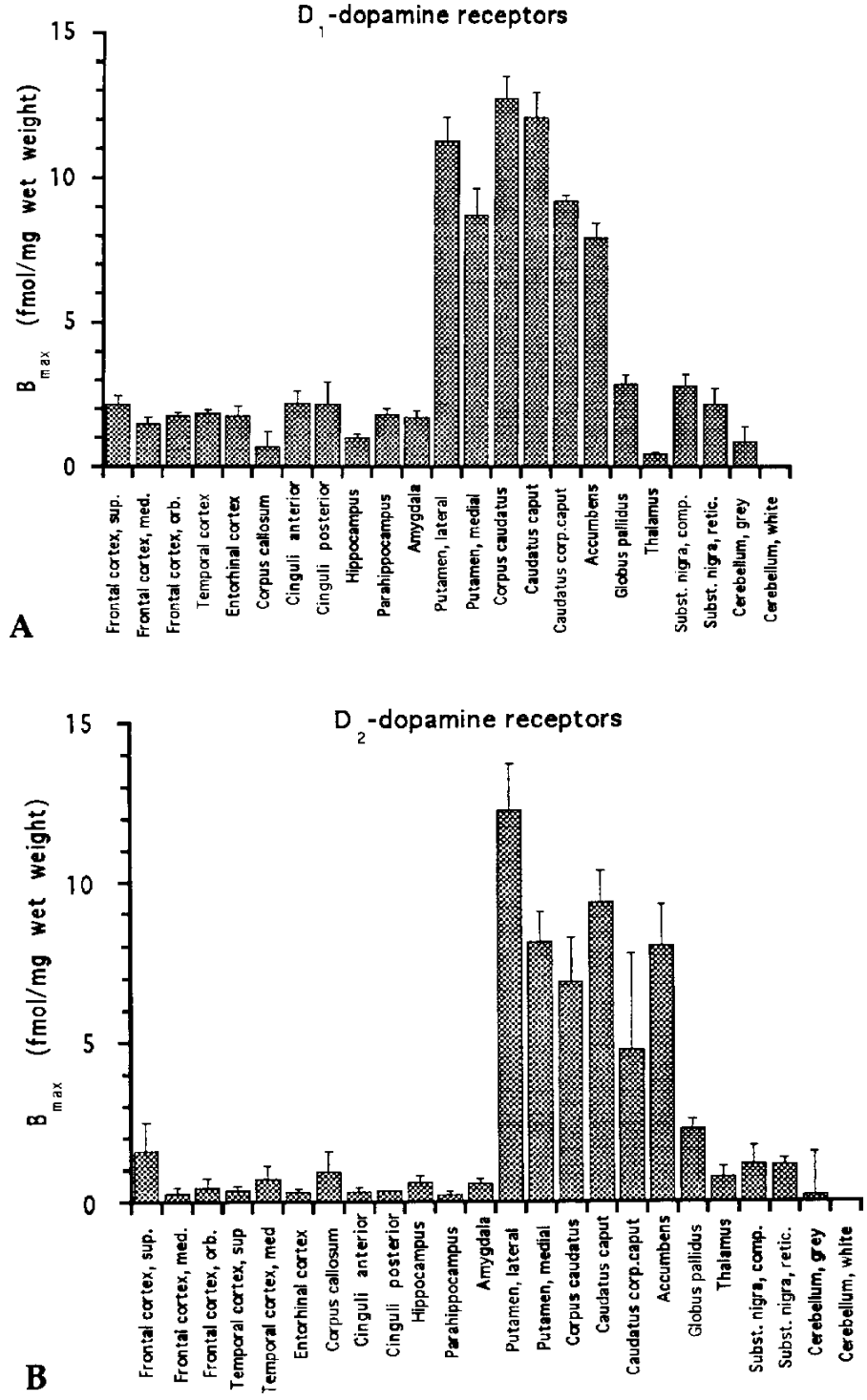


Figure 1-2: Regional distribution of D1 and D2 type receptors in the human brain (Adapted from Hall *et al* 1994, Figure 1.)

1.2.2 Psychostimulants: Neurochemical Mechanisms and Behavioral Effects

Nearly 200 reports have demonstrated the therapeutic efficacy of psychostimulants for treatment of ADHD, with 70% of patients in clinical trials experiencing significant improvements in inattentiveness and hyperactivity/impulsivity (Spencer et al., 1996). The two most widely prescribed psychostimulants, methylphenidate (MPH) and dextroamphetamine (*d*-AMPH), are believed to confer their therapeutic effects by increasing extracellular levels of monoamines.

Neuropharmacology: MPH increases extracellular concentrations of DA and NE by binding to the DA and NE transporters (DAT and NET) and blocking catecholamine reuptake (Cooper, 2003). Since MPH does not directly cause catecholamine release, its action is dependent on spike activity and calcium.

D-AMPH increases extracellular concentrations of DA, NE, and serotonin (5-HT), and its pharmacology is considerably more complex. *D*-AMPH can enter monoamine cells both through lipophilic diffusion (Mack & Bonisch, 1979) and through active transport by DAT and NET (but not by the 5-HT transporter) (Heal, Cheetham, & Smith, 2009; Zaczek, Culp, & De Souza, 1991). Once inside the cell, it displaces monoamines from newly synthesized and vesicular storage pools (Floor & Meng, 1996; Sulzer & Rayport, 1990) and induces DA overflow into the synaptic cleft by facilitating outward exchange diffusion and triggering channel-like monoamine release (Sulzer, Sonders, Poulsen, & Galli, 2005). This reverse transport is spike activity-independent. *D*-AMPH also delays the clearance of catecholamines from the synaptic cleft as it transiently occupies DAT and NET during its transport into the presynaptic terminal as substrate (Heal, Smith, Kulkarni, & Rowley, 2008). *D*-AMPH also enhances DAergic

transmission through a number of additional mechanisms: suppression of metabotropic glutamate receptor (mGluR) mediated DA neuron inhibition, thus increasing DA neuron burst firing (Paladini, Fiorillo, Morikawa, & Williams, 2001); enhancement of DA synthesis through its effects on tyrosine hydroxylase activity (Costa, Groppetti, & Naimzada, 1972; Kuczenski, 1975); inhibition of monoamine oxidase (Sulzer et al., 2005); and acute reduction of cell surface DAT expression (Saunders et al., 2000).

Notably, stimulant-induced increases in extracellular DA resulting from blockade and reversal of the DA transporter promote activation of the D2 presynaptic autoreceptors, which in turn leads to a decrease in DA cell firing (Bunney, Walters, Roth, & Aghajanian, 1973; Shi, Pun, Smith, & Bunney, 2000). Decreased excitability of DA neurons has been reported following systemic intravenous administration 0.25 to 2 mg/kg of amphetamine (Groves, Fenster, Tepper, Nakamura, & Young, 1981). Stimulants have also been found to cause inhibition of spontaneous firing rate in LC, which is likely mediated by stimulation α-2 NE autoreceptors (Devilbiss & Berridge, 2006; Graham & Aghajanian, 1971; Lacroix & Ferron, 1988).

The effects of stimulants on monoamine transmission are largely dependent on the dose administered and the brain region considered. *In vivo* microdialysis studies in rodents have demonstrated that stimulants dose-dependently increase the extracellular levels of DA and NE throughout the brain when administered at higher than standard therapeutic doses for humans (Carboni, Imperato, Perezzani, & Di Chiara, 1989; Florin, Kuczenski, & Segal, 1994; Kuczenski & Segal, 1989; Kuczenski, Segal, & Aizenstein, 1991; Kuczenski & Segal, 1997; Maisonneuve, Keller, & Glick, 1990; Robinson & Camp, 1990; Sharp, Zetterström, Ljungberg, & Ungerstedt, 1987; Zetterstrom, Sharp,

Marsden, & Ungerstedt, 1983). *D*-AMPH also releases 5-HT in the striatum (Kuczenski & Segal, 1997). However, doses of MPH that yield clinically significant plasma levels (similar to those in human patients: 8-40 *ng/mL*) have been found to produce minimal subcortical DA efflux, with more pronounced effects on NE (Kuczenski & Segal, 2001, 2002). Furthermore, some evidence suggests that clinically significant MPH doses preferentially induce catecholamine release in the PFC, producing smaller effects in subcortical areas (Berridge et al., 2006). *In vivo* radioligand PET imaging studies in non-human primates and humans using stimulant drug challenges in human therapeutic ranges have reliably produced data consistent with DA increases in the striatum (Boileau et al., 2006; Boileau et al., 2007; Drevets et al., 2001; Laruelle, 2000; Leyton et al., 2002; Martinez et al., 2003; Narendran et al., 2010; Oswald et al., 2005; Schneier et al., 2009; Volkow, Wang, Fowler, & Ding, 2005a; Volkow, Fowler, Wang, Ding, & Gatley, 2002a; Volkow et al., 2007b; Volkow et al., 2001; Volkow et al., 2003) and more recently in the extrastriatal regions including the PFC (Cropley et al., 2008; Mukherjee, Christian, Narayanan, Shi, & Collins, 2005; Narendran et al., 2009; Riccardi et al., 2006a; Riccardi et al., 2011; Slifstein et al., 2010; Slifstein et al., 2004). Notably, although microdialysis studies in rodents have reported about 3-fold greater increases in extracellular DA levels following *d*-AMPH compared to MPH (Kuczenski & Segal, 1992; Kuczenski & Segal, 1997), PET imaging studies in both humans and animals (Schiffer et al., 2006) find the two drugs to generate similar decreases in D2 receptor availability. Given that changes in radioligand binding might primarily reflect stimulant-induced changes in synaptic DA levels, whereas microdialysis captures changes in extracellular DA levels (Laruelle, 2000), the disparity between microdialysis and PET radioligand studies could potentially

reflect differences in neuopharmacological mechanisms of the two stimulants. *D*-AMPH may cause substantial increases in extracellular and synaptic DA, since it induces reverse DA transport (in addition to DAT blockade), and much of the DAT is located perisynaptically (Caron & Gainetdinov, 2010). MPH, in contrast, likely affects primarily synaptic DA since it only blocks the DAT, and extracellular DA increases would only reflect passive diffusion from the synapse.

1.2.2.1 Acute behavioral and cognitive effects. In both experimental animals and humans, stimulants increase locomotion at moderate doses and induce motor stereotypy at higher doses (≥ 5 mg/kg) (Beninger, 1983; Finn, Iuvone, & Holtzman, 1990; Stromberg & Svensson, 1975). Facilitation of locomotor activity is primarily attributable to post-synaptic stimulation of mesolimbic DA neurons, whereas stereotypy is mediated by the nigrostriatal system (Le Moal, 1996). However, a biphasic effect of stimulants on locomotion has occasionally been observed both in hyperactive animals (Davis, 1957; Helmeste & Seeman, 1982; Luthman, Fredriksson, Lewander, Jonsson, & Archer, 1989; Myers, Musty, & Hendley, 1982) and in normal animals with oral drug administration (Kuczenski & Segal, 2002), with low doses reducing locomotion and higher doses increasing locomotion. Likewise, in humans, low doses of stimulants (e.g. 0.2 - 0.6 mg/kg for *d*-AMPH and 0.3 - 0.6 mg/kg of MPH) reduce locomotor activity and distractibility and high doses (or overdosing) produce symptoms of excessive central nervous system excitation (Kuczenski & Segal, 2002; Rapoport et al., 1978; Seeman & Madras, 2002).

The observation that low doses of stimulants reduce locomotor activity has been explained by their differential effects on tonic levels versus phasic rise in extracellular DA. Studies using *in vivo* and *in vitro* amperometry have suggested that low doses of stimulants increase the tonic levels of extracellular DA substantially more than they increase phasic release (Seeman & Madras, 2002). This preferential potentiation of DA tone by low stimulant doses has been attributed to a greater activating effect of stimulant-induced extracellular DA increases on the presynaptic D2 autoreceptors than the postsynaptic D2 receptors (Grace, 2001). This is likely due to the greater sensitivity of the presynaptic autoreceptors to DA (Skirboll, Grace, & Bunney, 1979). As mentioned earlier, activation of presynaptic D2 autoreceptors by tonic DA down-regulates phasic DA release (Bunney et al., 1973; Shi et al., 2000). In fact, low stimulant concentrations have been shown to decrease electrically evoked DA release in striatal slices (Kamal, Arbilla, Galzin, & Langer, 1983). Moderate and high stimulant doses, on the other hand, might cause an overall pronounced elevation of both tonic and phasic DA levels, overriding the D2 autoreceptor-mediated inhibition of phasic DA release and resulting in a widespread stimulation of the post-synaptic DA receptors (Seeman & Madras, 2002). The D2 autoreceptor-mediated decrease in phasic DA release in response to the elevation of extracellular DA tone has been proposed to be the mechanism through which low stimulant doses reduce hyperactivity in ADHD (Grace, 2001; Seeman & Madras, 2002).

Stimulants have rewarding properties. Both *d*-AMPH and MPH and are self-administered by animals and maintain responding in conditioned reinforcement paradigms (Kollins, MacDonald, & Rush, 2001). In humans, amphetamines are well known to have a high abuse potential. While epidemiological data on methylphenidate

abuse are sparse, a substantial recent rise in the recreational use of MPH among teenagers has been documented (Klein-Schwartz & McGrath, 2003). Further, some studies have reported self-administration of MPH by humans in experimental paradigms (Kollins et al., 2001) and others have noted subjective reports of hedonic effects of the drug (Volkow et al., 1996b). The reinforcing properties of stimulants are mediated by the mesolimbic DA pathway (Di Chiara & Imperato, 1988; Kuczenski & Segal, 1989), which plays a role in signaling rewards, and coding incentive value (Berridge & Robinson, 1998; Burk & Mair, 2001; Koob, 1996; Wade, de Wit, & Richards, 2000). While there is currently no compelling evidence that stimulant treatment confers a risk for substance abuse in individuals with ADHD (Wilens, Faraone, Biederman, & Gunawardene, 2003), the ability of stimulants to increase incentive salience of relevant stimuli may contribute to their therapeutic effects by facilitating goal-directed behavior and reducing distractibility.

Stimulants also affect cognition. Research in rodents suggests that stimulants have biphasic effects on cognitive functions, such as attention, learning and memory, with low doses enhancing and higher doses impairing performance (Arnsten & Dudley, 2005; Berridge et al., 2006; Grilly & Gowans, 1988; Grilly, Gowans, McCann, & Grogan, 1989; Grilly & Simon, 1994; Haycock, Buskirk, & Gold, 1977; Katz, 1988; Ljungberg & Enquist, 1987; McGaughy & Sarter, 1995; Sara & Deweer, 1982). Although evidence has been equivocal, in healthy humans, therapeutic stimulant doses have been reported to enhance cognitive function in the areas of learning and working memory (Husain & Mehta, 2011; Smith & Farah, 2011). In individuals with ADHD, stimulant medications have been found to enhance executive functions, memory, attention, and processing speed (Kempton et al., 1999; Mehta, Sahakian, & Robbins,

2001; Riordan et al., 1999). Some studies have reported that the same dose of stimulants enhances cognitive performance in individuals with low baseline performance and putatively low prefrontal DA levels, while impairing performance in individuals with high baseline performance and putatively high prefrontal DA levels (Allman et al., 2010; Husain & Mehta, 2011; Mattay et al., 2000; Mattay et al., 2003). Since these higher order cognitive functions are largely dependent on the PFC (Chudasama & Robbins, 2006), the biphasic effects of stimulants are consistent with an inverted U relationship between cognitive performance and catecholamine levels in the PFC (Husain & Mehta, 2011; Seamans & Yang, 2004). Performance is optimal at moderate and impaired at both insufficient and excessive prefrontal catecholamine levels. Hence, stimulants would be expected to produce cognitive enhancements particularly in populations with low baseline levels of prefrontal catecholamines, such as Parkinson's disease and possibly ADHD.

1.2.3 Animal Models

Animal models have been a useful tool in the study of the pathophysiology of ADHD, as they allow for a direct investigation of the underlying neuropathological alterations through invasive manipulations and measurement techniques. Existing models are either genetic, from naturally occurring or artificially produced mutations, or created using an insult to the central nervous system early in development. These models generally implicate monoaminergic (in particular dopaminergic) systems, with some implicating DA system hypofunction, but others suggesting DA hyperfunction. There are also models in which dopamine system abnormalities have not been documented, such as

mice lacking the gene encoding the β-2 subunit of the nicotinic receptor, rats prenatally exposed to ethanol and nicotine, rats exposed to polychlorinated biphenyls around puberty, rats with developmental cerebellar stunting, and acallosal mice (Russell, 2011; Sontag, Tucha, Walitza, & Lange, 2010).

Probably the most extensively studied hypodopaminergic model of ADHD is the spontaneously hypertensive rat (SHR) (Sagvolden et al., 1992b), developed by inbreeding Wistar-Kyoto (WKY) rats to select for hypertension. Compared to the normotensive WKY rats, the SHR shows high levels of spontaneous activity in free-exploration open fields (Sagvolden, Hendley, & Knardahl, 1992a) and hyperactivity under the conditions of infrequent reinforcements (Sagvolden, 2000; Sagvolden, Johansen, Aase, & Russell, 2005). The SHR also has difficulty acquiring operant tasks, responds excessively under a fixed-interval/ extinction schedule, and shows increased sensitivity to immediate and reduced sensitivity to delayed reinforcements (Bull, Reavill, Hagan, Overend, & Jones, 2000; Sagvolden, 2000). The behavioral and cognitive abnormalities of the SHR are ameliorated by stimulants (Myers et al., 1982; Sagvolden et al., 1992b), though not in all behavioral paradigms (van den Bergh et al., 2006). Compared to WKY, the SHR has increased DA tone in the nucleus accumbens but decreased DA tone in the caudate, decreased electrically-evoked and MPH-evoked striatal and prefrontal DA release, increased number of DAT sites in the caudate-putamen, a higher density of post-synaptic D1 receptors, and decreased molecular indices of post-synaptic transmission (Carey et al., 1998; de Villiers et al., 1995; Papa, Sellitti, & Sadile, 2000; Russell, de Villiers, Sagvolden, Lamm, & Taljaard, 1998; Russell, Sagvolden, & Johansen, 2005; Watanabe et al., 1997). However, NE concentrations are increased in a number of brain regions,

including locus coeruleus, substantia nigra, and PFC (de Villiers et al., 1995). One of the criticisms of the SHR as a model is the questionable validity of the WKY as the control strain: WKY rats are less active compared to other rat strains and perform less well on a number of behavioral tasks (Bull et al., 2000; van den Bergh et al., 2006).

Another hypodopaminergic model is the coloboma mutant mouse, which has a hemizygous deletion of a segment on the chromosome 2q, including a gene that encodes the SNAP25 protein. SNAP25 regulates membrane trafficking, is required for the release of neurotransmitters and involved in the translocation of proteins (e.g. NMDA receptor subunits) to the post-synaptic cell membrane. Compared to wild types, the coloboma mice show increased impulsivity, impaired inhibition in a delayed reinforcement task, neuerodevelopmental delays, and spontaneous hyperactivity, which is reduced by low doses of *d*-amphetamine, but not by MPH (Bruno et al., 2007; Hess, Collins, & Wilson, 1996; Wilson, 2000). The depolarization-induced DA release is greatly reduced in the dorsal, but not the ventral striatum of the coloboma mice, and midbrain postsynaptic D2 receptors are upregulated (Jones, Williams, & Hess, 2001; Raber et al., 1997), consistent with the DA system hypofunction. The coloboma mice also show increased NE concentrations in the striatum, and NE depletion reduces hyperactivity, but not impulsivity (Bruno et al., 2007; Jones et al., 2001). Glutamate release form cortical synaptosomes is reduced (Raber et al., 1997). The main limitations of this model are the lack of expected reduction in hyperactivity with MPH and insufficient evidence of cognitive deficits mimicking those observed in ADHD, such as sustained attention (Gainetdinov, 2010; Sontag et al., 2010).

Direct insults to the DA system have also been shown to result in ADHD-like phenotypes. Juvenile rats with neonatal 6-hydroxydopamine (6-OHDA) lesions, which result in a selective removal of DA projections to the forebrain, show spontaneous hyperactivity, most prominent in pre-adolescence (Erinoff, MacPhail, Heller, & Seiden, 1979; Luthman, Bassen, Fredriksson, & Archer, 1997; Luthman et al., 1989; Shaywitz, Yager, & Klopper, 1976b), as well as deficits in learning and memory (Archer et al., 1988; Luthman et al., 1997). Neither impulsivity nor sustained attention deficits have been reported, which has been cited as a limitation of this model (Sontag et al., 2010). Both hyperactivity and cognitive deficits are reduced by low doses of stimulants (Davids, Zhang, Kula, Tarazi, & Baldessarini, 2002; Luthman et al., 1989; Shaywitz, Klopper, Yager, & Gordon, 1976a; Shaywitz et al., 1976b; Wool et al., 1987), though those effects may be mediated by the release of NE or serotonin (Davids et al., 2002). It should be noted, however, that along with chronic dopaminergic hypofunction (Luthman et al., 1989), 6-OHDA lesions in rats have been found to result acutely in a hyperdopaminergic state in the striatum and NAc, with increased DA turnover and upregulation of DAT and DA binding sites (Pycock, Kerwin, & Carter, 1980). Long term neuroadaptive changes consistent with DA function upregulation have also been seen, such as the ability of the remaining neurons to maintain relatively high extracellular DA concentrations given their scarcity (Castaneda, Whishaw, Lermer, & Robinson, 1990) and reduced density of D2 autoreceptors and DAT (Joyce, Frohna, & Neal-Beliveau, 1996). The neuroadaptive changes are not limited to the DA system: 5HT hyperinnervation of the striatum has also been observed (Descarries, Soghomonian, Garcia, Doucet, & Bruno, 1992; Kostrzewa,

Reader, & Descarries, 1998; Luthman, Brodin, Sundstrom, & Wiehager, 1990; Stachowiak, Bruno, Snyder, Stricker, & Zigmond, 1984).

Monkeys exposed to low doses of the dopamine neurotoxin 1-methyl-4-phenyl 1,2,3,6-tetrahydropyridine (MPTP) are a non-human primate model of ADHD implicating DA hypofunction. These monkeys show attentional and executive function deficits mimicking those seen in ADHD in the absence of substantial motor dysfunction, making this model more appropriate for predominantly inattentive subtype (Decamp & Schneider, 2004; Roeltgen & Schneider, 1991, 1994). These monkeys display cognitive impairments similar to those seen with frontal lesions, as well as with ADHD patients, such as working memory deficits, deficits in maintenance of a response set and in shifting of attentional sets, difficulties focusing and sustaining attention, deficits in motor planning and preparation, and time estimation deficits (Decamp & Schneider, 2004; Roeltgen & Schneider, 1991, 1994). However, it is unknown how cognitive deficits in this model respond to stimulants.

The most studied hyperdopaminergic model of ADHD is the DAT knockout mouse (DAT-KO). The genetically engineered DAT-KO mice lack functional DAT and show marked spontaneous hyperactivity and impaired learning and memory, compared to wild types (Gainetdinov & Caron, 2000, 2001). Striatal extracellular DA levels in the DAT-KO mice are elevated 5-fold, but electrically-stimulated DA release is decreased (Gainetdinov, Jones, & Caron, 1999a). Postsynaptic D1 and D2 receptors are downregulated approximately 50% (Gainetdinov et al., 1999a). High doses of stimulants have been shown to reduce hyperactivity, but given that stimulants do not alter levels of extracellular DA in these mice, this behavioral effect appears to be serotonergically rather

than dopaminergically mediated (Gainetdinov et al., 1999b). DAT-KO mice have been criticized as a model because they show abnormalities not found in ADHD, such as growth retardation and premature death (Gainetdinov et al., 1999a; Giros et al., 1996). DAT knockdown mice, expressing 10% of the wild-type DAT, do not show the growth retardation phenotype, but do display hyperactivity in novel environments (Zhuang et al., 2001). However, they also display sequential stereotypy, which has been argued to make them a more suitable model of Tourette's or obsessive compulsive disorder than for ADHD (Berridge, Aldridge, Houchard, & Zhuang, 2005).

Another hypodopaminergic model is the Naples High Excitability (NHE) rat. The NHE is a genetic model characterized by hyperexcitability in response to novelty and deficits in visuospatial attention (Aspide, Gironi Carnevale, Sergeant, & Sadile, 1998; Papa et al., 2000), as well as hyperfunctioning of the mesocorticolimbic DA system (Aspide et al., 1998; Papa et al., 2000; Viggiano, Grammatikopoulos, & Sadile, 2002). Compared to wild type controls, NHE have larger DA neurons in the VTA and higher levels of tyrosine hydroxylase in the VTA and substantia nigra, as well as increased DAT and decreased D1 receptor density in the PFC (Viggiano et al., 2002; Viggiano & Sadile, 2000). The limitations of this model include the lack of data on behavioral impulsivity and on the effect of stimulants on the reported deficits (Sontag et al., 2010).

Finally, male transgenic mice expressing a human mutant thyroid hormone receptor are another animal model with a hyperfunctioning DA system, showing increased striatal DA turnover (Siesser, Zhao, Miller, Cheng, & McDonald, 2006). This thyroid receptor mutation might lead to DA system abnormalities because thyroid hormone regulates the development of this and other neurotransmitter systems (Siesser et

al., 2006). These mice have slow reaction times in an operant task, hyperactivity in familiar environments, impaired extinction, and inability to delay responses (Siesser et al., 2006). The hyperactivity is reduced by methylphenidate (Siesser et al., 2006). The main criticism of this model is the lack of evidence for the role for the thyroid system in ADHD. However, many children with elevated levels of thyroid stimulating hormone display symptoms of ADHD (Burd et al., 2003; Sontag et al., 2010).

1.2.4 In-Vivo Investigations of DA Transmission in ADHD

The most direct approach to investigating the DA system in the pathophysiology of ADHD is the in-vivo imaging investigation of the dopamine system in individuals with ADHD.

1.2.4.1 DA synthesis and metabolism. Studies of DA synthesis in ADHD have yielded inconsistent findings. An [18F]fluorodopa PET study reported evidence of higher uptake (indicating more synthesis) in the midbrain of children with ADHD (Ernst et al., 1999), while another [18F]fluorodopa study reported reduced prefrontal uptake in adults (Ernst, Zametkin, Matochik, Jons, & Cohen, 1998). A study in adolescents using L-[11C]-DOPA suggested decreased uptake throughout the brain, especially in the midbrain (Forssberg, Fernell, Waters, Waters, & Tedroff, 2006). This inconsistency might reflect differences in ligand properties and sample characteristics, such as age and the amount of stimulant treatment history.

Studies of cerebral DA metabolism have focused on cerebrospinal fluid (CSF) levels of homovanillic acid (HVA) (a major catecholamine metabolite) and have not yielded compelling evidence of altered HVA levels in ADHD. Three studies reported no

patient-control differences (Cohen, Caparulo, Shaywitz, & Bowers, 1977; Reimherr, Wender, Ebert, & Wood, 1984; Shetty & Chase, 1976) and one suggested lower HVA levels in children with minimal brain dysfunction (Shaywitz, Cohen, & Bowers, 1977), although methodological issues caution against drawing firm conclusions from these earlier studies. Two studies reported positive correlations between hyperactivity levels and CSF HVA (Castellanos et al., 1994a; Castellanos et al., 1996a), and in one higher HVA concentrations predicted a superior treatment response to stimulants (Castellanos et al., 1996a). Notably, decrease in CSF HVA correlated with symptom improvement on *d*-AMPH (Shetty & Chase, 1976).

1.2.4.2 Dopamine transporter. Investigations of striatal DA transporter density in ADHD using PET and single photon emission computed tomography (SPECT) have yielded mixed findings, with some studies reporting elevated DAT levels in ADHD participants (Cheon et al., 2003; Dougherty et al., 1999; Dresel et al., 2000; Krause, Dresel, Krause, Kung, & Tatsch, 2000; Larisch et al., 2006; Spencer et al., 2005), others reporting decreased DAT levels (Hesse, Ballaschke, Barthel, & Sabri, 2009; Volkow et al., 2007a; Volkow et al., 2010), and yet others reporting no group differences (Jucaite, Fernell, Halldin, Forssberg, & Farde, 2005; Van Dyck et al., 2002). Although there are differences across studies in terms of radioligands used and sample characteristics, such as the age group of participants, characteristics of the control group (some studies used convenience control samples), and the amount of previous stimulant treatment history and the duration of stimulant wash-out, these differences are not systematically related to the direction of findings. The two largest studies in treatment-naïve adults from the same

group both reported decreased [^{11}C]cocaine binding to DAT in ADHD participants, although in different striatal sub-regions (Volkow et al., 2007a; Volkow et al., 2010). The earlier study reported decreased binding in the caudate of ADHD participants, which was significantly correlated with self-reported symptoms of inattention. However, the direction of that association was opposite to that of the group difference, with greater inattention associated with more binding (Volkow et al., 2007a). The later study reported decreased DAT binding in the ventral striatum of ADHD participants, with more severe inattention symptoms predicting less binding (Volkow et al., 2009). Thus within studies and within labs, direction of difference in DAT binding is inconsistent.

1.2.4.3. D2/ D3 receptor occupancy. A number of studies have examined striatal D2 receptor availability in ADHD. Because DRD2 occupancy reflects competition between the radioligand and endogenous DA for the D2 receptors (explained later), altered DRD2 availability in ADHD could reflect either an alteration in D2 receptor density, an alteration in endogenous DA levels, or a combination of both. Studies of DRD2 availability in ADHD have produced inconsistent findings. Two earlier studies reported increased DRD2 availability: one reported higher DRD2 binding in children with ADHD compared to that previously reported in young healthy adults (Ilgin et al., 2001); the other showed a positive association between DRD2 availability and cognitive measures of inattention in adolescents with a history of perinatal cerebral ischaemia suffering from attention deficit (Lou et al., 2004). However, two recent large studies reported decreased D2 receptor availability in adults with ADHD in the left caudate (Volkow et al., 2007b), as well as in the ventral striatum and the midbrain (Volkow et al.,

2009). The disagreement in the direction of findings may be due to differences in age groups studied, as well as the lack of adequate control groups in the two earlier studies.

1.2.4.4 Stimulant-induced DA response. Measurement of stimulant-induced change in radioligand binding has been used to estimate changes in concentration of endogenous extracellular DA in response to the stimulant (explained later). To date, two PET studies, both using [^{11}C]raclopride, have examined stimulant-induced change in D2 receptor availability in ADHD, and have reported conflicting findings. A study of 9 stimulant treatment naïve adolescents with ADHD reported a significant association between MPH-induced decreases in [^{11}C]raclopride binding and scores on a cognitive measure of inattention and impulsivity, with the higher inattention and impulsivity indices predicting greater MPH-induced increases in endogenous DA (Rosa-Neto et al., 2005). However, a subsequent larger study reported a blunted MPH-induced DA response in 19 stimulant treatment naïve adults with ADHD compared to 24 controls, with more severe symptoms of inattention predicting smaller MPH-induced changes in [^{11}C]raclopride binding in ADHD participants (Volkow et al., 2007b). Thus, the data on the response of the striatal DA to a stimulant challenge in ADHD are inconsistent.

1.2.5 Models of DA Neurotransmission in ADHD

Models of DAergic transmission in ADHD have been proposed in an attempt to elucidate the nature of DAergic alterations. Probably the most comprehensive model of DA transmission in ADHD is the model proposed by Grace (Grace, 2001), which postulates that ADHD is characterized by low striatal dopaminergic tone, coupled with an augmented phasic DA release. According to this model, striatal DAergic tone is reduced

in ADHD due to insufficient glutamatergic stimulation by the PFC of the striatal DA neurons. The low DA tone is proposed to result in an insufficient stimulation of D2 somatodendritic and terminal autoreceptors, which in turn leads to a reduced inhibition of DA synthesis, DA neuronal spike activity, and spike-dependent DA release. Stimulants are proposed to exert their therapeutic effects by elevating the DA tone. In the absence of a stimulant, the DA released into the synapse during spike bursts is cleared from the synaptic cleft by the DAT before any substantial amount can escape into the extrasynaptic space. The blockade and/ or reversal of the transporter by stimulants allows the DA released during spike firing to escape into the extracellular space and stimulate the D2 autoreceptors. Since DA produces a proportionately greater response in the more sensitive D2 autoreceptors than in postsynaptic D2 receptors (Skirboll et al., 1979), low doses of stimulants are proposed to have a more pronounced effects on DA tone than on the phasic DA release. Although there is an initial peak in phasic firing following stimulant administration, the phasic firing is proposed to be subsequently down-modulated by the stimulation of D2 autoreceptors due to the overflow of the extracellular DA.

While Grace's model postulates a subcortical locus of DAergic dysfunction in ADHD, others have focused on catecholaminergic function at the level of the PFC. One such model maintains that ADHD symptoms, result from insufficient stimulation of α_{2A}– adrenoreceptors and D1 receptors in the PFC (Arnsten, 2006). This model finds support in non-human primate findings that blockade of these receptors produces a behavioral profile similar to ADHD, including locomotor hyperactivity, impulsivity, and working memory deficits. It is also in agreement with evidence pointing to PFC dysfunction in

ADHD (reviewed earlier). Stimulants are proposed to exert their therapeutic effects by indirectly increasing endogenous stimulation of the α_{2A}–adrenoreceptors and D1 receptors receptors in the PFC, thus improving prefrontal regulation of behaviour and attention.

Another model of DA dysfunction in ADHD (Volkow, Wang, Fowler, & Ding, 2005b) postulates abnormally low levels of extracellular DA, without making a distinction between tonic and phasic DA or specifying the locus of the dysfunction in the brain. It suggests the abnormally low levels of extracellular DA result in lower subjective salience of relevant events, leading to inattention and distractibility. Stimulants are proposed to exert their therapeutic effects by amplifying DA responses to salient events and thus improving attention to relevant stimuli and decreasing distractibility. This model finds indirect support in the data from PET imaging studies of the striatal DA system showing methylphenidate-induced decreases in radioligand binding (suggestive of increases in the levels of extracellular DA) when the drug is coupled with salient but not with neutral stimuli (Volkow et al., 2004; Volkow et al., 2002a).

1.2.6 Other Neurotransmitter Systems

Although the role of the DA system in the pathophysiology of ADHD has received the most attention, other neurotransmitter systems may also be involved. The fact that stimulants interact with the NE transporter in much the same way that they interact with the DAT, suggests the possibility of noradrenergic involvement. This is further supported by the clinical efficacy of 'non-stimulant' medications, such as

atomoxetine, which shows preferential activity at the NET (Solanto, 1998; Viggiano, Ruocco, Arcieri, & Sadile, 2004). In addition, as mentioned earlier, alterations to prefrontal noradrenergic transmission in animal models can result in cognitive and behavioral impairments mimicking those in ADHD (Arnsten, 2006; Arnsten & Dudley, 2005). Glutamatergic transmission and interactions between the DA and glutamate systems might also play an important role, because DA is known to modulate glutamatergic transmission and vice versa, and there is extensive neuroanatomical connectivity between DA and glutamate neurons, including convergence in the midbrain, the cortex, and the striatum (Sesack & Grace, 2010). Studies investigating glutamate metabolites in ADHD using magnetic resonance spectroscopy (MRS) have reported alterations in levels of glutamate metabolites in children and adults with ADHD, although the findings have not been entirely consistent (Perlov et al., 2009).

1.3 In Vivo Measurement of Dopaminergic Transmission in Humans

In vivo neuroreceptor imaging with PET and SPECT provides a non-invasive method of measuring fluctuations in synaptic concentrations of neurotransmitters in the human brain. PET imaging with [^{11}C]raclopride, the radiotracer used in the present thesis, is a well established method of measuring changes in synaptic DA concentrations consequent to pharmacological or behavioral challenges (for review see Laruelle, 2000).

[^{11}C]raclopride is created by synthetically attaching an unstable neutron deficient isotope of carbon, which undergoes nuclear decay through positron emission, to molecules of raclopride. Raclopride is a substituted benzamide and a high affinity D2/D3 receptor antagonist. Due to its low nanomolar receptor affinity and fast dissociation rate,

raclopride is sensitive to competition from endogenous DA for D2/D3 receptors (Köhler, Hall, Ögren, & Gawell, 1985; Seeman, Guan, & Niznik, 1989). The competition model assumes that changes in levels of endogenous DA are translated into changes in the occupancy of D2/D3 receptors by [^{11}C]raclopride or its binding potential (BP) (Laruelle, 2000; Seeman et al., 1989). Consistent with the competition model, simultaneous *in vivo* microdialysis and PET experiments in non-human primates have demonstrated a linear relationship between microdialysis measurements of DA release and PET measurements of decreases in tracer BP in response to a *d*-AMPH challenge (Breier et al., 1997; Laruelle et al., 1997). Each percent decrease in [^{11}C]raclopride BP was estimated to correspond to a 44% increase in extracellular DA, with a 0.2 mg/kg dose of *d*-AMPH and to a 64% DA increase with a 0.4 mg/kg dose of *d*-AMPH (Breier et al., 1997). Thus, large increases in extracellular DA (400% - 1500%) are associated with relatively small decreases in radiotracer binding (10% - 38%) (Laruelle, 2000). Pharmacological challenges that increase DA through mechanisms including DAT blockade result in much larger DA increases measured by microdialysis than challenges that increase DA without affecting DAT (e.g. nicotine). Yet, both types of challenges result in similar changes in [^{11}C]raclopride BP (Breier et al., 1997; Freedman, Rock, Roberts, Cornblatt, & Erlenmeyer-Kimling, 1998; Tsukada et al., 1999). It is proposed that challenge-induced changes in [^{11}C]raclopride BP primarily reflect synaptic, rather than extrasynaptic DA increases (Laruelle, 2000). This is based on observed discrepancies across pharmacological challenges in their ability to affect (primarily extrasynaptic) microdialysis versus PET [^{11}C]raclopride measurements of changes in endogenous DA.

Consistent with the competition model, reductions in [^{11}C]raclopride BP relative to baseline have been reliably demonstrated in response to pharmacological challenges know to elevate extracellular DA, such as *d*-AMPH, methylphenidate, cocaine, nicotine, and ketamine (Barrett, Boileau, Okker, Pihl, & Dagher, 2004; Boileau et al., 2003; Breier et al., 1998; Breier et al., 1997; Cox et al., 2009; Leyton et al., 2002; Schlaepfer, Pearlson, Wong, Marenco, & Dannals, 1997; Volkow et al., 2005b; Volkow et al., 1994). Decreases in [^{11}C]raclopride BP have also been observed with behavioral manipulations expected to result in DA release, such as experimental stress challenge, monitory reward tasks, playing a video game, and feeding (Koepp et al., 1998; Pruessner, Champagne, Meaney, & Dagher, 2004; Small, Jones-Gotman, & Dagher, 2003; Zald et al., 2004). Conversely, increases in [^{11}C]raclopride binding have been observed following dopamine depletion using reserpine and an acute phenylalanine/tyrosine depletion procedure (Ginovart, Farde, Halldin, & Swahn, 1997; Leyton et al., 2004).

Nonetheless, the available data are not entirely consistent with the competition model since challenge-induced changes in BP are not completely accounted for by changes in levels of endogenous DA. For example, decreases in [^{11}C]raclopride in response to challenges have not been observed to exceed 50% (Laruelle, 2000). This *ceiling effect* has been explained by invoking the affinity state configuration of D2/D3 receptors. D2/D3 receptors exist in high and low affinity states for agonists, with approximately 50% of the receptors contributing to each state *in vitro* (George et al., 1985; Richfield, Penney, & Young, 1989; Seeman & Grigoriadis, 1987; Sibley, De Lean, & Creese, 1982; Zahniser & Molinoff). While the antagonist raclopride binds with equal affinity to the D2/D3 receptors in both their high and low affinity states, DA only binds

to high affinity receptors, which limits the competition model to only the high affinity DA receptors. Furthermore, the observed linear relationship between *d*-AMPH-induced changes in extracellular DA levels and the [^{11}C]raclopride (described above) is not reliably present within individual subjects (Breier et al., 1997). This suggests that changes in [^{11}C]raclopride binding might not solely reflect changes in levels of extracellular DA, or that both measurement methods are associated with a substantial amount of noise. One potential factor contributing variance to changes in radiotracer binding to D2/D3 receptors is G-protein-coupled receptor internalization in the presence of a DA receptor agonist (Vickery & von Zastrow, 1999). Endocytosis in response to DA release following a challenge can decrease the availability of externalized receptors and has been found to contribute to *d*-AMPH-induced decreases in [^{11}C]raclopride binding (Sun, Ginovart, Ko, Seeman, & Kapur, 2003).

1.4 Hypotheses

The primary purpose of the present thesis was to investigate striatal DA function in treatment-naïve adults with ADHD using the [^{11}C]raclopride PET method with a *d*-AMPH challenge. Based on the most comprehensive model to date of DA transmission in ADHD (Grace, 2001), we expected to find evidence of augmented synaptic DA release (proposed to result from low DA tone) in ADHD participants relative to healthy controls following the *d*-AMPH challenge. Given that phasic DA release results in synaptic DA levels that are orders of magnitude higher than DA tone, we expected that the augmented phasic DA release in the ADHD group would be reflected in larger decreases in [^{11}C]raclopride BP than would be seen in healthy controls. Given that cardinal symptoms

of ADHD represent abnormal levels of functioning in domains where there is much inter-individual variability in both those with ADHD and controls (such as activity levels, impulsivity, and attention), we also hypothesized that levels of ADHD symptomatology would be related to the magnitude of changes in [^{11}C]raclopride BP, with higher symptom levels predicting greater decreases in BP.

Since a wealth of both direct and indirect evidence points to the PFC as a significant locus of dysfunction in ADHD, our secondary purpose was to relate striatal DA transmission to indices of frontal function and integrity. We administered a neurocognitive battery consisting of tasks that are sensitive to both the prefrontal function and DAergic transmission. We expected that ADHD participants would perform more poorly than controls on this neurocognitive battery, and that performance on neurocognitive tasks producing impairments in ADHD participants would be associated with *d*-AMPH-induced changes in [^{11}C]raclopride BP, with poorer performance predicting larger decreases in BP. We hypothesized that performance on tasks of working memory, set shifting, and planning, which is primarily mediated by regions of the dorsolateral prefrontal cortex, would be mainly associated with DA function in the associative striatum to which dorsolateral prefrontal cortex projects (Fuster, 1999; Haber, 2010; Lichter & Cummings, 2001). We expected the effects of rewards and punishments on performance, mediated by the ventrolateral PFC, to be preferentially associated with DA function in the ventral (limbic) striatum (Fellows, 2007; Haber, 2010; Lichter & Cummings, 2001). According to a recent account of the neural bases of inhibitory function, response inhibition emerges as a result of representation and maintenance of abstract information by distributed prefrontal substrates involved in the task at hand

(Munakata et al., 2011). One of our inhibitory tasks, the stop signal paradigm, has been found to engage ventrolateral and dorsomedial prefrontal cortex (Aron et al., 2003; Aron & Poldrak, 2006; Aron, 2007), whereas the other inhibitory task, the antisaccade, activates the dorsolateral prefrontal cortex, anterior cingulate, and the precentral gyrus [Everling & Fischer,1998; Munoz & Everling, 2004; Hutton & Ettinger, 2006; Polli et al., 2005). Because these regions project to the limbic, associative and sensorimotor striatum, we hypothesized that performance on our inhibitory tasks would be associated with DA release in the striatum generally.

In addition, given the multitude of ascending and descending projections between the frontal cortex and the striatum, involving the DA system, and a wealth of evidence suggesting that the frontal cortex modulates striatal DA release (Jackson, Frost, & Moghaddam, 2001; Karreman & Moghaddam, 1996; Kolachana, Saunders, & Weinberger, 1995; Murase, Grenhoff, Chouvet, Gonon, & Svensson, 1993; Taber & Fibiger, 1995; You, Tzschentke, Brodin, & Wise, 1998), we performed an exploratory analysis of the relationship between prefrontal cortical thickness and *d*-AMPH-induced change in striatal [^{11}C]raclopride BP. Cortical thickness has been considered an index of functional integrity of the cortex, with thicker cortex in healthy adults typically associated with better cognitive performance (Dickerson et al., 2008; Hartberg et al., 2010; Narr et al., 2007; Walhovd et al., 2006; Westlye, Grydeland, Walhovd, & Fjell, 2011). Given that disturbances of the frontal cortex have been found to result in elevated measures of subcortical DA transmission (Bertolino et al., 2000; Jaskiw et al., 1990; Meyer-Lindenberg et al., 2002; Pycock et al., 1980), we hypothesized that thinner frontal cortex would be associated with more pronounced *d*-AMPH-induced striatal DA release.

Because of reported alterations in frontal cortical function and development in ADHD (reviewed earlier), we also expected that the relationship between frontal cortical thickness and DA release may differ as a function of group.

Finally, we hypothesized that the magnitude of *d*-AMPH-induced change in [^{11}C]raclopride BP would be related to the DAT gene polymorphisms, such that participants carrying the 10 repeat VNTR allele variant of the DAT1 gene would show greater *d*-AMPH-induced changes in striatal [^{11}C]raclopride BP (Joober et al., 2006; Lott et al., 2004; Stein et al., 2005).

CHAPTER 2:

METHODS

2.1 Participants

Thirty adult males (ADHD n=15, Control n=15) completed the study and were included in the analyses. Four additional participants completed the study but could not be included, one control due to a structural anomaly found in his striatum, and three others (1 control) due to excessive movement artifact or improper positioning in the scanner. Two people who began the study could not complete it due to equipment failure. The ages of the ADHD participants ranged from 18-43 (M = 29.87, SD = 8.65) and for the controls from 18-42 (M = 24.87, SD = 7.28). The ADHD participants were recruited through ADHD clinics in the Montréal area, as well as through community advertisements. The diagnosis of ADHD, as evidenced by the presence of at least 6 of 9 inattention symptoms (with or without 6 of 9 hyperactivity/ impulsivity symptoms) since childhood, was ascertained by one of three psychiatrists of the participating clinics. Healthy controls were recruited through community advertisements. Participants were excluded from the study for: any current or past DSM-IV axis I disorder other than ADHD and a history of a single mild major depressive episode (present in 2 of 15 ADHD participants). Additional exclusion criteria were: first degree family history of substance dependence; current use of psychotropic medications; Beck Depression Inventory Score > 13, estimated IQ < 80; neurological disorders (e.g. Tourette's); head injury with loss of consciousness > 5 minutes; history of cardiovascular or any other physical disorder that might be aggravated by participation in the study or might complicate interpretation of the results; and a positive urine toxicology screen (cocaine, opiates, phencyclidine, barbiturates, benzodiazepines, Δ^9-tetrahydrocannabinol, amphetamines) as ascertained by the Triage Drugs of Abuse urine test device (Biosite Inc, San Diego). In addition, control

participants were excluded for a history of ADHD in a first-degree relative. Fourteen of the 15 ADHD participants were naïve to stimulant treatment, and one had received a 6-month methylphenidate trial 2 years prior to his participation. All ADHD and control participants were free of stimulant exposure for at least 24 months prior to their participation; lifetime stimulant exposure did not exceed 2 uses for any of the participants except the one who underwent the methylphenidate trial (Table 1). All participants gave written informed consent prior to their enrollment in the study.

	Controls (n = 15)	**ADHD (n = 15)** 5 Combined/ 10 Inattentive	N	*p*
Age	24.87 ± 7.29	29.87 ± 8.65	15, 15	.17
Handedness (# right-handed)	15	13	15, 15	.54
Estimated Full Scale IQ (WAIS-R, WAIS-III)	116.83 ± 16.07	107.13 ± 12.78	13, 15	.06
Father's SES (Hollingshead, 1958)	2.85 ± 1.17	2.93 ± 1.22	14, 15	.85
Years of Education	17.4 ± 3.58	16.20 ± 3.63	15, 15	.23
CAARS (t-scores)				
Inattention/ Memory Problems	43.77 ± 7.41	74.00 ± 10.49	13, 15	< .0001*
Hyperactivity/ Restlessness	43.76 ± 6.08	62.27 ± 12.93	13, 15	< .0005*
Impulsivity/ Emotional Lability	42.92 ± 9.42	58.53 ± 11.28	13, 15	< .0005*
Problems with Self-Concept	43.08 ± 5.89	63.07 ± 7.64	13, 15	< .0005*
DSM-IV Inattention	48.73 ± 12.49	84.4 ± 8.73	13, 15	< .0005*
DSM-IV Hyperactivity	44.69 ± 8.54	68.13 ± 14.48	13, 15	< .0005*
DSM-IV Total	46.69 ± 11.64	81.47 ± 10.30	13, 15	< .0005*
ADHD Index	42.00 ± 8.45	66.86 ± 8.74	13, 15	< .0005*
BDI at intake	1.57 ± 2.17	6.04 ± 3.86	14, 14	<.0005*
Drug exposure history				
Stimulants (# lifetime uses)	.07 ± .26	12.33 ± 46.39	15, 15	.33
Marijuana (# lifetime uses)	20.20 ± 34.72	49.27 ± 90.07	15, 15	.94
Nicotine (# lifetime uses)	1747.36 ± 4117	1729.43 ± 5347.18	14, 14	.45

Table 2-1. Sample characteristics.

2.2 Procedure

2.2.1 Screening

Participants' eligibility for the study was determined using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID I; (First, Spitzer, Gibbon, & Williams, 1996)), supplemented with a semi-structured family history interview. The Beck Depression Inventory (BDI) (Beck & Steer, 1987) was used in addition to the SCID I to

ascertain current level of any subclinincal depressive symptomatology. For 21 participants (10 ADHD and 11 controls), the IQ was estimated using a 7-subtest version of the Wechsler Adult Intelligence Scale – III (WAIS-III) validated for use in a neuropsychological populations (Pilgrim, Meyers, Bayless, & Whetstone, 1999). For the remaining participants, the IQ was estimated using a 4-subtest version of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) (Reynolds, Willson, & Clark, 1983). In addition, all participants underwent a comprehensive physical examination, including blood analysis and EKG, in order to screen for any physical contraindication to participation in the study.

2.2.2 Diagnostic Procedure for Adult ADHD

The diagnosis of adult ADHD was made based on a clinical interview and questionnaires (see below) completed by the participant along with two informants, one of whom knew the participant well in childhood (e.g. a parent or a older sibling), and another who was close to the participant at the time of the study (e.g., a spouse or a significant other). ADHD symptoms in childhood were measured using self-report and informant versions of the Barkley's Childhood Symptom Scale (Barkley & Murphy, 1998), an 18-item retrospective measure of DSM-IV ADHD symptoms during the ages of 5 to 12 years, and a well-validated 25-item subset of the 61-item Wender Utah Rating Scale (WURS) (Ward, Wender, & Reimherr, 1993), which is a retrospective measure of childhood ADHD symptoms in adults. Current ADHD symptoms were measured using the Barkley's Current Symptom Scale (Barkley & Murphy, 1998), an 18-item measure of DSM-IV ADHD symptoms within the past 6 months, and the Conners Adult ADHD

Rating Scale (CAARS) Long Version (Conners, Erhart, & Sparrow, 1999), which is a 66-item measure of ADHD symptoms in adults with age- and sex-specific norms and the following symptom domains: inattention & memory problems, hyperactivity/restlessness, impulsivity/emotional lability, and problems with self-concept. Both measures of adult symptoms were completed by the participant and an informant. Because the CAARS provides a normative view of ADHD and related symptoms, this questionnaire was also completed by the control participants for the purposes of between-group comparison and correlation with amphetamine-induced DA response.

2.2.3 Neurocognitive Testing

Participants completed a battery of neurocognitive tests for the purpose of characterizing the neurocognitive profile of the ADHD sample and to evaluate performance in relation to amphetamine-induced DA release. The testing was carried out a minimum of 24h from the time of either PET scan (to avoid possible effects of stimulant administration during the scan) using computerized and written neurocognitive tests. With the exception of the antisaccade task (see task description for information on the apparatus), all computerized tasks were administered using a Toshiba Satellite A70 laptop with a 15-inch screen. Each participant was seated comfortably in a quiet room with an investigator who explained and administered the tasks. The cognitive testing session lasted approximately 2.5 hours, with a break in the middle. The battery (detailed below) consisted of tasks assessing inhibitory function, reactivity to reward and punishment, working memory, cognitive flexibility, planning and problem-solving, and motor hyperactivity.

2.2.3.1 Stop-Signal Reaction Time Task. The stop-signal paradigm (Logan, Cowan, & Davis, 1984; Williams, Ponesse, Schachar, Logan, & Tannock, 1999) assesses inhibitory control by measuring the time required to stop a planned response, i.e. stop signal reaction time (SSRT). Go signal reaction times and within-subject reaction time variability on this task have been suggested to reflect attentional functioning, such as freedom from distractibility (Castellanos & Tannock, 2002). The SSRT task involves two concurrent components: the Go component and the Stop component. The Go component is a choice reaction time task, which requires participants to respond as quickly as possible (with a left- or right-mouse button press) to the on-screen presentation of an X or O. On 25% of the trials, the stop-signal (a tone) instructs the participant to withhold the response. The participant's success in withholding the response is posited to depend on the latency of the inhibitory response to the stop-signal relative to the reaction time to the go-signal (Logan et al., 1984). The delay between the onset of the go stimulus and the stop signal is varied with an algorithm that tracks the participant's responses to ensure that the participant successfully inhibits responses of 50% of Stop trials. This approach is thought to control for between-subject variations in reaction time (Logan, 1994). The Stop-Signal task consisted of eight blocks of 32 trials each preceded by 2 practice blocks.

A recent meta-analytic review of 33 studies found longer Go signal reaction times, longer SSRTs and higher RT variability in children and adults with ADHD compared to matched controls (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005). MPH has been reported to improve SSRT, without significantly affecting Go RT, in both

children (DeVito et al., 2009; Konrad, Gunther, Hanisch, & Herpertz-Dahlmann, 2004; Lijffijt et al., 2006) and adults with ADHD (Aron, Dowson, Sahakian, & Robbins, 2003).

2.2.3.2 Antisaccade. The antisaccade task (Hallett, 1978) is an oculomotor task that measures inhibitory control. Saccades (or quick shifts of gaze) to suddenly appearing visual targets in the periphery are considered reflexive (Leigh & Kennard, 2004). The antisaccade task requires the participant to inhibit a reflexive saccade to the peripheral target and instead generate a saccade to its mirror location in the opposite hemifield – an antisaccade (Figure 3). An antisaccade error, or a reflexive saccade towards the target, is the measure of inhibitory failure. In addition, the antisaccade task provides a measure of voluntary oculomotor control, since it requires a voluntary eye movement to an approximate location without the benefit of a visual target. This volitional component is associated with increased response latencies compared to reflexive saccades (i.e. prosaccades) (Everling & Fischer, 1998).

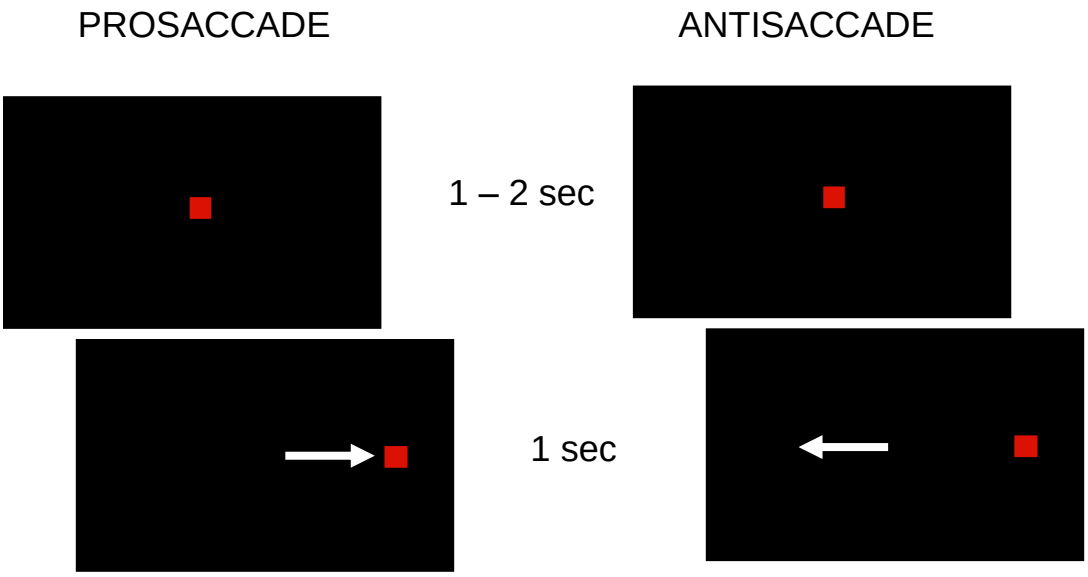


Figure 2-1.
Schematic of the antisaccade task. The red square represents the target (not to scale). The white arrow depicts the required eye movement.

Participants completed two prosaccade (PS) and two antisaccade (AS) blocks of 30 trials each, preceded by one practice block of each task. Blocks were presented in palindromic order (PS-AS-AS-PS, or AS-PS-PS-AS), counterbalanced across participants in each group. Stimuli were identical for prosaccades and antisaccades; only the instructions differed. Each trial began with a central fixation target (a red square subtending 0.5° x 0.5° of visual angle) presented for a period of 1 to 2 seconds (generated randomly for each trial). The offset of the central fixation coincided with the presentation of an identical peripheral target at 12° left or right of centre (direction pseudorandomized across trials within each block), which remained on for 1000 ms.

Participants were seated at 57 cm from a 17-inch ViewSonic LCD monitor running at 60 Hz, on which the stimuli were presented. Eye movements were monitored using the Eyelink II high-speed (500 Hz) infrared pupil tracker (SR Research, Osgoode,

ON). Recordings were made from the dominant eye. Prior to each block, a three-point calibration was performed.

Higher antisaccade error rates, as well as higher rates of anticipatory saccades, have been consistently reported in children (Goto et al., 2010; Karatekin, 2006; Klein, Raschke, & Brandenbusch, 2003; Loe, Feldman, Yasui, & Luna, 2009; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Munoz, Armstrong, Hampton, & Moore, 2003; O'Driscoll et al., 2005) and adults with ADHD (Carr, Nigg, & Henderson, 2006; Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Munoz et al., 2003; Nigg, Butler, Huang-Pollock, & Henderson, 2002a). In addition some studies have reported increased antisaccade latencies in both children (Karatekin, 2006; Klein, Fischer, Fischer, & Hartnegg, 2002; Mostofsky et al., 2001; Munoz et al., 2003) and adults with ADHD (Carr et al., 2006; Munoz et al., 2003). Similar findings have been reported in Parkinson's disease, a population with low DA levels (Amador, Hood, Schiess, Izor, & Sereno, 2006; Briand, Strallow, Hening, Poizner, & Sereno, 1999; Chan, Armstrong, Pari, Riopelle, & Munoz, 2005). Pharmacological manipulations that increase the levels of DA have been reported to affect antisaccade performance (Allman et al., 2010; Duka & Lupp, 1997).

2.2.3.3 Go/No-Go discrimination learning. The computerized Go/No-Go Discrimination Learning task (Iaboni, Douglas, & Baker, 1995) measures the effects of reward and punishment on the ability to inhibit responding.

In each block of this task, participants were presented with eight two-digit numbers in a random order over 80 trials (10 times each). Half of these numbers were "active" stimuli, requiring a mouse button press response, while the other half were

"passive" stimuli requiring a lack of response. Participants were not informed which stimuli were "active" and which were "passive", but were instructed to learn this by trial and error using the feedback. The task included four blocks with different sets of stimuli in each block. There were four different feedback conditions that crossed active and passive responses with feedback for correct and incorrect responses in a 2 x 2 design. In the Reward-Punishment (Active Feedback) condition, only active responses (mouse clicks) received feedback: correct mouse click responses to active stimuli were rewarded (win 10 cents), and incorrect mouse clicks to passive stimuli (commission errors) were punished (lose 10 cents). Feedback was not provided when the active response was withheld. In the Reward-Reward (Correct Feedback) condition, correct responses to active stimuli and correct non-responses to passive stimuli were rewarded; there was no punishment for incorrectly responding or incorrectly withholding response. In the Punishment-Punishment condition (Incorrect Feedback), incorrectly withholding a response to an active stimulus was punished and incorrectly responding to passive stimuli was punished. As correct behavior was not rewarded, participants could only lose money. Finally, in the Punishment-Reward condition (Passive Feedback), participants received feedback only on trials in which they withheld responses. They were rewarded for correct withholding and punished for incorrect withholding of responses but received no feedback on trials in which they made an active response, even when the active response was correct. Each condition included a pretreatment phase of 12 unscored trials, during which the participants could learn by trial and error which stimuli were "active" and which were "passive".

Commission errors on the Go/No-Go Discrimination Learning task are a measure of disinhibition. Omission errors could reflect deficits in attending to or encoding the stimuli or in maintaining them in working memory, or a response bias toward passivity in the face of uncertainty. Boys with ADHD have been found to make more commission errors than controls irrespective of the condition (Iaboni et al., 1995). Populations that are considered disinhibited, such as psychopaths, extraverts and those with Cluster B personality disorders, have been found to make more commission errors than controls in the Reward-Punishment (Active Feedback) and Punishment-Reward (Passive Feedback) conditions, but not in the Reward-Reward (Correct Feedback) or Punishment-Punishment (Incorrect Feedback) conditions (Leyton et al., 2001; Newman, 1987; Newman & Kosson, 1986; Newman, Patterson, Howland, & Nichols, 1990; Newman, Widom, & Nathan, 1985; Patterson, Kosson, & Newman, 1987), which may reflect tendency to respond to rewards combined with a difficulty withholding responding to learn a task. Acute phenylalanine/tyrosine depletion, which lowers resting striatal DA levels (Leyton et al., 2004) has been reported to increase commission errors in the conditions where correct active responses were rewarded (Reward-Punishment and Reward-Reward) (Leyton et al., 2007).

2.2.3.4 Concrete and Abstract computerized self-ordered working memory tasks. These tasks are computer analogs of the 12-item self-ordered pointing tasks developed by Petrides & Milner (1982) (Petrides & Milner, 1982) to assess the planning and monitoring aspects of working memory.

Participants are presented with 12 consecutive arrays of the same 12 stimuli, but the position of each stimulus varies from one array to the next. The participant's task is to select a stimulus in each array that the participant has not yet selected in any of the previous arrays (each stimulus is to only be selected once). In the "concrete" version of the task the stimuli are easily-recognized objects, such as a bus or a light-bulb, whereas in the "abstract" version of the task, the stimuli are abstract images that cannot not easily be given verbal descriptors. The participants were not permitted to select the same stimulus position on consecutive trials in order to prevent use of a spatial strategy and were asked to refrain from rehearsing aloud as they completed the tasks.

Meta-analytic studies of neurocognitive functions in ADHD vs. controls have found spatial working memory to be associated with some of the highest effect sizes (Nigg, 2005), and visual-spatial working memory deficits have been proposed as an endophenotype for ADHD (Castellanos & Tannock, 2002). Visual-spatial working memory has been demonstrated to be sensitive to DA modulation in fronto-striatal circuits (Mattay et al., 2000; Mattay et al., 2002; Sawaguchi & Goldman-Rakic, 1991; Williams & Goldman-Rakic, 1995).

2.2.3.5 Trail-making test. The trail-making test (Reitan, 1958) is a measure of cognitive flexibility.

The task has two components. In part A, participants are required to quickly trace a path connecting a series of consecutive numbers (one to twenty-five) positioned randomly on a page. In part B, participants are required to trace a path alternating between 12 numbers and 12 letters, in the ascending order (i.e. 1, A 2, B etc.). Both A

and B tap into spatial scanning ability and visuomotor speed. Part B adds the requirement to rapidly shift mental sets. Participants were instructed to connect the numbers (and letters) using a continuous line, and their performance was timed with a stopwatch. Prior to starting the task, the participants were given 8-item practice versions of parts A and B to ensure that they understood the task.

Children and adults with ADHD have been found to have longer completion times on Trail B than controls, with meta-analytic studies reporting moderate effect sizes (Hervey et al., 2004; Nigg, 2005). Performance on Trail B has also been reported to correlate with a measure of striatal DA synthesis (Vernaleken et al., 2007).

2.2.3.6 Tower of Hanoi. The Tower of Hanoi (TOH) is a task assessing problem-solving ability and planning (Shallice, 1982). Participants are presented with three equally distanced pegs of the same length. On one of these pegs, five rings are stacked in order of decreasing size. The participant's task is to transfer this stack to another peg, one ring at a time, in as few moves as possible, and never placing a larger ring on top of a smaller one. The participants completed the computerized version of the TOH task (Davis & Keller, 1998), using the computer mouse to move the rings. They were first administered a single three-ring trial as practice, followed by two five-ring trials consecutively. They were instructed to complete the tasks in as few moves as possible and were not given a time limit.

Children and adults with ADHD have been shown to perform more poorly than controls on the Tower of Hanoi task, as well as on the Tower of London task which is similar (Hervey et al., 2004; Nigg, 2005; Willcutt et al., 2005). Performance on Tower of

Hanoi and Tower of London tasks has been reported to correlate with striatal D2 and DAT binding in healthy controls and in people with the genotype for Huntington's disease, which is characterized by striatal atrophy (Backman, Robins-Wahlin, Lundin, Ginovart, & Farde, 1997; Lawrence et al., 1998).

2.2.3.7 Motor hyperactivity. Motor hyperactivity is a prominent feature of two of the three subtypes of ADHD. We used actimetry as an objective measurement of motor activity levels to complement self and informant ratings of hyperactivity. An actiwatch AW-L (Mini Mitter, Bend, Oregon), which is a small device with an internal accelerometer, was worn by each participant for a period of 48 hrs, including sleep, on the non-dominant ankle. Sampling was obtained every two minutes. A number of studies using activity monitors have provided objective evidence of increased motor activity levels in children (Dane, Schachar, & Tannock, 2000; Halperin, Matier, Bedi, Sharma, & Newcorn, 1992; Halperin et al., 1993; Porrino et al., 1983; Teicher, 1995; Tryon, 1993; Wood, Asherson, Rijsdijk, & Kuntsi, 2009) and adults with ADHD (Boonstra et al., 2007) relative to controls. In children, actimitry measures have been found to correlate significantly with parent and teacher ratings of hyperactivity (Reichenbach, Halperin, Sharma, & Newcorn, 1992). Actimetry has also been used to demonstrate reduction in motor activity following stimulant treatment (Boonstra et al., 2007; Borcherding, Keysor, Cooper, & Rapoport, 1989; Donnelly et al., 1989; Porrino et al., 1983; Teicher, 1995; Uebel et al., 2010). Individual differences in motor activity in ADHD adults have been reported to correlate with [^{11}C]raclopride binding in the caudate (Jucaite et al., 2005).

2.2.3.8 Verbal fluency. Verbal fluency is a task that requires participants to generate words starting with a given letter (phonetic fluency) or belonging to a certain semantic category (semantic fluency). This task taps into several cognitive processes, such as working memory, self-monitoring, and cognitive flexibility (Rosen & Engle, 1997; Schwartz, Baldo, Graves, & Brugger, 2003; Troyer, Moscovitch, Winocur, Alexander, & Stuss, 1998). Phonetic fluency has been found to rely primarily on the frontal-subcortical circuits, whereas semantic fluency has been suggested to be place greater demands on temporal lobe, although it also relies on frontal function (Baldo, Schwartz, Wilkins, & Dronkers, 2006; Gourovitch et al., 2000; Henry & Crawford, 2004; Tröster, Woods, & Fields, 2003). A meta-analysis of earlier studies in the literature using this task in ADHD found the effect size to be small (Pennington & Ozonoff, 1996); however, a number of more recent studies have reported significant deficits primarily in phonetic verbal fluency in children with ADHD (Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004; Hurks et al., 2004; Koziol & Stout, 1991; Marzocchi et al., 2008; Scheres et al., 2004; Tripp, Ryan, & Peace, 2002). With the inconsistency in results and the small sample size in the present study, no deficits on this task were anticipated. Thus this measure was included primarily as a task to control for non-specific factors, such as non-compliance or lack of effort.

To assess verbal fluency, an adaptation of the Controlled Word Association Task was used (Geurts et al., 2004). In the phonetic fluency task, participants were asked to generate as many words as possible within one minute starting with the letters *K* and *M*. They were instructed to avoid word repetitions and different forms of the same word (e.g.

man and *men*). In the semantic fluency task, the participants were asked to generate as many words as possible within one minute in the categories *animals* and *food*, avoiding word repetitions.

2.2.4 Personality Assessment

Participants completed the following personality questionnaires: the Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987; Cloninger, Przybeck, & Svrakic, 1991); the Revised NEO Personality Inventory (NEO-PI-R) (Costa & McCrae, 1992); and the Barratt Impulsivity Scale (BIS-11) (Patton, Stanford, & Barratt, 1995).

The TPQ measures three personality dimensions, Novelty Seeking, Harm Avoidance, and Reward Dependence, each comprising four subscales. These dimensions have been proposed to be related to neurotransmission, with Novelty Seeking related to dopamine, Harm Avoidance to serotonin and Reward Dependence to norepinephrine (Cloninger, 1987). The Novelty Seeking scale includes the following subscales: 1) Exploratory Excitability; 2) Impulsiveness; 3) Extravagance; 4) Disorderliness. The Exploratory Excitability and Impulsivity subscales have been found to correlate with individual differences in amphetamine- and alcohol-induced changes in [^{11}C]raclopride binding in limbic striatum (Boileau et al., 2003; Leyton et al., 2002). Individuals with ADHD have been reported to have higher novelty seeking scores than controls (Anckarsater et al., 2006; Downey, Stelson, Pomerleau, & Giordani, 1997; Jacob et al., 2007; Tillman et al., 2003). They have also been reported to have higher scores on the Harm Avoidance scale (Anckarsater et al., 2006; Downey et al., 1997; Jacob et al., 2007;

Nigg, 2006), which is comprised of the following subscales: 1) Exploratory Worry; 2) Fear of Uncertainty; 3) Shyness with Strangers; 4) Fatigability and Asthenia. Reward Dependence, as operationalized by the TPQ, appears to be unrelated to ADHD (Anckarsater et al., 2006; Downey et al., 1997; Jacob et al., 2007; Tillman et al., 2003).

From the NEO, the most relevant personality dimension was Extraversion. Extraversion is considered a human homologue of behavioral approach in animals, which has been associated with mesolimbic DA transmission (Depue & Collins, 1999; Depue, Luciana, Arbisi, Collins, & Leon, 1994). Extraversion has been reported to predict the magnitude of activation in the mesolimbic circuitry in response to a gambling task (Cohen, Young, Baek, Kessler, & Ranganath, 2005), suggesting that extraversion may be related to DA transmission in humans as well. Findings have been inconsistent regarding extraversion in ADHD, with some reporting higher (Braaten & Rosén, 1997) and others reporting lower extraversion in adults with ADHD than controls (Jacob et al., 2007), and yet others reporting no significant differences (Nigg et al., 2002b; Ranseen, Campbell, & Baer, 1998). With regard to other factors of the NEO, adults with ADHD were found to have higher neuroticism (Jacob et al., 2007; Miller, Miller, Newcorn, & Halperin, 2008; Nigg et al., 2002b; Ranseen et al., 1998) and lower conscientiouness (Jacob et al., 2007; Miller et al., 2008; Nigg et al., 2002b; Ranseen et al., 1998), agreeableness (Miller et al., 2008; Nigg et al., 2002b), and openness to experience scores (Jacob et al., 2007) compared to controls.

The BIS-11 has three subscales, Attentional Impulsivity (lack of focus on the task at hand), Motor Impulsivity (acting without thinking), and Non-Planning (orientation toward the present rather than the future). Impulsivity is a prominent feature of two of

the subtypes of ADHD, and scores on all subscales of the BIS-11 are higher in adults with ADHD, e.g. (Malloy-Diniz, Fuentes, Leite , Correa, & Bechara, 2007). BIS-11 total scores have been shown to correlate with striatal D2/ D3 receptor availability (Lee et al., 2009) and amphetamine-induced DA release (Buckholtz et al., 2010).

2.2.5 Genotyping

To investigate the potential associations between genetic variation, symptomatology, personality, and dopamine release, we collected blood samples to genotype allelic variation of the potentially relevant genes. For the SLC6A3 gene that codes for the DAT1, we examined the VNTR polymorphism of the 3′ untranslated region (UTR), as well as two common single nucleotide polymorphisms (SNPs) in the exon 9 (rs6347), and the intron 9 (rs8179029) reported to be in linkage disequilibrium with DAT1 3′ UTR VNTR (Greenwood et al., 2002). Although consistent associations with ADHD have not been found for the 3′ UTR VNTR (Faraone & Mick, 2010), this polymorphism has been reported to affect expression of the DAT1 gene (Fuke et al., 2001), and predict striatal DAT density (Brody et al., 2006; Heinz et al., 2000; Jacobsen et al.), as well as reward- and smoking- related activation in the striatum (Brody et al., 2006; Dreher, Kohn, Kolachana, Weinberger, & Berman; Franklin et al., 2009). In addition, allelic variation in the DAT SLC6A3 gene has been found to be associated with response to stimulants, with subjects homozygous for the 9-repeat allele showing a diminished response (Joober et al., 2006; Lott et al., 2004; Stein et al., 2005). We also examined the polymorphisms of the exon III 48-bp VNTR of the DRD4, since associations have been reported between the 7-repeat allele polymorphism and ADHD,

for review see (Faraone & Mick, 2010), and in vitro studies have found that the 7-repeat allele polymorphism is associated with a blunted a blunted response to DA in the DRD4 (Asghari et al., 1995; Van Tol et al., 1992). Associations between the 7-repeat allele polymorphism and individual differences in novelty seeking and exploratory behavior have been reported, albeit inconsistently (Schinka, Letsch, & Crawford, 2002) and were examined here. Finally, we examined the catechol *O*-methyltransferase (COMT) *Val*$^{108/158}$*Met* polymorphism (rs4680), where valine to methionine substitution results in higher enzymatic activity (lower synaptic DA). COMT is a major enzyme in prefrontal synaptic dopamine catabolism, and may impact DAergic transmission downstream of the prefrontal cortex (PFC) (Brody et al., 2006; Drabant et al., 2006; Dreher et al., 2009).

2.2.6 Neuroimaging

2.2.6.1 Positron Emission Tomography.

2.2.6.1.1 Acquisition. Participants received two PET scans at least 3 days apart between 13:00h and 17:00h on a Siemens ECAT HR+ PET scanner (CTI/Siemens, Knoxville, Tennessee) with lead septa removed (63-slice coverage, with a maximum resolution 4.2-mm, full width half maximum (FWHM) in center of field of view). Participants were asked to fast and to abstain from caffeine and smoking for 4 hours before each PET session. Toxicology screening was performed prior to all other procedures. Sixty minutes prior to tracer injection, an oral dose of 0.3 mg/kg of *d*-AMPH or placebo (lactose) was administered double-blind and in random order. Approximately 15 minutes before tracer injection, the participant was positioned inside the scanner, and a catheter was inserted into his antecubital vein for tracer injection and collection of

blood samples. Attenuation correction was performed using a 12-minute ^{68}Ga transmission scan immediately prior to tracer injection. The emission scan was started simultaneously with the injection of approximately 7 mCi of [^{11}C]raclopride as an i.v. bolus. Emission data were acquired for 60 minutes in 26 time frames of progressively longer duration. Vital signs were monitored and blood samples for plasma amphetamine analysis collected at baseline (prior to drug/ placebo administration), and then at various points throughout the scan (see Figure 4 for the timeline).

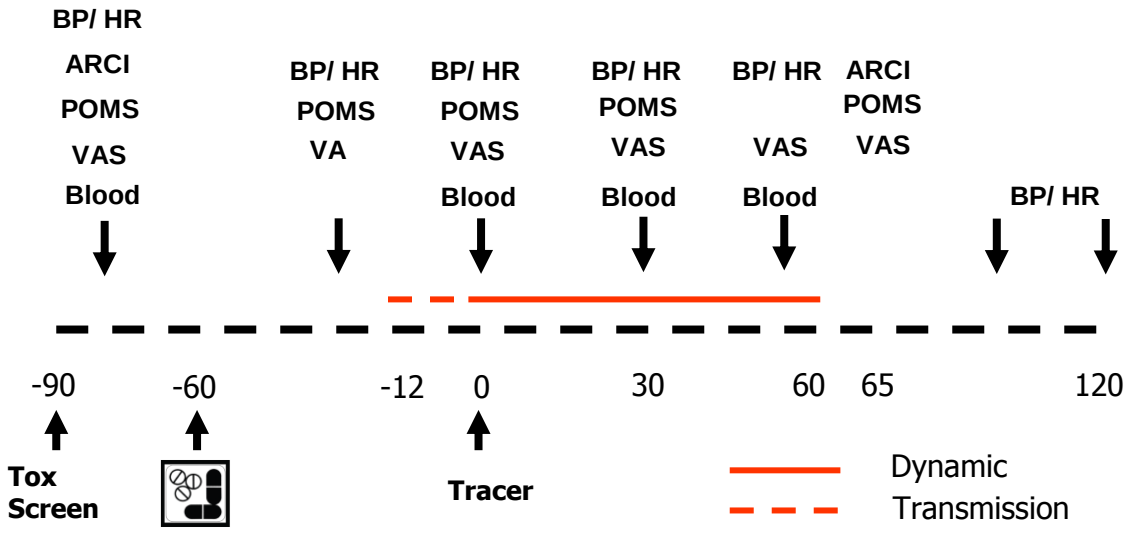


Figure 2-2: Timeline of the PET scans

2.2.6.1.2 Kinetic modeling of tracer distribution. Quantification of changes in radiotracer binding to D2/D3 receptors requires the use of a bio-mathematical kinetic model of tracer distribution in the brain. Such models rely on a theoretical framework of tissue compartments, usually a plasma compartment, an intracerebral compartment where the tracer is free and non-specifically bound, and a compartment where the tracer is specifically bound (receptor compartment), assuming that the tracer concentration is homogenous within each compartment at all times. According to the kinetic model used

in the present thesis, [^{11}C]raclopride BP (or equilibrium volume of distribution in the bound compartment) can be expressed as $B_{\max} f_2 / K_D^t (+ N_f / K_D^d)$, where $B_{\max}$ is the total concentration of D2/D3 binding sites, f_2 the free fraction of radioligand in tissue, K_D^t the equilibrium dissociation constant of the radioligand, N_f the concentration of free DA in tissue, and K_D^d the equilibrium dissociation constant of DA at the D2/D3 receptor (Gunn, Lammertsma, Hume, & Cunningham, 1997; Lammertsma & Hume, 1996).

Radiotracer binding to D2/D3 receptors was quantified using a compartmental kinetic model, which requires an input function that can be derived from either arterial blood or from a reference tissue with a negligible number of binding sites. This allowed us to circumvent the use of arterial cannulation. The simplified reference-tissue model (SRTM) used here is a robust and well-documented reference tissue method for the estimation of the [^{11}C]raclopride binding to D2/D3 receptors following a bolus tracer injection (Lammertsma & Hume, 1996).

2.2.6.2 Magnetic Resonance Imaging. High resolution (1 mm) T1-weighted magnetic resonance images (MRI) were obtained for all participants on a 1.5-Tesla Siemens scanner, using gradient echo pulse sequence (repetition time = 22 ms, echo time = 9.2 ms, flip angle = 30°, and matrix 256 X 256) for co-registration to the PET images, as well as cortical thickness analyses.

2.2.6.3 Self-Report Scales. Subjective responses to *d*-AMPH were assessed using three self-report instruments at baseline and various points throughout the scan (see Figure 2 for timeline). The three instruments used were: 1) Visual Analogue Scales (VAS) including 10 items (rush, high, euphoria, excited, anxious, energetic, mind-racing, alert, drug liking, and drug wanting); 2) the bipolar Profile of Mood States (POMS),

which comprises 6 scales (Elated – Depressed, Composed – Anxious, Agreeable – Hostile, Confident – Unsure, Energetic – Tired, and Clearheaded – Confused) and is highly sensitive to non-clinical changes in mood states (Lorr, McNair, & Fisher, 1982; McNair, Lorr, & Droppleman, 1988) and; 3) the Addiction Research Center Inventory (ARCI), a measure of subjective effects of different classes of drugs, including amphetamines, with items based on solicited responses of former addicts under the influence of those drugs (Haertzen, Hill, & Belleville, 1963).

2.3. Analyses

2.3.1. Image Analysis

2.3.1.1 Positron Emission Tomography. For the purpose of co-registration with PET images, MR volumes were corrected for image intensity non-uniformity (Sled, Zijdenbos, & Evans, 1998) and linearly and non-linearly transformed into standardized stereotaxic space (Talairach & Tournoux, 1988) using automated feature-matching to the MNI305 template (Collins & Evans, 1997; Collins, Neelin, Peters, & Evans, 1994). The PET images were reconstructed using a 6-mm full-width half-maximum Hanning filter. To correct for possible motion artifacts, PET frames were realigned with an algorithm using cross-correlation similarity criteria for the determination of inter-frame motion parameters and emission-transmission mismatch for each frame (Costes et al., 2009). The dynamic radioactivity PET data were averaged across the time dimension and then co-registered to the participant's MRI (Evans et al., 1992). Parametric images were generated by calculating [^{11}C]raclopride binding potential values ($BP_{ND}=B_{Avail}/K_D$; BP_{ND} = binding potential non-displaceable, B_{Avail} = density of available receptors) at each voxel

using a simplified reference tissue compartmental model (SRTM) with cerebellum as the reference tissue with a very low density of D2/D3 receptors (Gunn et al., 1997; Lammertsma & Hume, 1996). This method assumes that non-specific [^{11}C]raclopride binding is equivalent in the striatum and the reference region. A voxel-wise statistical mapping method using the SRTM model was then utilized to determine the t-statistic associated with the difference in [^{11}C]raclopride BP between the *d*-AMPH and the placebo conditions. This method applies nonlinear least squares theory on the scan's dynamic information to estimate the parameters of the kinetic model (SRTM) and uses the residuals to calculate associated variance (Aston et al., 2000). Clusters of statistically significant change are identified by thresholding the *t*-map at a value of $t \geq 3.8$, which corresponds to $p < 0.05$ corrected for multiple comparisons and a search volume of the striatum (Aston et al., 2000; Worsley et al., 1996).

A region of interest (ROI) analysis was performed to examine amphetamine-induced changes in [^{11}C]raclopride binding in five striatal subregions based on the functional organization of limbic, associative, and sensory motor sub-compartments proposed by Laruelle, Haber and colleagues (Haber & McFarland, 1999; Martinez et al., 2003; Mawlawi et al., 2001): ventral striatum (limbic striatum), pre-commissural dorsal caudate (anterior caudate / associative striatum), pre-commissural dorsal putamen (anterior putamen / associative striatum), post-commissural caudate (posterior caudate / associative striatum), and post-commissural putamen (posterior putamen / sensory motor putamen) (Figure 2-3).

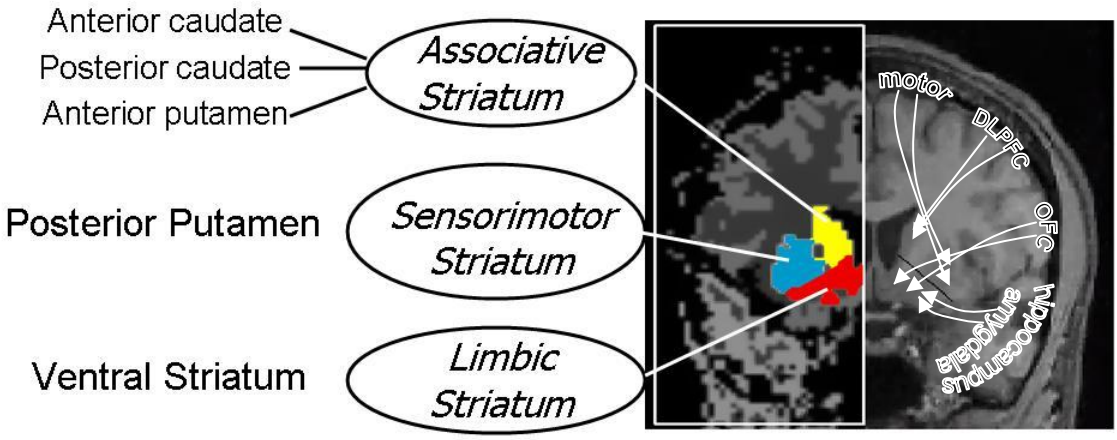


Figure 2-3: Striatal ROIs based on Mawlawi et al (2001) and Martinez et al (2003).

To define the ROIs, each participant's MRI was automatically classified into tissue type (gray matter, white matter, cerebrospinal fluid (CSF) (Collins & Evans, 1997) and segmented into anatomical brain structures including ventral striatum, caudate, and putamen (Collins, Peters, & Evans, 1995). Caudate and putamen were then manually divided into anterior and posterior aspects. The resulting five ROIs were visually inspected and manually adjusted, if necessary, to match the participant's individual neuroanatomy. Mean [^{11}C]raclopride BP_{ND} values were then extracted from each anatomical ROI for each scan. BP values uncorrected for partial volume effects (PVE) were used because: 1) partial volume effects are most pronounced for structures with much smaller volumes than those of caudate and putamen (< 2 x FWHM of the PET

scanner) (Labbe, Froment, Kennedy, Ashburner, & Cinotti, 1996; Rousset, Ma, & Evans, 1998); and 2) given that the BP values were extracted from identical ROIs in both the *d*-AMPH and the placebo conditions, PVE were expected to be the same for both conditions and not bias our measures of *d*-AMPH-induced change in BP. Further, we did not expect PVE to introduce a significant bias into our between-group comparison of baseline BP values, because voxel-based morphometry showed no differences in the volumes of the striatal structures in our two groups (see below), suggesting that any differences in BP could not be attributed to structural brain changes, such as atrophy (Labbe et al., 1996; Meltzer, Leal, Mayberg, Wagner, & Frost, 1990) in one group.

2.3.1.2 Voxel Based Morphometry. Because reductions in striatal volumes and abnormalities in caudate volume asymmetry have been reported in subjects with ADHD (Castellanos et al., 1996b; Castellanos et al., 2002; Castellanos et al., 2003; Filipek et al., 1997; Giedd et al., 1994; Hynd et al., 1993; Overmeyer et al., 2001; Semrud-Clikeman et al., 1994; Wang et al., 2007), and could constitute a source of bias in the analysis of [^{11}C]raclopride binding, voxel based morphometry (VBM) was used to investigate the possibility of group differences in striatal volumes.

The MRIs were processed using the CIVET pipeline (Ad-Dab'bagh et al., 2006; Zijdenbos, Forghani, & Evans, 2002), comprising the following stages: native MRIs were first corrected for intensity non-uniformity (Sled et al., 1998) and transformed into standardized stereotaxic space (MNI ICBM-152 non-linear 6th generation template with a 9-parameter linear registration) (Collins et al., 1994; Mazziotta, Toga, Evans, Fox, & Lancaster, 1995); the corrected and transformed volumes were then classified into white

matter, gray matter, CSF, and background, using an artificial neural network classifier (Tohka, Zijdenbos, & Evans, 2004; Zijdenbos, Forghani, & Evans, 1998); binary volumes consisting of gray matter voxels were then extracted from classified images, smoothed using a 8-mm FWHM smoothing kernel to convert the binary data into continuous data (with the signal at each voxel weighted according to the signal in neighboring voxels, reflecting the density of gray matter within the smoothing kernel). The subsequent statistical analysis focused on the volumes of caudate and putamen defined on an averaged MR image.

2.3.1.3 Cortical thickness. After processing the MRIs with CIVET pipeline (Ad-Dab'bagh et al., 2006; Zijdenbos et al., 2002), cortical surfaces were produced using the Constrained Laplacian Anatomic Segmentation Using Proximities (CLASP) surface extraction procedure (Kim et al., 2005; MacDonald, Kabani, Avis, & Evans, 2000). This process generates a triangulated mesh at the interface of gray matter (cortex) and white matter and then expands the mesh outwards toward the pial surface. Cortical thickness was measured in native space (by applying to the surface mesh an inverse of the linear transformation matrix of the native volume into the stereotaxic space) as the distance between corresponding vertices on the inner and outer surfaces of the mesh across 40,962 sets of vertices in each hemisphere (Ad-Dab'bagh et al., 2005; Lerch & Evans, 2005). The cortical thickness values were then smoothed using a diffusion-smoothing kernel of 20 mm FWHM that preserves cortical topology (Chung & Taylor, 2004; Chung et al., 2001).

2.3.2 Plasma Amphetamine Analysis

Plasma was isolated through centrifugation. Amphetamine was derivatized under basic conditions using pentafluorobenzenesulfonyl chloride (PFBSC). For 11 of the participants (5 ADHD and 6 controls), the derivatives were analyzed with electron-capture gas chromatography (Asghar, Baker, Rauw, & Silverstone, 2002). For the other 19 participants (10 ADHD and 9 controls), the derivatives were analyzed using gas chromatography/ mass spectrometry–negative ion chemical ionization detection, since electron-capture gas chromatography was not possible due to interference peaks from plastic containers used to store the plasma.

2.3.3 Genotyping Analysis

A 30 ml blood sample (two 8.5 ml ACD tubes and two 7.0 ml EDTA tubes), was collected from each participant by a nurse at the same time as blood samples were collected for the routine physical exam. The genotyping was carried out in the Neurogenetic laboratory of the Douglas General Hospital Research Center, according to previously published methods (Joober et al., 2000). Briefly, polymerase chain reaction (PCR) with polymorphism- and allele-specific sets of primers was used, followed by gel electrophoresis and visualization of reaction products agarose gels (ethidium bromide). Allele calling was made by two independent technicians blind to group membership. Conflicts in allele calling were resolved by the laboratory director (RJ), who was also blind to group membership or by reanalyzing the sample in question.

2.3.4 Eye Movement Analysis

Eye movements were analyzed with a semi-automated custom analysis software package (SR Research, Osgoode, ON) and verified by visual inspection. Saccades were identified using velocity (> 22°/ sec) and acceleration (> 4,000°/ sec^2) criteria. Trials were discarded if a blink or a saccade greater than 0.5^o occurred in the 100 ms prior to fixation offset or if gaze was more than 2^o off the fixation target in the same period. The trial's first saccade > 2^o in amplitude with a latency >80ms was analyzed. Saccades of ≤80ms were classified as anticipatory and excluded from the analysis; this cut-off was determined by viewing latency distributions for correct and misdirected prosaccades (Munoz et al., 2003). Latency values > 3 SD from each participant's own mean were excluded.

2.3.5 Actimetry

The actimetry analyses were conducted using the Actiware analysis software (Mitter, Bend, Oregon). The average number of activity counts per minute was used as the measure of overall motor activity over the 48-hour period. In addition, waking and sleep activity levels were examined separately, since higher levels on nocturnal activity have been reported in children and adults with ADHD (Cortese, Konofal, Yateman, Mouren, & Lecendreux, 2006; Konofal, Lecendreux, Bouvard, & Mouren-Simeoni, 2001; Philipsen et al., 2005). Sleep onset and offset were determined using the wake threshold of ≥ 40 activity counts per 2-minute epoch over 5 consecutive epochs. Activity variables examined for sleep and wake periods included overall activity levels, total duration of

sleep and wake periods, and sleep mobility index (i.e. percentage of sleep periods within which there are 1 or more activity counts) used as an index of sleep quality, particularly in clinical populations (Kooij, Middelkoop, van Gils, & Buitelaar, 2001). Four participants removed their actiwatches 6, 12, 120, and 310 minutes prior to the completion of the 48 hours. For those participants, average overall activity levels and average waking activity levels were calculated using the available data. Sleep onsets of two ADHD participants were not detected by the software. Both of these individuals showed consistent activity throughout the 48-hour period. Their data were removed from sleep and wake period analyses, but were maintained in the analysis of the overall activity. Four participants showed zero activity throughout their sleep intervals. Since these participants were unable to confirm that they had not removed the actiwatches during sleep, their data were excluded from both sleep and overall activity analyses.

2.3.6 Statistical Analyses

For all statistical analyses, extreme values outside 3 standard deviations of the mean for a given variable, which constituted < 0.5% of all values, were Winsorized (replaced by the value of their nearest neighbor) (Dixon & Yuen, 1974). The majority of statistical analyses (detailed below) were carried out using parametric tests. When variables deviated from normality, transformations were applied to normalize the data, and subsequent analyses were conducted on the transformed data. In some cases, normality assumptions were violated for a minority of variables in a task with many conditions. In this case, because parametric tests allow more elegant consideration of factors and because ANOVAs are robust to violation of normality (Howell, 2010;

Rasmussen, 1987), parametric analyses were applied. When non-normally distributed data constituted the majority of the data for a task, and transformations did not normalize the distribution, the analyses were conducted with non-parametric tests. Analyses of variance were followed up with post hoc Bonferroni tests.

2.3.6.1 ADHD symptom scores. ADHD symptoms as measured by the CAARS, were analyzed using a 2-way mixed ANOVA, with Group as the between-subjects factor and Scale of the CAARS as the within-subjects factor.

2.3.6.2 Personality and neurocognitive performance. Data were analyzed with 2-way mixed ANOVAs with Group (ADHD vs. controls) as the between-subjects factor and Condition (e.g. subscale or task version) as the within subjects factor.

2.3.6.3 Blood pressure, heart rate, amphetamine plasma levels. Changes in these measures in response to *d*-AMPH were analyzed with three-way, Group x Drug x Time Point mixed ANOVAs with Group as a between-subjects factor and Drug (amphetamine vs. placebo) and Time Point (i.e. baseline, transmission, tracer injection, mid-scan, end of scan) as within-subjects factors. For between-group comparisons of the peak plasma levels of amphetamine on the amphetamine day, independent t-tests of the square root transformed values were used.

2.3.6.4 Subjective response to amphetamine. The POMS data were normally distributed with the exception of the Agreeable-Hostile scale. Thus, the POMS data were

analyzed with a four-way, Group x Drug Order x Drug x Time Point mixed ANOVAs. The data on the Agreeable-Hostile scale could not be normalized with a transformation so untransformed data were analyzed with Group x Drug Order Drug x Time Point ANOVA, and the results were verified using pairwise non-parametric tests. For the 6 mood dimensions, the alpha level was set at p = .008, keeping the family-wise error rate at .05; trends at the uncorrected alpha level of $p < .05$ were also explored. In addition, area under the curve (AUC) values were calculated for POMS scores on the placebo and *d*-AMPH days using the following formula:

$$AUC_G = \sum_{i-1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2}$$ (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

The difference values between *d*-AMPH and placebo AUCs were used in a regression analysis of subjective rating change in relation to individual differences in *d*-AMPH-induced change in binding (see below).

Given the number of points at which the VAS measurements were taken, VAS data were analyzed as AUC values on the placebo and amphetamine days (Pruessner et al., 2003). Since placebo VAS AUC values deviated from normality on four of the dimensions, a square root transformation was applied to all the VAS AUC values. The transformed values were analyzed with a four-way Group x Drug Order x Drug x VAS Scale mixed ANOVA. The placebo AUC value on the Rush scale could not be normalized with the transformation. Therefore, the results of the ANOVA on this scale were confirmed with pairwise non-parametric tests.

For the ARCI, analyses were conducted on change scores, calculated as the difference between baseline and post scan ratings on the *d*-AMPH and placebo days.

These data were analyzed with a two-way mixed ANOVA with Group as the between-subjects factor and Drug (*d*-AMPH vs. placebo) as the within-subjects factor.

2.3.6.5 Amphetamine-induced DA release and D2/ D3 Binding Potential (BP). *d*-AMPH-induced changes in [^{11}C]raclopride BP were analyzed in two ways. First, parametric mapping was conducted using the Simplified Reference Tissue Compartmental model, and *t*-maps were generated using values of $t \geq 3.8$ ($p < 0.05$ corrected for multiple comparisons). Second, *d*-AMP-induced changes in BP values extracted from the three *a priori* striatal ROIs were calculated as % decrease in BP following *d*-AMP relative to placebo (% Δ BP). These percent change values were normalized with a square root transformation and analyzed with a four-way Group x Drug Order x ROI x Hemisphere mixed ANOVA with Group and Drug Order (*d*-AMPH first vs. placebo first) as the between subjects factors and ROI and Hemisphere as within-subjects factors. Group differences in baseline D2/D3 binding were also explored by analyzing BP values on the placebo day in the three *a-priori* ROIs using separate univariate ANOVAs.

2.3.6.6 Symptoms, personality, and neurocognitive performance in relation to % Δ BP. The relationship between individual differences in *d*-AMP-induced change in [^{11}C]raclopride BP (% Δ BP) and ADHD symptom scores, as well as between % Δ BP and neurocognitive performance on measures where significant group differences were detected, were analyzed using linear regression analyses and curve fitting. For

questionnaire scales comprised of multiple subscales, stepwise regression analyses were used to account for multiple comparisons (Darlington, 1968; Howell, 2010).

2.3.6.7 Subjective responses to amphetamine in relation to in relation to % Δ BP. The relationship between subjective responses to the drug (i.e. *d*-AMPH induced changes in the VAS and the POMS) were analyzed in a stepwise regression analysis with % Δ BP as the dependent variable.

2.3.6.8 Voxel Based Morphometry. Statistical analyses of the VBM data were conducted using the SurfStat (http://www.math.mcgill.ca/keith/surfstat/) toolbox for Matlab. Statistical maps of differences in striatal gray matter density between controls and ADHD participants were obtained using a general linear model containing a Group main effect term. The presence of significant peaks at $p < 0.05$ in the statistical maps was assessed by a method based on 3D Gaussian random-field theory, which corrects for multiple comparisons for the search volume (Worsley et al., 1996).

2.3.6.9 Cortical thickness. Cortical thickness analyses were conducted using the SurfStat toolbox for Matlab. In all vertex-wise analyses, random-field theory for non-isotropic images was used to detect significant clusters (Worsley, Andermann, Koulis, MacDonald, & Evans, 1999), which limited the chance of reporting a false positive to be < 0.05. A linear model containing a Group main effect term was used for the vertex-wise analysis of group difference (controls vs. ADHD) in cortical thickness. The relationship between cortical thickness and % Δ BP in each of the three striatal ROIs was first analyzed by fitting a fixed-effects regression model predicting cortical thickness at each

vertex from % Δ BP collapsing across groups. Subsequently, the Group main effect term and the Group x % Δ BP interaction term were entered into the model to predict cortical thickness. Intake BDI was added to the model as a covariate because BDI scores were found to be correlated with % ΔBP in the ADHD group and because the ADHD and control groups differed in their BDI scores at intake (described below). The relationship between cortical thickness and % change in BP was compared between groups by testing the significance of the Group x % change in BP interaction term. If the interaction term was significant, meaning that the regression slopes differed significantly between groups, the relationship between cortical thickness and % Change in BP was examined separately within each group. Cortical thickness analyses included only frontal cortex because: 1) dopamine system cortical projections are primarily to frontal regions (Haber, 2010); 2) findings of cortical thinning in ADHD have been focused in the frontal cortex ((Almeida et al.; Batty et al., 2010; Makris et al., 2007; Monuteaux et al., 2008; Shaw et al., 2007b; Shaw et al., 2006b) although parietal thinning has also been reported (Makris et al., 2007; Shaw et al., 2006b)); and 3) developmental trajectories suggest a lag specifically in frontal cortical development in ADHD (Shaw et al., 2007a).

2.3.6.10 Genotype in relation to symptomatology and % Δ BP. The relationship between DAT1, DRD4, and COMT genotypes and ADHD symptomatology as measured by the eight scales of the CAARS was analyzed with a two-way mixed ANOVA with Genotype as the between-subjects factor and CAARS Scale as the within-subjects factor. Based on some previous reports (Benjamin et al., 1996; Ebstein & Belmaker, 1997; Ebstein et al., 1996; Okuyama et al., 2000; Strobel, Wehr, Michel, & Brocke, 1999), but see also (Kluger, Siegfried, & Ebstein, 2002; Schinka et al., 2002) we

hypothesized associations between the 7-repeat allele polymorphism of the DRD4 exon III 48-base pairs VNTR and scores on the Novelty Seeking scale of the TPQ and the BIS-11. The effects of genotypes on % Δ BP were analyzed using a two-way mixed ANOVA with Genotype as the between-subjects factor and ROI as the within-subjects factor.

CHAPTER 3:

RESULTS

3.1 Sample Characteristics

The ADHD group did not differ significantly from Controls on any of the demographic variables, with the exception of the estimated IQ being marginally higher in the control group compared to the ADHD group ($p = .06$)(Table 1). IQ tends to be lower in individuals with ADHD than controls (Bridgett & Walker, 2006; Frazier, Demaree, & Youngstrom, 2004), with the difference reflecting either true population differences (Dennis et al., 2009; Kuntsi, Andreou, Ma, Borger, & van der Meere, 2005) or negative effects of symptoms on performance (form example the effects of working memory deficits on Digit Span and Arithmetic performance) (Nigg, 2005). Thus, correcting for differences in IQ in ADHD is controversial (Seidman, 2006), since it involves eliminating variance attributable to the independent variable of interest (i.e. the illness), or variance shared by the independent and dependent variables (i.e. IQ and symptoms of the illness). Neither of these are correct uses of covariance (Miller & Chapman, 2001). Here, the analyses were conducted without covarying for the trend level difference in IQ.

As expected, the ADHD group had significantly higher scores on all scales of the CAARS relative to the controls ($p_s < .0005$). In addition, although no participant was clinically depressed, the ADHD BDI scores at intake were higher than those of Controls ($p_s < .0005$).

3.2 Personality

Scores on the TPQ, the NEO, and the BIS-11 personality questionnaires are given in Table 2. Scores on the TPQ were analyzed with separate two-way Group x Subscale repeated measures ANOVAs for each scale: Novelty Seeking, Harm Avoidance, and

Reward Dependence. The ANOVAs revealed a significant main effect of Group for the Harm Avoidance scale ($F_{(1, 27)} = 10.45$, $p = .02$), with higher scores in the ADHD group, and no group differences in Novelty Seeking or Reward Dependence. Since the total scores on the Harm Avoidance scale deviated from normality, a confirmatory Mann-Whitney U test was performed, which also yielded significantly higher scores in the ADHD group than controls ($U = 53.00$, $p = .02$). For the NEO, a significant Group x Subscale interaction emerged ($F_{(4, 21)} = 9.45$; $p < .0005$), indicating the expected finding of higher Neuroticism ($p = .001$) and lower Conscientiousness ($p = .001$) in the ADHD group. Finally, a main effect of Group ($F_{(1, 26)} = 21.64$; $p < .0005$) on the BIS-11 scores indicated, as expected, higher impulsivity scores in the ADHD group across all three subscales.

	Controls (n = 15)	**ADHD (n = 15)** 5 Combined/ 10 Inattentive	N	*p*
TPQ				
Novelty Seeking	18.40 ± 4.67	20.68 ± 6.75	15, 14	.30
Exploratory Excitability	5.87 ± 1.88	6.07 ± 1.90	15, 14	.77
Impulsiveness	3.00 ± 1.77	3.90 ± 2.43	15, 14	.27
Extravagance	4.07 ±1.79	4.50 ± 2.21	15, 14	.57
Disorderliness	5.47 ± 1.41	6.21 ± 2.22	15, 14	.29
Harm Avoidance	7.27 ± 4.33	12.11 ± 6.46	15, 14	.02*
Exploratory Anxiety	2.20 ± 1.66	3.39 ± 2.24	15, 14	.11
Fear of Uncertainty	2.20 ± 1.61	2.86 ± 2.35	15, 14	.38
Shyness with Strangers	1.33 ± 1.23	2.86 ± 2.03	15, 14	.02*
Fatigability	1.53 ± 1.41	3.00 ± 2.66	15, 14	.07
Reward Dependence	18.8 ± 4.52	17.86 ± 4.87	15, 14	.60
Sentimentality	3.33 ± 1.40	3.71 ± 1.14	15, 14	.43
Persistence	5.60 ± 2.03	4.54 ± 2.61	15, 14	.23
Attachment	7.20 ± 2.18	6.29 ± 2.81	15, 14	.34
Dependence	2.67 ±1.23	3.32 ± 1.17	15, 14	.16
NEO				
Neuroticism	13.62 ± 6.70	23.85 ± 7.73	13, 13	.001*
Extraversion	30.62 ± 4.25	28.54 ± 5.51	13, 13	.29
Openness to experience	29.69 ± 2.93	29.46 ± 7.18	13, 13	.92
Agreeableness	31.00 ± 5.18	30.38 ± 6.90	13, 13	.80
Conscientiousness	33.23 ± 6.04	20.31 ± 10.27	13, 13	.001*
BIS-11	62.60 ± 11.01	81.42 ± 10.39	14, 14	< .0005*
Attentional Impulsivity	15.07 ± 2.52	23.21 ± 2.49	14, 14	< .0005*
Motor Impulsivity	23.69 ± 5.17	28.21 ± 5.58	14, 14	.04*
Non-Planning Impulsivity	23.84 ± 4.79	29.99 ± 4.53	14, 14	.002*

Table 3-1: Personality. The *p*-values are derived from parametric analyses.

3.3 Neurocognitive Performance

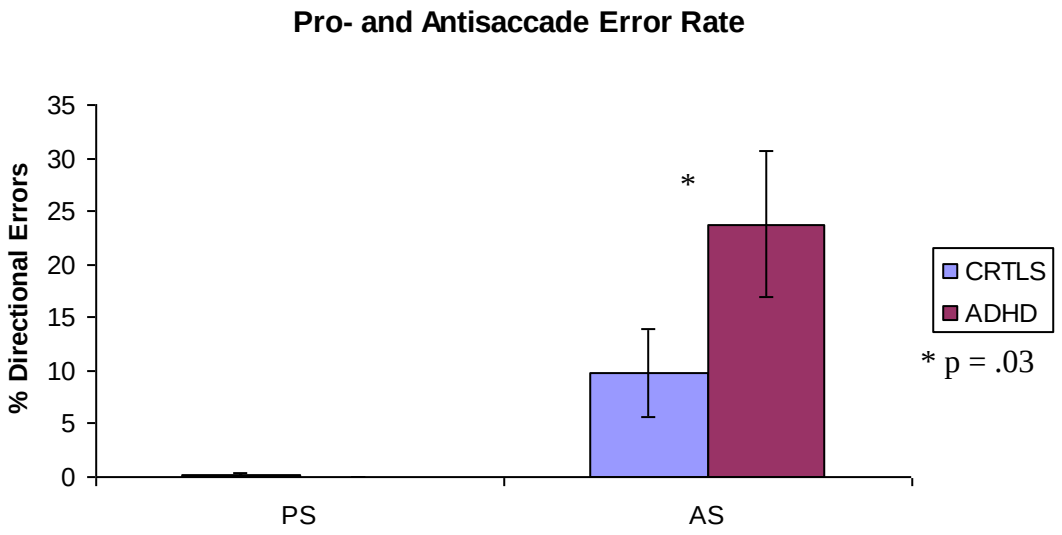
3.3.1 Stop Signal Reaction Time Task

To normalize the data, a square root transformation was applied to both the stop-signal and the go reaction times. The transformed RTs were analyzed using a two-way mixed ANOVA with Group as the between-subjects factor and RT type (Go RT vs. Stop Signal RT) as the within-subjects factor. The ANOVA revealed a significant Group x RT type interaction ($F_{(1, 24)} = 5.83$, $p = .02$). The interaction was driven by the fact that the ADHD group had longer stop-signal RTs than controls ($t_{(24)} = 3.0$; $p = .008$) but did not differ on Go RTs (see Figure 3-1).

Figure 3-1: Stop Signal Reaction Time Task performance. The ADHD group had significantly longer SSRTs than the control group (p-value based on t-test). The groups did not differ in Go signal RTs (Group x RT type, p=.02). The figure uses untransformed scores.

3.3.2 Antisaccade

To examine group differences in inhibitory function, the antisaccade error rate and the proportion of anticipatory saccades (with latency ≤ 80ms) across pro- and antisaccade trials were analyzed using independent samples t-tests (repeated measures ANOVAs could not be applied due to inhomogeneity of variance). The % error and % anticipations data deviated from normality, so a square root transformation was applied. Relative to Controls, the ADHD participants made significantly more antisaccade errors ($t_{(19)} = 2.36$; $p = .03$) and significantly more anticipatory responses ($t_{(19)} = 2.67$; $p = .02$) (see Figure 3-2). As expected, errors on prosaccade trials were rare ($M = 0.1\%$, $SD = .44$), and did not differ across the two groups ($t_{(19)} = 1.00$; $p = .35$). For prosaccade and antisaccade latencies, a two-way mixed ANOVA with Saccade Type as the within-subjects factor and Group as the between-subjects factor revealed the expected main effect of Saccade Type ($F_{(1,17)} = 129.78$; $p < .0005$); antisaccades had longer latencies than prosaccades, but there was no main effect of Group nor interaction of Group with other variables ($p_s > .1$).



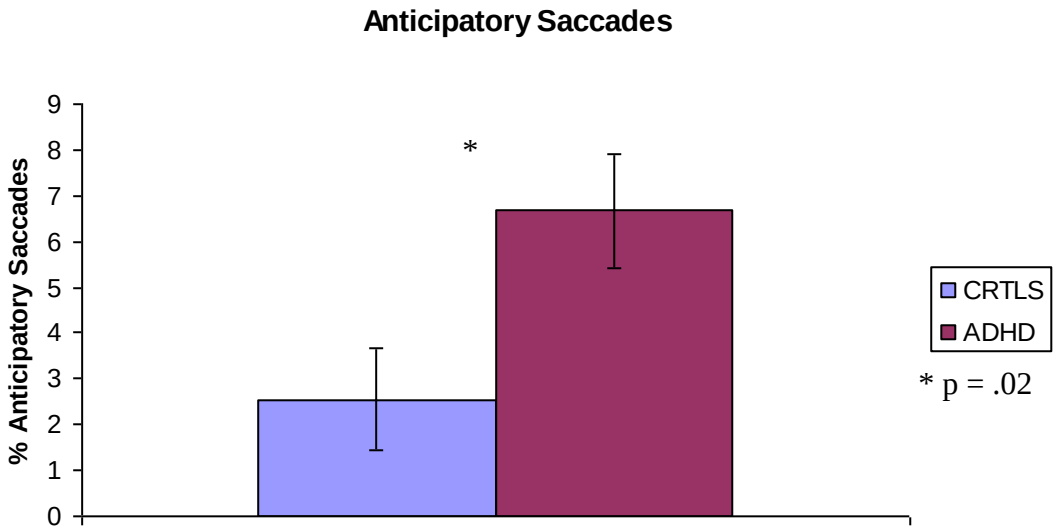


Figure 3-2: Antisaccade Performance. Antisaccade error rate and proportion of anticipatory saccades is higher in the ADHD group compared to controls (p values in figures are based on t-tests). The figure uses untransformed data.

3.3.3 Go/No-Go Discrimination Learning

A two-way repeated measures ANOVA on overall response rate with Group as the between-subjects factor and Condition (Reward-Punishment, Reward-Reward, Punishment-Punishment, and Punishment-Reward) as the within-subjects factor revealed a trend-level Group x Condition interaction ($F_{(3,22)} = 2.29$; $p = .09$), suggesting higher overall response rate in ADHD relative to the Control participants in the Punishment-Punishment (Incorrect Feedback) condition ($p = .07$). This finding parallels a previous report of a higher response rate on this task in children with ADHD than controls (Iaboni et al., 1995). The percentage of omission errors deviated from normality in the Reward-Reward (Correct Feedback), Punishment-Punishment (Incorrect Feedback), and Punishment-Reward (Passive Feedback) conditions. Normalization could not be achieved by applying transformations so the untransformed % error data were analyzed with a three-way mixed ANOVA with Group as the between-subjects factor and Condition and

Error Type (commission vs. omission) as within-subjects factors. Significant results were verified with pairwise Mann-Whitney U tests.

The ADHD group made more errors than Controls across all conditions (Group: $F_{(1,23)} = 4.25$; $p = .05$) . Across all conditions, errors of commission were more frequent than errors of omission (Error Type: $F_{(1,23)} = 28.82$; $p < .0005$). There was also a significant main effect of Condition ($F_{(3,21)} = 6.58$; $p = .001$), driven by the fact that the the Reward-Punishment (Active Feedback) and the Punishment-Reward (Passive Feedback) conditions generated significantly more errors than the other two conditions both of which provided consistent reward or consistent punishment for correct responses or errors, regardless of whether the response was active or passive. In addition, there was a trend-level Group x Condition x Error Type interaction ($F_{(3,21)} = 2.46$; $p = .08$). This reflected the fact that the groups tended to be similar in terms of the difference between commission and omission errors in each of the 4 conditions. However, the difference between the rate of commission and omission errors differed between groups in the Punishment-Reward (Passive Feedback) (see Figure 3-3) with the Controls continuing to show more commission than omission errors, and the AHD group showing more omission than commission errors. The difference between omission and commission errors between the groups was significant in comparisons of the Punishment Reward (Passive Feedback) condition to both the Punishment-Punishment (Incorrect Feedback) and Reward-Reward (Correct Feedback) conditions (PR vs. PP: $t_{(19.87)} = 2.66$, $p = .02$; PR vs. RR: $t_{(20.13)} = 2.48$, $p = .02$). Post hoc analyses showed that the ADHD group made significantly more omission errors than Controls in the Punishment-Reward (Passive Feedback) condition ($t_{(24)} = 2.86$ $p = .009$) (Figure 3-3). Mann Whitney U tests

confirmed the significant Group difference in the % omission errors in the Punishment-Reward (Passive Feedback) condition (U = 30.50; p = .008). The groups did not differ in omission errors in the Reward-Reward (Correct Feedback) and Punishment-Punishment (Incorrect Feedback) conditions (p_s > .12).

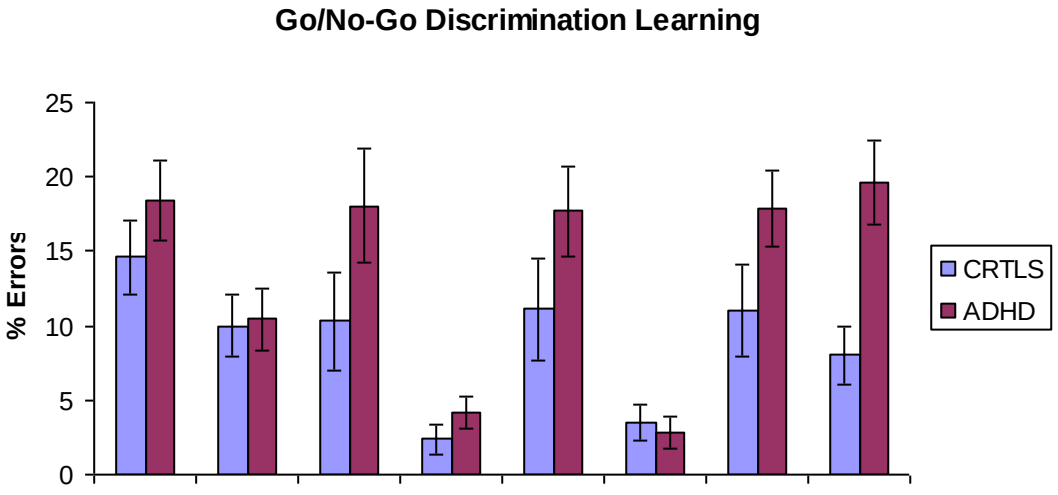


Figure 3-3: Go/No-Go Discrimination Learning task performance. RRc = Reward-Punishment commission errors; RPo = Reward-Punishment omission errors; RRc = Reward-Reward commission errors; RRo = Reward-Reward omission errors; PPc = Punishment-Punishment commission errors; PPo = Punishment-Punishment omission errors; PRc = Punishment-Reward commission errors; PRo = Punishment-Reward omission errors.

Learning curves on the Go/No-Go Discrimination Learning task have been reported to differ between ADHD and control children, with the ADHD children making more commission errors on later trials (Iaboni et al., 1995). To examine the learning curves of the ADHD vs. Control participants, the 92 total trials in each condition were subdivided into five bins, one containing the 12 practice trials, and the other four containing 20 consecutive test trials each (Figure 3-4). Since the binned % error data deviated from normality and could not be normalized by applying a transformation, we could not compare the groups on change in % error across trial bins using a mixed

ANOVA approach. Therefore, we compared the slopes of the learning curves (change in error rate across trial bins) between the two groups. Visual inspection of the learning curves (Figure 3-4) suggested that these curves likely represent either a linear or an exponential decrease in error rate over trial bins. The comparison of the correlation coefficients for the two types of fit using each participant's data suggested that that the linear and the exponential fits described the data equally well. (The exponential fit was determined by applying a linear trend to the log-transformed % error data.) We therefore used the slopes of the linear fits, that is, regression slopes predicting untransformed error rate from trial bin, for comparison of the learning curves between groups. Some individuals made no errors in some conditions, making a learning slope impossible to calculate. To prevent the loss of data points from other conditions, we did not analyze the slopes with a mixed ANOVA to prevent the loss of data points from other conditions. Instead, we compared the slopes between groups for each error type and each condition using independent samples t-tests (the slopes were normally distributed, so parametric tests were appropriate). The t-tests revealed that the slope of decrease in commission errors on the Punishment-Reward (Passive Feedback) condition was significantly steeper for Controls than for the ADHD participants ($t_{(17.6)} = 3.02$; $p = .008$). No other differences were significant.

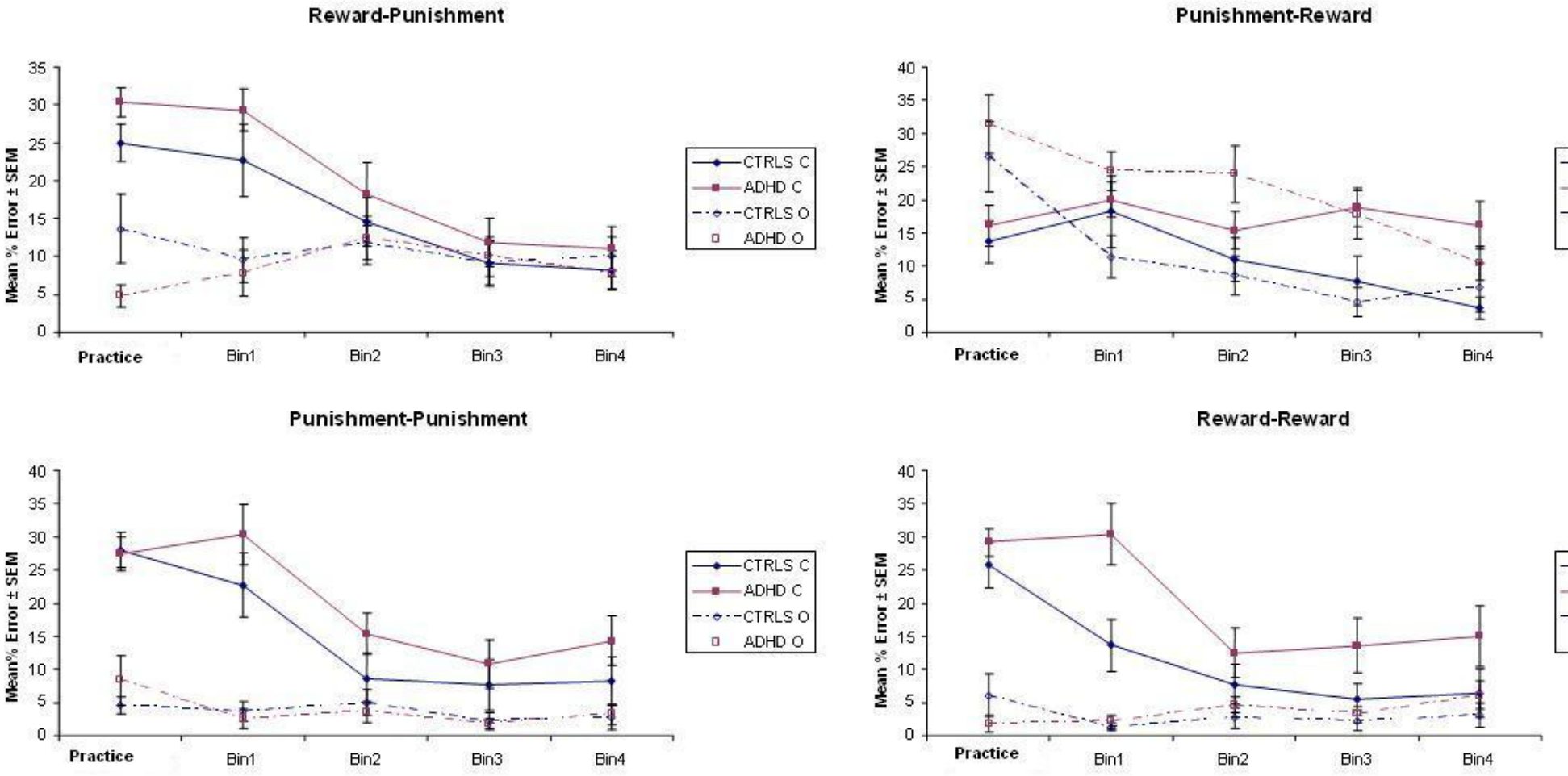


Figure 3-4: Learning curves of ADHD participants vs. controls on the Go/No-Go Discrimination leaning task. Commission errors are represented as solid lines, and omission errors are represented as dotted lines.

3.3.4 Concrete and Abstract Computerized Self-Ordered Working Memory Tasks

The data on these tasks could not be normalized with transformations, so pairwise non-parametric tests were used to compare the groups in each condition. The ADHD group tended to make more errors than Controls in the abstract version of the task but this was not sugnificant (Mann Whitney $U = 52.00$; $p = .09$). No other differences were observed.

3.3.5 Verbal Fluency

A two-way mixed ANOVA with Group as the between-subjects factor and Fluency Type (phonetic and semantic) as the within-subjects factor revealed a significant main effect of Fluency Type ($F_{(1,18)} = 398.6$; $p < .0005$) with more words generated in the semantic condition. ADHD participants tended to generate fewer words in both conditions (Group: $F_{(1,18)} = 4.29$ $p = .053$).

3.3.6 Trails A and B

A square root transformation was applied to normalize both Trails A and Trails B data. A two-way mixed ANOVA with Group as the between-subjects factor and Trails Type (Trails A vs. Trails B) as the within-subjects factor revealed the expected main effect of Trails Type ($F_{(1,24)} = 77.01$; $p < .0005$), with Trails B taking longer to complete. The ADHD group took non-significantly longer to complete the task (main effect of Group: $F_{(1,24)} = 2.84$; $p = .1$). No other effects approached significance (all $p>.1$).

3.3.7 Tower of Hanoi

A square root transformation was applied to the trials-to-completion data. A two-way repeated measures ANOVAs with Group as the between-subjects factor and Trial (trial 1 vs. trial 2) as the within-subjects factor revealed no significant main effects or interactions ($p_s > .17$).

3.3.8 Motor Hyperactivity:

Overall activity level, waking activity level, sleep duration, sleep activity level, and sleep mobility index were analyzed using independent samples t-tests comparing the ADHD group vs. controls. The alpha level was set at .01 to keep the family wise error rate at .05. Groups were not significantly different on any of the measures ($p_s > .1$) (Table 3-2).

	Controls	ADHD	N
Total Activity Level	322.59 ± 128.02	400.97± 150.75	8/12
Waking Activity Level	512.82 ± 167.86	675.87 ± 381.74	11/12
Sleep Duration	1126.5 ± 279.98	962.54 ± 141.65	11/12
Sleeping Activity Level	13.93 ± 9.13	21.54 ± 20.02	9/11
Sleep Mobility Index	32.78 ± 10.70	35.09 ± 11.29	9/11

Table 3-2: Actimetry parameters for Control and ADHD participants.

3.4 Blood Pressure, Heart Rate, and Plasma Amphetamine Levels

For blood pressure, heart rate and amphetamine levels, there were no significant main effects of Group and no interaction of Group with other variables.

For systolic blood pressure, there was significant main effect of Drug ($F_{(1,24)} = 57.27$; $p < .0005$), a significant main effect of Time Point ($F_{(4,21)} = 26.86$; $< .0005$), and a Significant Drug x Time Point interaction ($F_{(4,21)} = 32.64$; $< .0005$). The pattern of findings was similar for diastolic blood pressure with a significant main effect of Drug

($F_{(1,24)} = 26.92$; $p < .0005$), a significant main effect of Time Point ($F_{(4,21)} = 3.04$; $p = .05$), and a Significant Drug x Time Point interaction ($F_{(4,21)} = 15.17$; $p < .0005$). Increases in systolic blood pressure were evident on the amphetamine day, but not on the placebo day. The difference between baseline and subsequent time points was already significantly higher on the amphetamine day 1 hour after drug administration (i.e. at the time of tracer administration). It remained significantly higher at all the subsequent time points ($p_s \leq .03$). Increases in diastolic blood pressure between baseline and subsequent time points on the amphetamine day compared to the placebo day were evident starting mid-scan ($p_s < .0005$) and remained significant at all subsequent time points (see Figure 3-5).

For heart rate, there was a significant main effect of Drug ($F_{(1,24)} = 5.01$; $p = .04$), and a significant main effect of Time Point ($F_{(4,21)} = 10.97$; < .0005). Overall, heart rate was higher on the amphetamine day relative to placebo. Heart rate was also higher at baseline than at subsequent time points ($p_s \leq .002$). The effect of Group was at trend level ($F_{(1,24)} = 3.68$; $p = .07$), suggesting that the ADHD participants had marginally higher heart rates than Controls (Controls: 60.83 ± 4.87; ADHD: 66.96 ± 10.65).

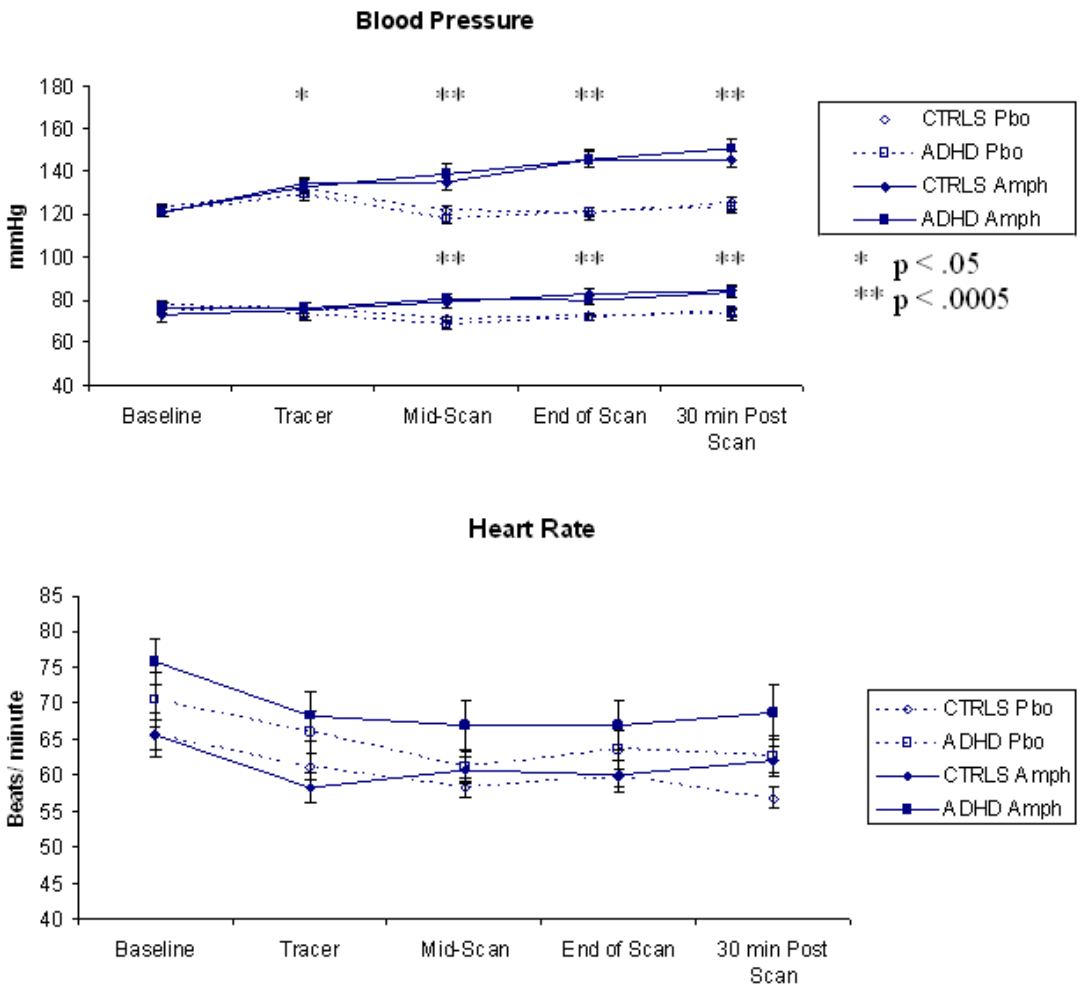


Figure 3-5: Blood pressure and heart rate. The placebo condition is represented using empty symbols and dotted lines, and the amphetamine condition is represented using filled symbols and solid lines.

Peak plasma amphetamine levels did not differ between the ADHD group (M = 15.16; SD = 13.72) and Controls (M = 14.66; SD = 12.35) ($t_{(27)}$ = .10; p =.92).

3.5 Subjective Response to Amphetamine

For the POMS, two Control participants' data were missing at one of the four time points on all the scales. To avoid the loss of these participants from the ANOVA,

mean substitution was used. Analyses excluding those two participants yielded the same pattern of results as those using substitution.

In the POMS analyses, there was a trend for a Group x Drug interaction on the Confident-Unsure scale ($_{(1,24)}$ = 4.25; $p < .05$); that was at trend level after Bonferroni correction. This result was driven by the fact that ADHD participants felt significantly more confident on *d*-AMPH relative to placebo (p = .006), while Controls did not. Group did not affect other scales as a main effect nor in interaction with other variables. Three of the POMS scales showed main effects of Drug qualified by a significant Drug by Time Point Interaction, indicating that the change between baseline and subsequent time points was larger on the amphetamine day than on the placebo day (Interaction: Elated-Depressed scale ($F_{(3,81)}$ = 9.26; $p < .0005$); Energetic-Tired ($F_{(3,81)}$ = 15.00; $p < .0005$) Agreeable-Hostile ($F_{(3,81)}$ = 7.96; $p < .0005$). Both groups felt significantly more Elated and Energetic on *d*-AMPH than placebo at the time of tracer administration, mid-scan, and immediately post-scan ($p_s \leq .04$). Both groups also felt more Agreeable on *d*-AMPH mid-scan and immediately post-scan ($p_s \leq .009$) than on placebo, which was confirmed with the Wilcoxon Signed Ranks test ($p_s \leq .01$). For the Composed-Anxious scale, there was a significant Drug x Time Point x Drug Order interaction ($F_{(2.45, 66)}$ = 4.84; $p = .007$), indicating that participants felt significantly more composed at baseline on the placebo day when placebo was given on the second scan ($p = .03$) (Figure 3-6).

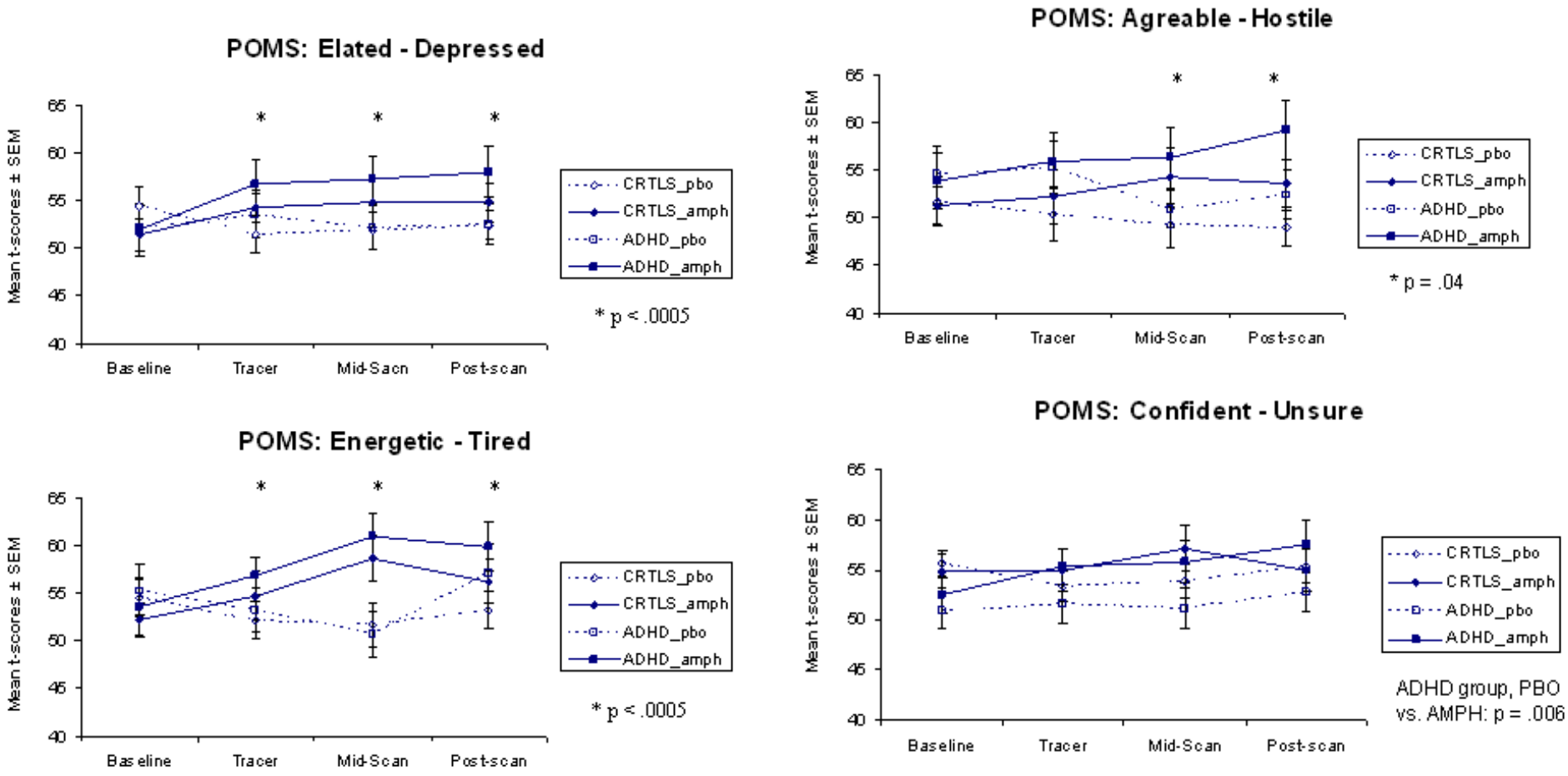


Figure 3-6: Profile of Mood States. The placebo day is represented using open symbols and dotted lines; the amphetamine day is represented using filled symbols and solid lines. Asterisks indicate significant differences between drug and placebo at the indicated time point

For the VAS AUC values, there was a significant main effect of Drug ($F_{(1,25)}$ = 11.86; p = .002), qualified by a significant Drug x VAS Scale interaction ($F_{(5.92, 148.02)}$ = 14.07; p = .04), indicating that AUCs were larger on the *d*-AMPH than the placebo day across all VAS scales (p_s < .05), except the Anxiety scale (p = .93). This indicated greater increases from baseline in ratings of activating and pleasurable effects of the drug on the *d*-AMPH day. The Wilcoxon Signed Ranks test confirmed the effect of Drug on the Rush scale, which deviated from normality (Z = -3.10; p = .002) (Figure 3-7). There was also a trend for a three-way Group x Drug x VAS scale interaction ($F_{(5.9,148.1)}$ = 1.9; p = .08), suggesting that positive subjective effects of the drug were evident on more VAS scales for ADHD participants than Controls. Both Controls and ADHD participants reported feeling more High (Controls: p = .05; ADHD: p = .04), Energetic (Controls: p = .02; ADHD: p = .01), and Alert (Controls: p = .006; ADHD: p = .003) on the drug than placebo. However, ADHD participants also reported feeling more Excited (p= .01), as well as more drug liking (p = .003) and drug wanting (p = .008) on the drug than placebo, which Controls did not report (p_s > .1). On the other hand, Controls reported feeling more Rush (p = .02) on drug than placebo, which ADHD participants did not report (p > .1).

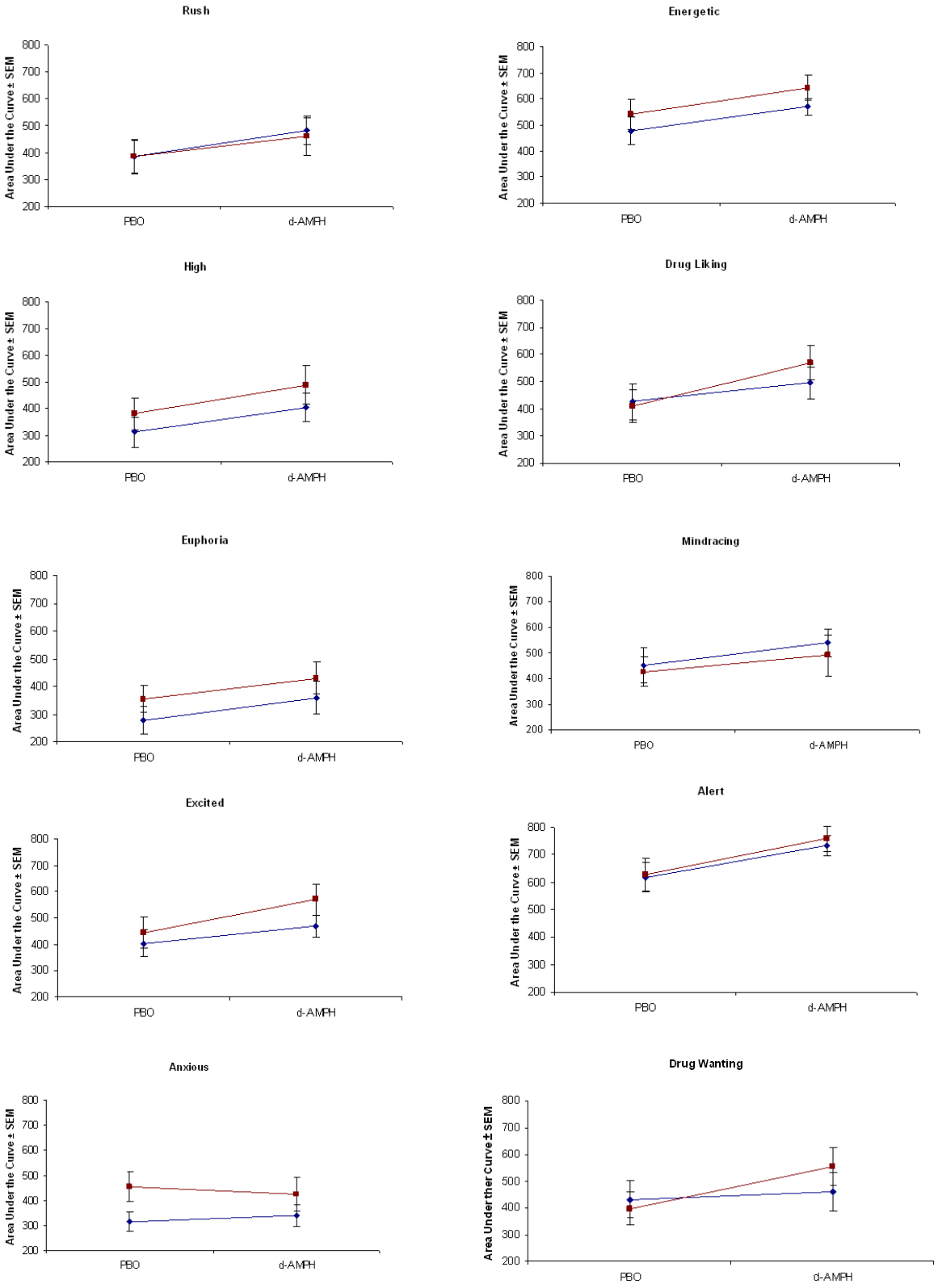


Figure 3-7: Visual Analogue Scales. Area Under the Curve on placebo and *d*-AMPH days. Red symbols represent ADHD, and blue symbols represent controls.

For the ARCI, both groups showed a greater change from baseline in subjective experience of amphetamine on *d*-AMPH than on placebo (Drug: $F_{(3,26)} = 30.40$; $p < .0005$ (Figure 3-8). There was no effect of Group ($p > .1$).

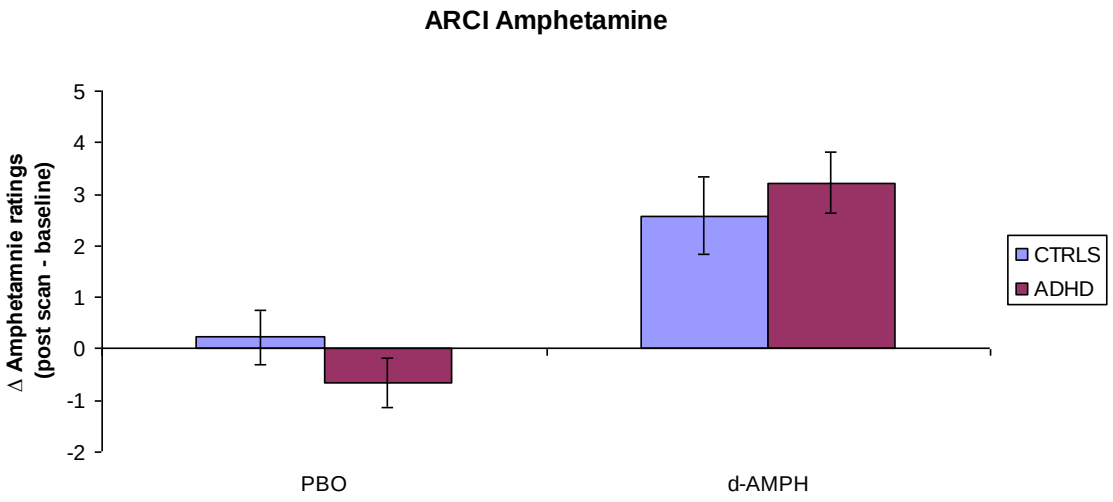


Figure 3-8.ARCI. Change from baseline in Amphetamine rating on the ARCI on placebo and *d*-AMPH days.

3.6 *d*-AMPH-Induced Change in D2/D3 Binding

3.6.1 Voxel-Wise t-Maps

For the Control group, the voxel-wise analysis revealed a significant decrease in [^{11}C]raclopride binding between *d*-AMPH and placebo only in the right post-commissural putamen (peak: t = 4.31; x = 30.6, y = -7.7, z = 1.8). For the ADHD group, a significant decrease in [^{11}C]raclopride binding was detected in the post-commissural putamen bilaterally (peak: t = 6.72; x = -27.9, y = -8.8, z = 2.2), in the pre-commissural caudate

bilaterally (peak: t = 5.32; x = -16.1, y = 14.2, z = 1.6), and in the right ventral striatum (peak: t = 4.62; x = 18.3, y = 14.0, z = -5.9)(Figure 3-9).

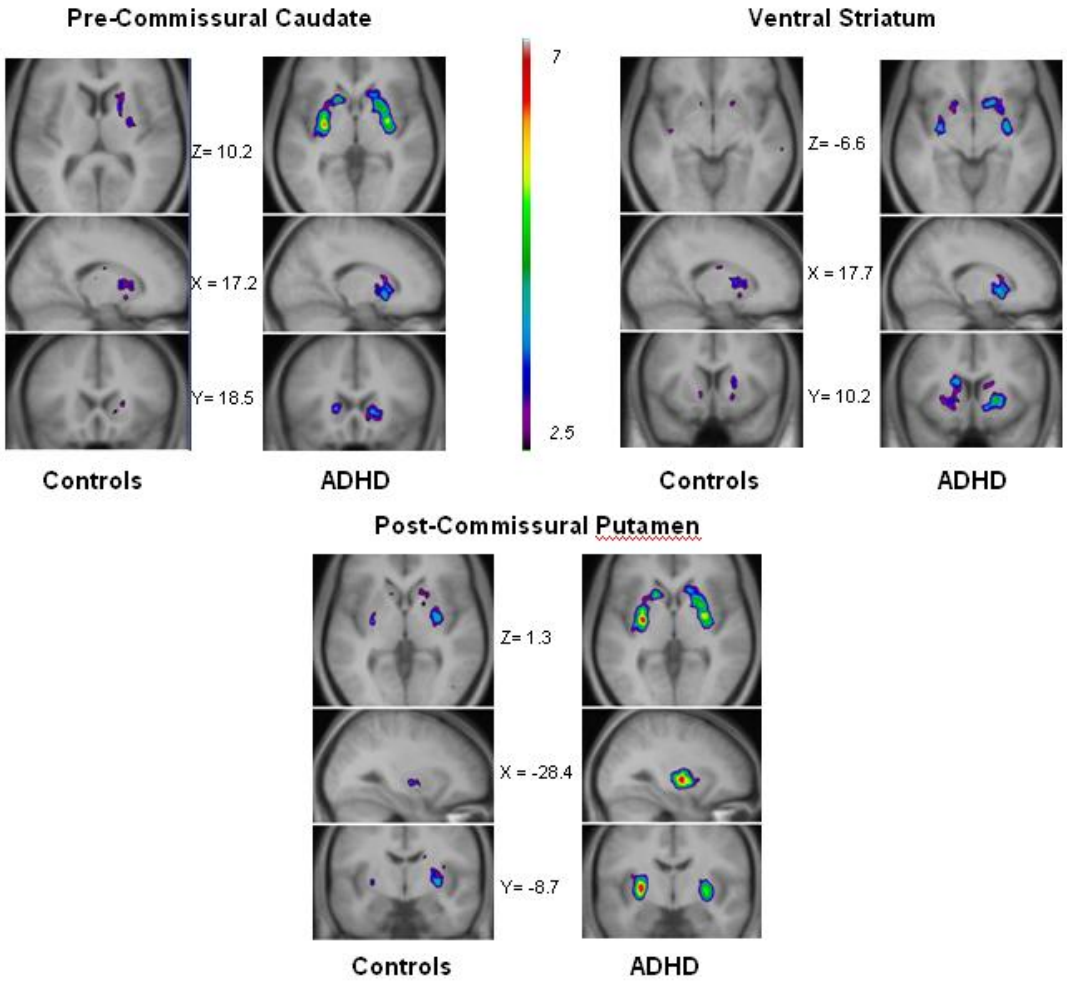


Figure 3-9. Voxel-wise t-maps showing d-AMPH-induced reductions in [^{11}C]raclopride binding in pre-commissural caudate, ventral striatum, and pos-commissural putamen in the ADHD and controls groups.

3.6.2 The ROI Analysis

The *d*-AMPH-induced %ΔBP in the Limbic, Associative, and Sensorimotor striatal ROIs for the ADHD and Control groups are given in Table 3-3. The *d*-AMPH-induced %ΔBP was significantly correlated with BDI scores at intake in the ADHD group (r = .56; p = .04), but not in the Control group (r = .06; p = .85). Since the intake BDI scores in ADHD participants were significantly higher than Controls and also predicted *d*-AMPH-induced % ΔBP, intake BDI was entered as a covariate in the 3-way Group x ROI x Hemisphere ANOVA on the % ΔBP. One ADHD and one Control participant were missing BDI scores at intake; their missing values were replaced by the mean of their respective groups to prevent the loss of those participants from the ANOVA. (The ANOVA excluding those participants produced the same results.)

Consistent with the voxel-wise analysis, the ANOVA on the ROI data revealed a significant main effect of Group ($F_{(1,25)}$ = 5.98; p = .02), indicating that amphetamine produced a more pronounced decrease in [^{11}C]raclopride binding in the ADHD group than Controls across the three ROIs. The group difference was significant in the sensorimotor ROI (p = .004) and at trend level in the Limbic (p = .07) and Associative (p = .07) ROIs (see Figure 3-10). The ANOVA also revealed a 3-way Group x Region x Drug Order interaction ($F_{(2,25)}$ = 5.50; p = .02), indicating that in the limbic ROI, the more pronounced decrease in BP in the ADHD group than Controls was only evident if the placebo scan took place first (ADHD vs. Controls (placebo first): $F_{(1,25)}$ = 5.76; p = .02), but not when the drug scan took place first (p > .1). In addition, there was a significant Region x Hemisphere x Drug Order interaction ($F_{(1,50)}$ = 4.93; p = .03), driven by the fact that in the Associative ROI, there was a significant left > right asymmetry in *d*-AMPH-

induced decrease in binding only when placebo was given first (Left > Right: $F_{(1,25)} = 4.8$ $p = .04$), but not when d-AMPH was given first ($p > .1$).

	Limbic		Associative		Sensorimotor	
	Left	Right	Left	Right	Left	Right
CTRLS	-5.88 ± 10.90	-6.30 ± 10.06	-3.21 ± 10.83	-4.41 ± 10.22	-3.09 ± 10.22	-3.86 ± 9.65
ADHD	-10.14 ± 11.02	-11.63 ± 11.41	-5.96 ± 11.16	-6.91 ± 11.44	-10.06 ± 11.80	-10.40 ± 12.42

Table 3-3: *d*-AMPH-induced % decrease in [^{11}C]raclopride binding in the Limbic, Associative, and Sensorimotor ROIs.

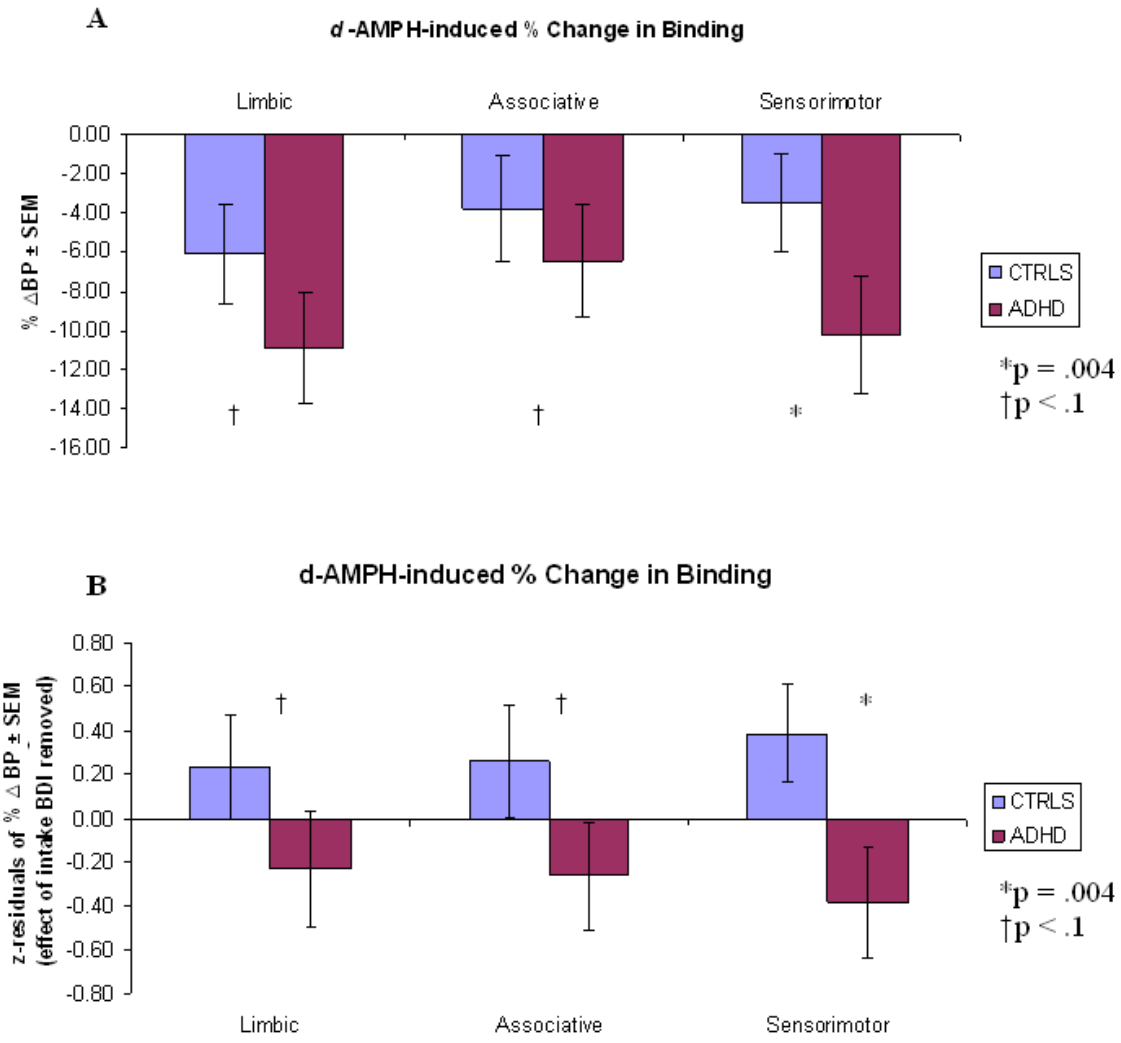


Figure 3-10. ROI analysis: *d*-AMPH-induced % decrease in [^{11}C]raclopride binding in the ADHD vs. Controls. A represents original data, and B represents standardized residuals of the % change in BP, with the effect of intake BDI removed. The p values indicate the significance of the between-group differences in % change in BP in each region and are based on BP values extracted from the three ROIs drawn on MRIs.

3.7 Baseline D2/D3 Binding

Stimulant-induced changes in levels of extracellular dopamine at baseline have been postulated to be linked to baseline DA levels (Grace, 2001). A number of previous studies have reported alterations in baseline binding in ADHD (Ilgin et al., 2001; Lou et al., 2004; Volkow et al., 2007b; Volkow et al., 2009). Given the significant group difference in the ΔBP, the possibility of a group difference in baseline [^{11}C]raclopride binding in the three striatal ROIs was also examined. First, we tested the association between baseline binding and age, as these variables have previously been reported to be correlated (Ichise et al., 1998; Rinne, Lönnberg, & Marjamäki, 1990; Volkow et al., 1996a). As expected, baseline binding was negatively correlated with age across all striatal ROIs ($r = -.60$; $p < .0005$) (see Figure 3-11).

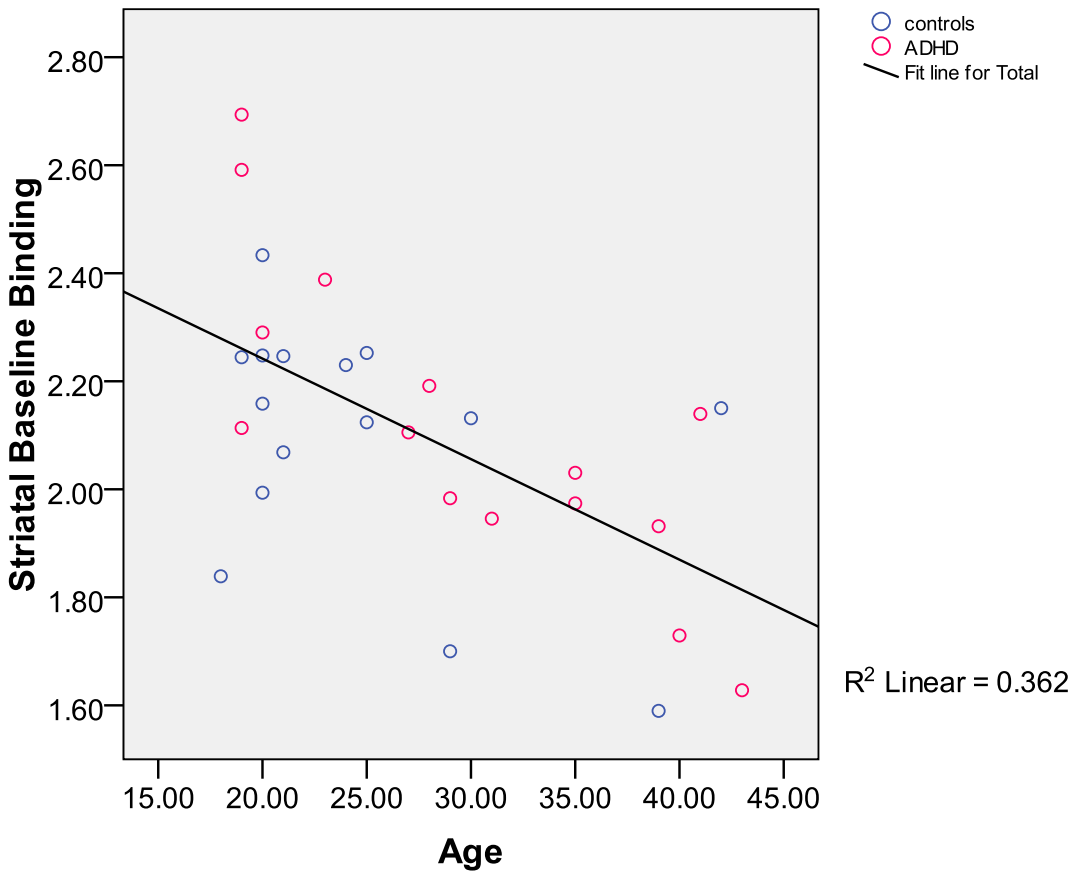


Figure 3-11. The relationship between baseline [^{11}C]raclopride binding and age.

Thus, in group comparisons of the baseline BP values in each ROI, Age was entered as a covariate. Significantly higher [^{11}C]raclopride binding in the sensorimotor ROI was found in the ADHD group than Controls ($F_{(1,27)} = 4.11$; $p = .05$). There were no group differences in baseline binding in the other two ROIs ($p_s \geq .13$) (Figure 3-12).

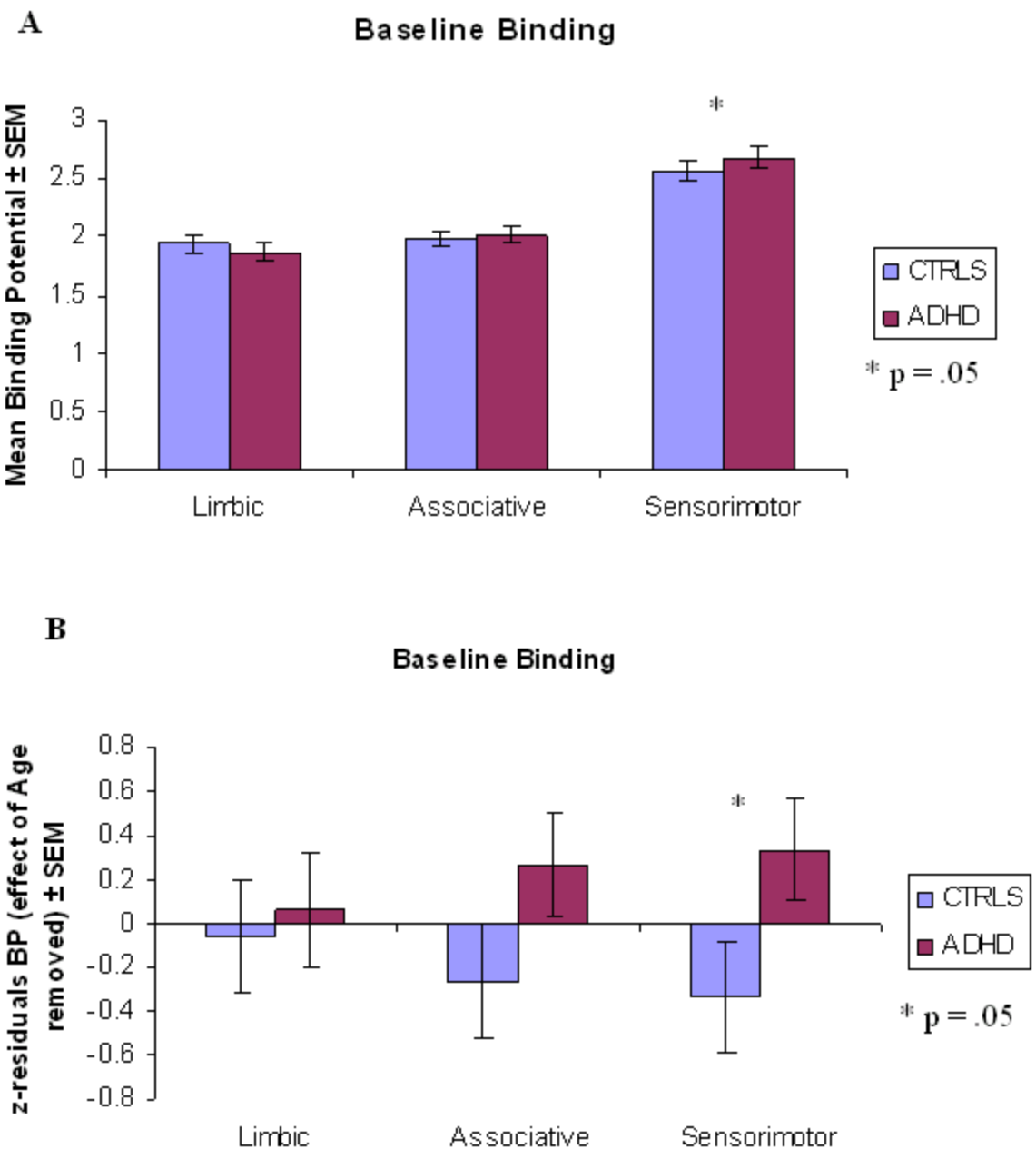
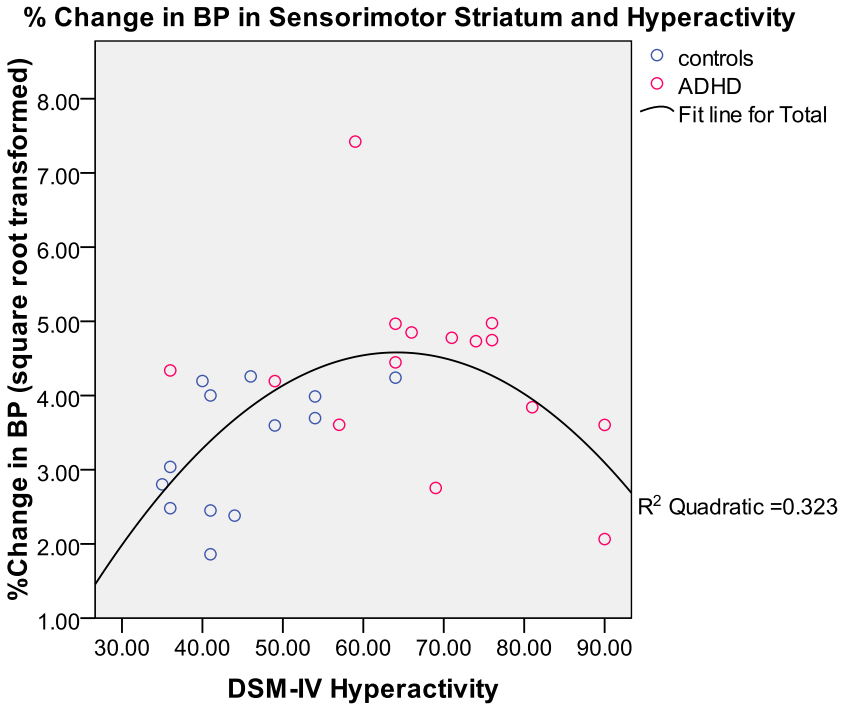


Figure 3-12. Baseline binding in Limbic Striatum, Associative Striatum and Sensorimotor Striatum in the ADHD group vs. controls: A represents original data, and B represents standardized residuals of baseline BP, with the effect of age removed.

3.8 Personality, Symptoms, and Neurocognition in relation to % ΔBP

Regression analyses were used to examine the relationship between % ΔBP in the three striatal ROIs and symptoms of inattention and hyperactivity as measured by the E

(DSM-IV Symptoms of Inattention) and the F (DSM-IV Symptoms of Hyperactivity) scales of the CAARS. A Bonferroni correction for multiple comparisons yielded an alpha level of p = .008. Significant quadratic associations were observed between hyperactivity scores and % ΔBP in the sensorimotor (r = .57; p = .008), and in the associative (r = .57; p = .007) ROIs across both groups. The largest changes in [^{11}C]raclopride binding were observed in individuals reporting moderate levels of activity; smaller changes were found in non-hyperactive and highly hyperactive individuals (see Figure 3-13).



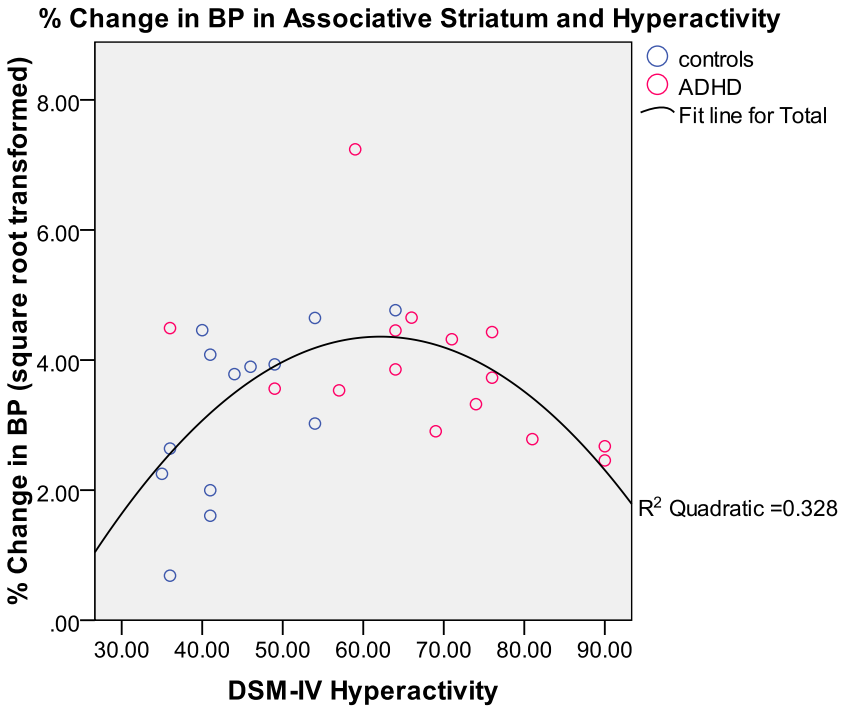
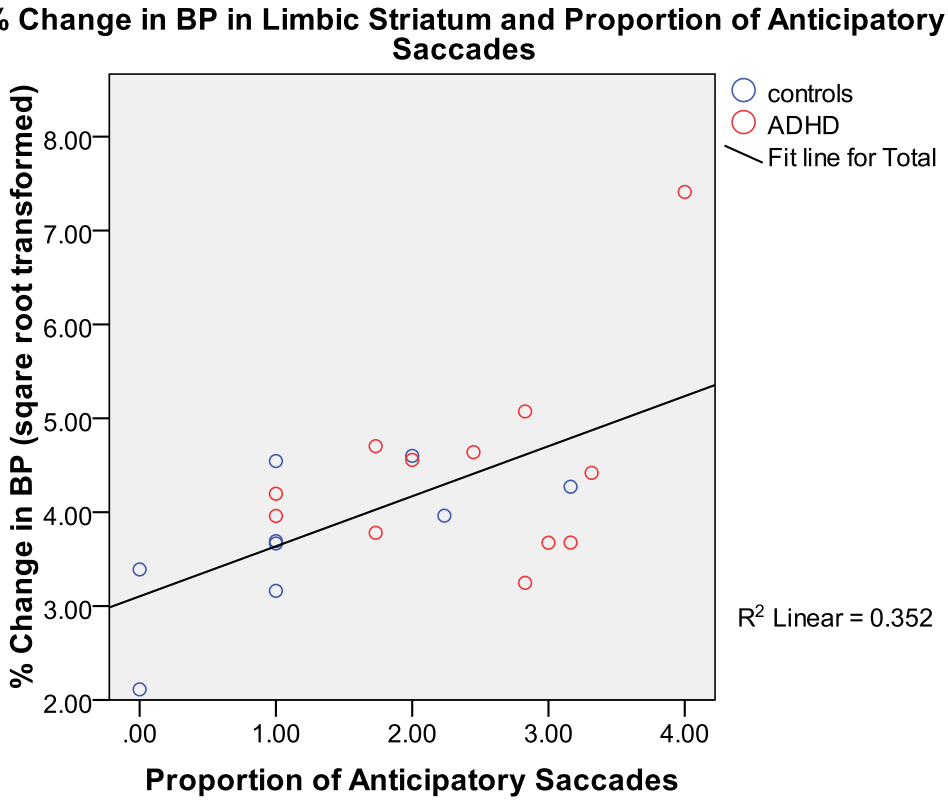


Figure 3-13. Quadratic U-shaped associations between symptoms of hyperactivity and *d*-AMPH-induced % ΔBP in the sensorimotor and associative ROIs. Square root transformed values for % change in BP are used, with higher values indicating greater decreases in [^{11}C]raclopride binding.

Potential associations were explored between % ΔBP and personality variables that have been linked to dopaminergic function, i.e. the Novelty Seeking scale on the TPQ, Extraversion on the NEO, and the BIS-11 scores. No significant associations were found between these personality measures and % ΔBP (p_s > .1).

Finally, the relationship was examined between % ΔBP and performance on the neurocognitive tasks that best differentiated the ADHD group and the controls, i.e. the Stop Signal paradigm and the Antisaccade task (% antisaccade errors and % anticipatory saccades). A Bonferroni correction for multiple comparisons (3 neurocognitive measures x 3 ROIs) resulted in the alpha level of p = .005. Significant linear associations were observed between the proportion of anticipatory saccades and % ΔBP in the limbic (r =

.59; p = .005) and the sensorimotor (r = .62; p = .003) ROIs across both groups, with greater % change in BP associated with a greater proportion of anticipatory saccades (Figure 3-14). However, visual inspection of the scatter plot (Figure 3-14) revealed that one data point had an extreme value on % ΔBP. To ensure that the results were not being driven by this extreme value, we re-ran the analysis using a non-parametric correlation (Spearman's Rho). The associations between the proportion of anticipatory saccades and % ΔBP in the limbic (ρ = .45; p = .04) and the sensorimotor (ρ = .52; p = .02) ROIs remained, indicating that the extreme value did not account for the associations. There was no significant relationship between % ΔBP and antisaccade error rate or SSRT.



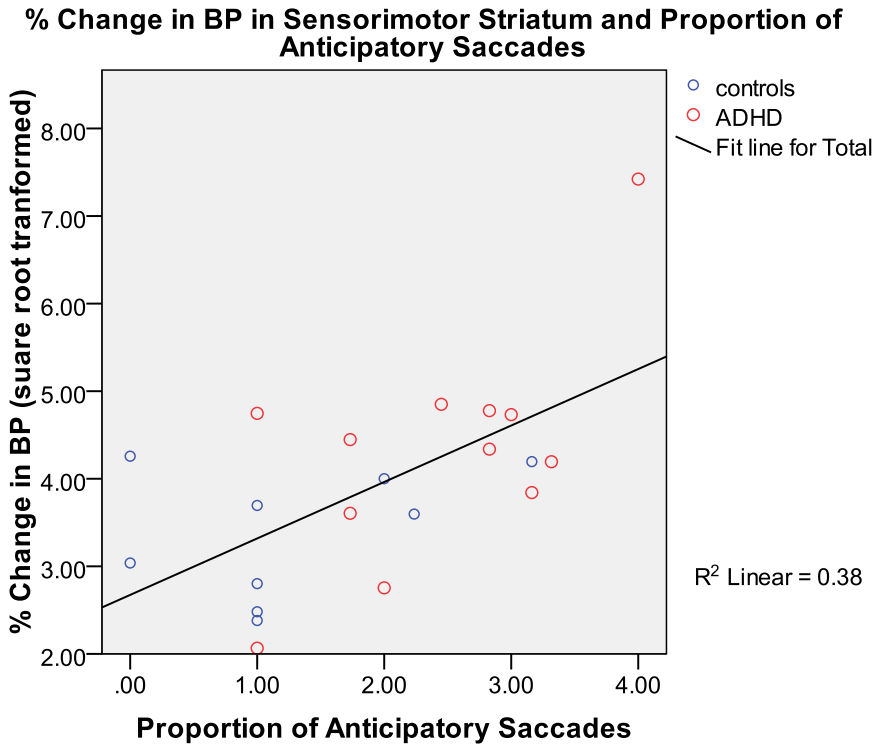


Figure 3-14. Associations between proportion of anticipatory saccades on the antisaccade task and *d*-AMPH-induced % ΔBP in the limbic and sensorimotor ROIs. Square root transformed values for % ΔBP are used, with higher values indicating greater decreases in [^{11}C]raclopride binding.

3.9 Subjective Response to *d*-AMPH in Relation to *d*-AMPH-Induced %ΔBP

The relationship between individual differences in % ΔBP and subjective response to amphetamine on the scales that showed significant drug-induced changes were examined using stepwise regression analyses. No significant associations were observed between % ΔBP and subjective response to *d*-AMPH as measured by the VAS or the ARCI (p_s > .05). On the POMS, greater *d*-AMPH-induced increases in feeling energetic predicted larger % ΔBP in the sensorimotor ROI (r = .40; p = .03) (Figure 3-15).

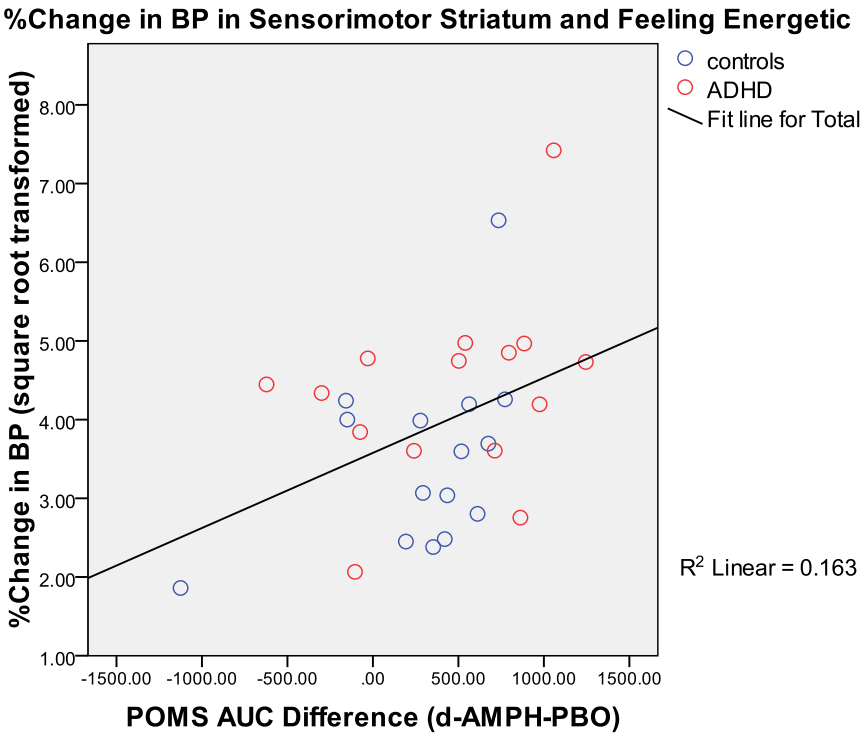


Figure 3-15. Association between self-reported feeling energetic (vs. tired) subsequent to *d*-AMPH administration and *d*-AMPH-induced % ΔBP in the sensorimotor ROI. Square root transformed values for % ΔBP are used, with higher values indicating greater decreases in [^{11}C]raclopride binding. Higher AUC difference values indicate more pronounced increases in feeling energetic on the *d*-AMPH scan.

3.10 Voxel Based Morphometry

The VBM analysis did not reveal any significant differences in caudate or putamen gray matter density between the ADHD and Control groups ($p > .1$).

3.11 Cortical Thickness

A vertex-wise analysis of group differences in frontal cortical thickness did not reveal any significant differences between the ADHD group and Controls. Diagnostics

on the initial regression analyses looking at the relationship between cortical thickness and % ΔBP (using both the untransformed and the square root transformed data), indicated that one data point in the ADHD group and one data point in the Control group had a large influence on the regression slopes (leverage values: ≥ .2; Standardized DF Betas: ≥ .35), in both cases due to a large % ΔBP. Hence the data were reanalyzed using the Winsorized values for these two participants (Dixon & Yuen, 1974; Tukey, 1962), and the results reported below are based on the Winsorized data. Once the values for these two participants were Winsorized, data were normally distributed. The Group by % ΔBP interaction term was significant for the association between % ΔBP in the sensorimotor striatum and cortical thickness throughout most of the frontal regions, predominantly in the right hemisphere. These included the following five clusters: right medial superior frontal gyrus (x = 6, y = 34, z = 49) ($t > 3.54$; $p < .001$); right middle frontal gyrus (x = 36, y = 52, z = 22) ($t > 4.1$; $p < .001$); left dorsal premotor cortex (x = -17, y = 4, z = 69) ($t = 4.44$; $p < .001$); right precentral sulcus (x = 31, y = -10, z = 63) ($t > 3.68$; $p < .001$); and right gyrus rectus (x = 1, y = 42, z = -25) ($t > 3.71$; $p < .001$). These interactions suggest a different relationship between cortical thickness and % ΔBP in Controls than the ADHD group. Although this was not initially hypothesized, dissimilar associations between gray matter volume/ thickness and cognitive function have been previously observed in clinical populations versus controls (Duarte et al., 2006; Hartberg et al., 2010) and interpreted as evidence of disrupted structure-function relationships in patients. We therefore explored the relationship between cortical thickness and DAergic function in each group.

For the Controls, thicker cortex in a cluster in the right middle frontal gyrus (x = 36, y = 52, z = 21) was associated with smaller % ΔBP ($t > 4.26$; $p < .001$). Conversely, in the ADHD group, thicker cortex in this cluster was associated with larger %ΔBP ($r = .62$; $p = .01$), though this association did not reach significance in the within group vertex-wise analysis, which corrects for the number of vertices in the frontal volume. For the ADHD group, thicker cortex in clusters in the right medial superior frontal gyrus (x = 6, y = 35, z = 46), the left dorsal premotor cortex (x = -15, y = 5, z = 68), and the right gyrus rectus (x = 1, y = 42, z = -25), was associated with greater % ΔBP ($t > 3.68$; $p < .001$) (Figure 3-16). In Controls, there were trends for thicker cortex in these regions to be associated with smaller % ΔBP, though these associations did not reach significance in the vertex-wise analyses (right medial superior frontal gyrus: $r = .45$; $p = .09$; left dorsal premotor cortex: $r = .45$; $p = .09$; right gyrus rectus: $r = .54$; $p = .04$). In the right precentral sulcus, associations of cortical thickness with % ΔBP did not reach significance in vertex-wise regressions in either group. However, in line with the above findings, thicker cortex in this region was associated with smaller % ΔBP in Controls ($r = .66$; $p = .007$) and with larger % ΔBP in ADHD participants ($r = .56$; $p = .03$).

Similar relationships were observed between cortical thickness and % ΔBP in the associative striatum. The Group by % ΔBP interaction term was significant in a cluster in the left central sulcus (x = -36, y = -25, z = 62) ($t > 3.84$; $p < .001$). In the Control group, thicker cortex in this region was associated with smaller % ΔBP ($r = .47$; $p = .08$), whereas in the ADHD group the direction of the association was opposite ($r = .844$; $p < .0005$), although vertex-wise regressions in each group did not reach significance in this specific locus.

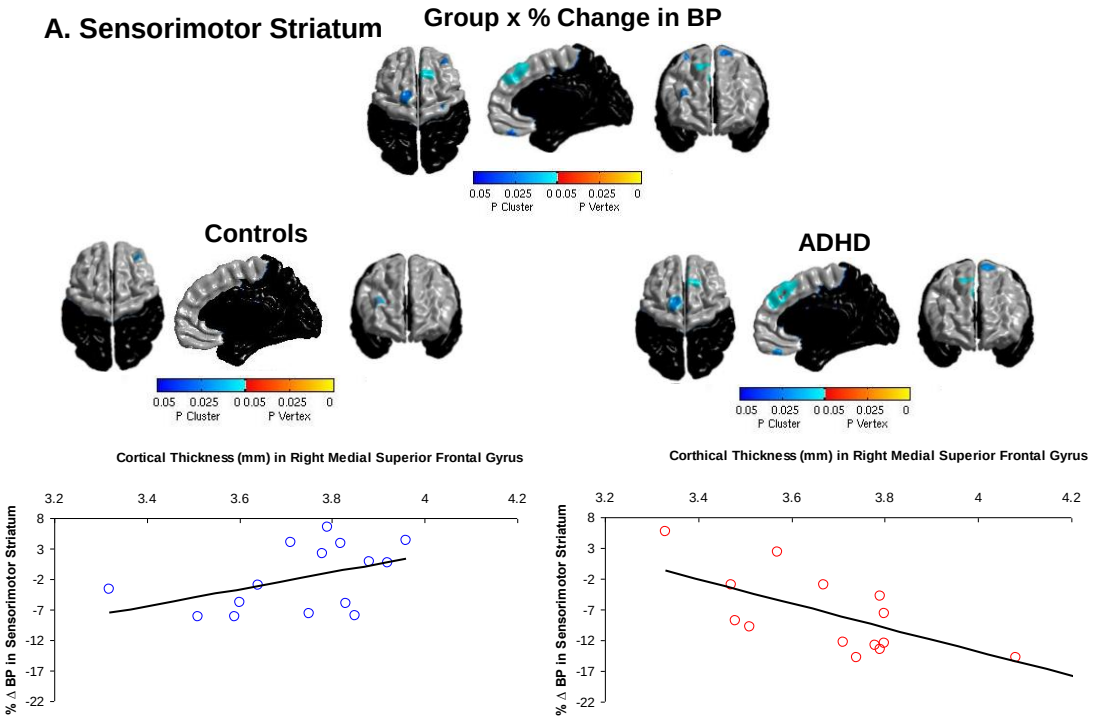


Figure 3-16. (A) P-maps show clusters of significant associations between %Δ BP in Sensorimotor striatum and frontal cortical thickness for Controls and ADHD participants; scatter plots show associations between %Δ BP in Sensorimotor striatum and thickness in the right medial superior frontal gyrus (x = 6, y = 35, z = 46). (B) P-maps show clusters of significant associations between %Δ BP in Associative striatum and frontal cortical thickness for Controls and ADHD participants; scatter plots show associations between %Δ BP in Associative striatum and thickness in the left central sulcus (x = -36, y = -25, z = 62).

3.12 Genotyping

The distribution of the DAT1, DRD4, and COMT genotypes in the ADHD and Control groups are given in Appendix 1. Across the groups, there was a non-significant trend for carriers of the 7-repeat allele of the 48-babse pairs DRD4 VNTR to have higher ADHD symptom scores than the non-carriers (main effect of Genotype: $F_{(1,22)} = 3.05$; $p = .1$). In addition, 7-repeat allele carriers had higher impulsivity scores across all subscales of the BIS-11 (main effect of Genotype: $F_{(1,22)} = 6.64$, $p = .02$) and marginally higher Novelty Seeking scores on the TPQ (main effect of Genotype: $F_{(1,22)} = 3.83$, $p = .06$), consistent with some previous reports (Faraone & Mick, 2010; Schinka et al., 2002).

There were no significant effects of DRD4, DAT1, or COMT genotypes on *d*-AMPH-induced change in binding ($p_s > .1$).

CHAPTER 4:

DISCUSSION

Converging evidence from various lines of research has strongly implicated the dopamine system in the pathophysiology of ADHD. However, studies directly examining dopamine transmission in ADHD have yielded inconsistent findings, and the nature of the putative dopaminergic alterations remains poorly understood. The present dissertation examined the response of the dopamine system to a *d*-AMPH challenge in treatment-naïve adults with ADHD and control participants and considered the dopamine response in relation to symptomatology, neurocognitive function, subjective responses to the drug, neuroanatomy, and genotypic variation.

The ADHD group showed greater striatal *d*-AMPH induced [^{11}C]raclopride binding (% ΔBP) than Controls, suggesting greater release of endogenous dopamine. This group difference was most pronounced in the sensorimotor region of interest. As expected, the ADHD participants also had significantly higher symptom scores, as well as higher self-reported impulsivity on personality measures, and performed more poorly on neurocognitive tasks tapping response inhibition.

Individual differences in *d*-AMPH induced % ΔBP varied with ADHD symptomatology and inhibitory function. There was a quadratic U-shaped association between the *d*-AMPH induced % ΔBP in sensorimotor and associative ROIs and CAARS hyperactivity scores across both groups, with the largest % ΔBP in individuals reporting moderate levels of activity and smaller responses in both non-hyperactive and highly hyperactive individuals. Linear relationships were observed between *d*-AMPH induced % ΔBP and proportion of anticipatory saccades on the antisaccade task. Finally, there were significant linear associations between frontal cortical thickness and % ΔBP in associative and sensorimotor ROIs; however the direction of the association was opposite

in the two groups. In the control group, thicker cortex predicted smaller *d*-AMPH induced % ΔBP, in the ADHD group the relationship was reversed, with greater cortical thickness predicting greater *d*-AMPH induced % ΔBP.

The present investigation is the first to examine *d*-AMPH induced % ΔBP in treatment naïve ADHD adults. A previous study examined methylphenidate-induced dopamine response in this population. It is also the first to examine the relationship between neurocognitive performance, cortical thickness, genotype and *d*-AMPH induced % ΔBP. Thus, the present investigation bridges the neuroimaging literature on frontal abnormalities in ADHD and the neuroreceptor imaging studies suggesting alterations at the level of the striatal dopamine function.

4.1 Demographics and Symptom Scores and Previous Drug Exposure

The ADHD and the control groups were well-matched in terms of demographic characteristics, including age, years of education, and father's socio-economic status. There was a trend for ADHD participants to have lower estimated Full Scale IQs than controls, which is in line with previous findings (Bridgett & Walker, 2006; Frazier et al., 2004). The ADHD group consisted of 10 participants with the Inattentive and 5 participants with the Combined subtype, which is consistent with the reports of greater persistence of inattention than hyperactivity symptoms into adulthood (Brown & Gammon, 1995; Hart et al., 1995; Millstein et al., 1997). As expected, the ADHD participants had significantly higher symptom scores as measured by the CAARS.

Participants were free of any current or past psychopathology (other than ADHD), with the exception of two ADHD participants who had a history of a single mild major

depressive episode. Given the high rates of comorbidity of adult ADHD with other forms of psychopathology (Biederman et al., 2006; Cumyn, French, & Hechtman, 2009; Mannuzza et al., 1993; Weiss, 1993), our non-comorbid ADHD sample may not be considered highly representative. However, lack of comorbidities allowed us to eliminate potential confounding influences of comorbid psychopathology on brain function and attribute the observed group differences to ADHD.

Participants had very low levels of lifetime stimulant drug exposure, with no stimulant exposure within two years prior to participation. The ADHD participants were naïve to pharmacological treatment, except for one subject who underwent a month-long methylphenidate trial two years previously. The low levels of prior stimulant exposure in our participants allowed us to minimize the likelihood of observing sensitized stimulant-induced dopamine responses, which can result from repeated stimulant exposure in both animals and humans (Boileau et al., 2006; Leyton, 2007). Furthermore, both groups had very low levels of previous exposure to other drugs of abuse, which can increase extracellular DA levels in the striatum (Di Chiara et al., 2004; Di Chiara & Imperato, 1988), and could also have lasting influences in dopamine system function with repeated use.

4.2 Personality and Neurocognitive Performance

The ADHD group demonstrated personality profile characteristics consistent with those previously reported in the literature. Relative to Controls, the ADHD participants reported higher levels of impulsivity on the BIS-11. The ADHD group also reported lower Conscientiousness, higher Neuroticism, and higher Harm Avoidance relative to

Controls, which has been documented previously (Anckarsater et al., 2006; Downey et al., 1997; Jacob et al., 2007; Nigg, 2006; Nigg et al., 2002b; Ranseen et al., 1998). Deficits in maintaining task focus and concentration, characteristic of ADHD, may be reflected in low Conscientiousness. On the other hand, higher emotional lability, negative emotionality, and difficulty coping with stress (Shea & Fisher, 1996; Wender, 1995) may be reflected in higher Neuroticism, as well as in higher Harm Avoidance scores (this scale includes such items as "*I often have to stop what I am doing because I start worrying about what might go wrong*" and "*I need much extra rest, support, or reassurance to recover from minor illnesses or stress*"). Although previous studies also reported higher Novelty Seeking scores in ADHD participants than Controls (Anckarsater et al., 2006; Downey et al., 1997; Jacob et al., 2007; Tillman et al., 2003), we did not find this in our sample. This was likely due to the higher Novelty Seeking scores in our control group (18.4 ± 4.67), than has been reported in normative data (13.0 ± 4.9) (Cloninger et al., 1991). Controls with higher levels of Novelty Seeking may be more likely to volunteer for research involving administration of a stimulant drug and a radiolabeled compound.

The neurocognitive profile of our ADHD sample was consistent with a deficit in response inhibition: significant group differences were found in the SSRT and the proportion of reflexive directional errors and anticipatory saccades on the antisaccade task. The learning curves of the ADHD group vs. Controls on the Go/No-go Discrimination Learning Task were also consistent with an inhibitory deficit. Unlike Controls, the ADHD participants did not to show a reduction in commission errors over trials on the Punishment-Reward (Passive Feedback) version of the task, where correct

non-responses were rewarded, which suggests a failure to learn to withhold responses. Our finding of an inhibitory deficit is consistent with meta-analytic findings reporting some of the largest effect sizes for response inhibition (Nigg, 2005; Willcutt et al., 2005). They are also in line with a model postulating response inhibition as a core neuropsychological deficit in ADHD (Barkley, 1997). Trend-level group differences were also detected on tasks of visual working memory (Self-Ordered Working Memory Tasks), verbal fluency, and visuomotor speed and set shifting (Tails A and B), as well as IQ. Deficits on tasks assessing these functions have also been demonstrated repeatedly in ADHD, although they tended to yield somewhat smaller effect sizes in meta-analyses than inhibition (Nigg, 2005; Willcutt et al., 2005). The trend level findings are likely attributable to our relatively small sample size; these effect sizes (d = .52 - .8) would require samples sizes of > 26 participants in each group to detect significant differences at $p < .05$, with a power of .8 (Cohen, 1988).

4.3 Genotypes

The low sample size does not permit any firm conclusions regarding our genotyping data. However, the trend for the carriers of the 7-repeat allele of the 48-base pairs DRD4 VNTR to have higher ADHD symptom scores, as well as higher impulsivity and novelty seeking is consistent with much of the previous literature (Faraone & Mick, 2010; Schinka et al., 2002). No significant effects of genotype on the *d*-AMPH induced % ΔBP was observed; this could reflect a true absence of association or could be attributable to the small sample size, considering that most of the genes we examined have more than two polymorphisms.

4.4 *d*-AMPH-Induced Change in [^{11}C]Raclopride Binding

The ADHD group showed a more pronounced % ΔBP than Controls, which suggests greater *d*-AMPH-induced increases in levels of endogenous DA in ADHD participants (Laruelle, 2000). Assuming that the displacement of [^{11}C]raclopride primarily reflects changes in synaptic, rather than extrasynaptic DA concentrations (Laruelle, 2000), *d*-AMPH-induced changes in BP should primarily reflect the synaptic DA influx from phasic bust firing, which cannot be cleared by the DAT (the primary clearing mechanism) due to interference from *d*-AMPH. (Due to the perisynaptic location of the DAT, the reverse transport function of *d*-AMPH would primarily result in a rise in extrasynaptic, rather than synaptic DA concentrations (Caron & Gainetdinov, 2010).) Although the [^{11}C]raclopride PET method does not distinguish between changes in binding due to tonic vs. phasic DA levels, given that phasic DA effluxes are orders of magnitude higher than tonic DA concentrations, phasically released synaptic DA might contribute most of the ΔBP signal. Hence, the finding of greater decreases in [^{11}C]raclopride binding in the ADHD group could be interpreted as evidence of augmented phasic DA release. Such an interpretation would be in line with Grace's model of ADHD which postulates augmented phasic DA release ensuing from abnormally low striatal DA tone (Grace, 2001). According to Grace's model, the blockade and transport reversal by *d*-AMPH by stimulants at therapeutic doses would increase DA tone; this has the downstream effect of stimulating D2 autoreceptors and attenuating phasic DA efflux (Grace, 2001; Seeman & Madras, 2002).

We found that ΔBP in limbic and sensorimotor ROIs was linearly related to the proportion of anticipatory saccades on the antisaccade task – a behavioral measure of impulsivity – with those generating more anticipations having greater ΔBP in response to *d*-AMPH. DA levels in the striatum might modulate the activity of output neurons in the superior colliculus via effects on D1 receptors (Hikosaka, Takikawa, & Kawagoe, 2000). Stimulation of striatal D1 receptors causes inhibition of the substantia nigra pars reticulata, which weakens its tonic inhibition of the superior colliculus, making saccades more likely to occur. Thus, higher DA levels in the striatum would result in weaker inhibition of saccades. The fact that similar associations were not observed between ΔBP and antisaccade errors or SSRT was not predicted, and thus any explanation is necessarily speculative. However, it is possible that anticipatory errors could reflect different cognitive processes than those involved in antisaccade directional errors. While antisaccade errors tap the ability to inhibit a prepotent response, anticipatory errors are made when no peripheral target is present and thus might index other functions implicated in ADHD, such as delay aversion (Sonuga-Barke, 2002). Sonuga-Barke's dual pathway model of ADHD proposes that inhibitory errors are related to the mesocortical branch of the DA system, while the delay aversion symptoms are linked to mesolimbic DA circuitry subserving reward processing. That antisaccade inhibitory errors are dissociable from the processes involved in anticipations is supported by an empirical study of the factor structure of the antisaccade task, which found anticipations to load on a different factor than antisaccade errors (Klein, 2001).

The relationship between hyperactivity levels and *d*-AMPH induced change in [^{11}C]raclopride binding was quadratic rather than linear, with a tendency toward a more

attenuated DA response in highly than in moderately hyperactive individuals. This finding could reflect a more rapid down-modulation of phasic DA release in the highly hyperactive individuals, resulting from a more pronounced augmentation in DA tone in these participants. Grace's (2001) model predicts stronger therapeutic effects of stimulants in those with more severe symptoms than in those with less severe symptoms by the means of a greater/ more rapid augmentation of DA tone and attenuation of phasic release. This hypothesized association is consistent with reports of the greatest clinical response to stimulants in patients with the most severe ADHD symptoms and with rate-dependency of behavioral effects of stimulants, where stimulant-induced changes in the rate of responding are negatively associated with the baseline rate of responding (Buitelaar, Van der Gaag, Swaab-Barneveld, & Kuiper, 1995; Robbins & Sahakian, 1979), as well as with reports of the greatest clinical response to stimulants in patients with the most severe ADHD symptoms (Buitelaar et al., 1995; Robbins & Sahakian, 1979). Findings supporting an inverted U relationship between behavioral function and DA levels are abundant for the PFC (Goldman-Rakic, Muly, & Williams, 2000; Robbins, 2000; Seamans & Yang, 2004), and have recently been reported for some striatal measures: for example, smaller MPH-induced [^{11}C]raclopride displacements of endogenous DA were associated with improved reversal learning performance, whereas larger displacements were associated with impaired performance, and the opposite relationship was reported for spatial working memory (Clatworthy et al., 2009). The type of relationship between DAergic transmission and cognitive measures, linear vs. quadratic, may vary with linear effects reported for some measures and quadratic for others (Allman et al., 2010). Differing relationships are consistent with the notion that

for a given individual, a given level of DA transmission may be associated with different levels of performance on different motor and cognitive functions (Cools, 2006; Robbins & Arnsten, 2009). The finding here that symptoms of hyperactivity/impulsivity were quadratically related to ΔBP and proportion of anticipatory saccades were linearly related are less surprising given that the correlation between these two variables was low, suggesting they measure independent constructs.

The larger ΔBP in ADHD participants than Controls could have resulted from an increased DAT density in ADHD participants (Cheon et al., 2003; Dougherty et al., 1999; Dresel et al., 2000; Krause et al., 2000; Larisch et al., 2006; Spencer et al., 2005). The interference of *d*-AMPH with DA reuptake would be expected to result in greater net increases in levels of synaptic DA in individuals with higher DAT density. This mechanism of producing greater increases in synaptic DA levels could be complementary to augmented phasic DA release, since DAT downregulation and upregulation can occur under the conditions of low and high DA activity, respectively (reviewed in (Zahniser & Doolen, 2001)). Hence, an augmented phasic DA release in ADHD participants would also be expected to produce a concomitant DAT upregulation. Treatment with stimulants, putatively causing a down-modulation of the phasic DA release, has been found to result in a downregulation of surface DAT levels in ADHD participants (Vles et al., 2003). Thus, our finding of a grearter *d*-AMPH induced ΔBP could reflect either and augmented phasic DA release or an increased DAT density in ADHD participants, or both. The method does not allow us to differentiate among these possibilities.

The larger *d*-AMPH induced ΔBP in ADHD participants than controls was only observed in the limbic ROI only when the *d*-AMPH scan occurred after the placebo scan.

For Controls, but not ADHD participants, ΔBP was greater when the *d*-AMPH scan took place first. The larger ΔBP in Controls who received the drug scan first can be understood in terms of the effects of novelty on DA. Responses to novelty are thought to be mediated by the mesolimbic DA system (Hooks, Jones, Smith, Neill, & Justice, 1991; Marinelli & White, 2000; Piazza, Deminiere, Le Moal, & Simon, 1989; Pierce, Crawford, Nonneman, Mattingly, & Bardo, 1990). When the first scan was drug, BP would have reflected the combined effects on DA of both *d*-AMPH and the novelty of the scanner environment. When the placebo scan took place first, novelty of the scanner environment would have had the opposite effect on ΔBP due to novelty-induced DA increases occurring on the placebo scan. Unlike in the Controls, order had no effect on ΔBP in the ADHD group. The fact that the between group differences in the limbic region were significant only when the drug was received in the second scan suggests that Controls showed greater habituation to the scanner environment between the first and second scans (so BP reflected only the effects of drug); ADHD participants did not show this effect, possibly due to the higher levels of neuroticism in this group or to the aversive nature of the requirement to stay still in the scanner.

An alternative explanation could be that the Controls experienced a negative prediction error on the placebo scan when it took place after the drug scan. Since the majority of participants were stimulant naïve and blind to whether they were receiving dug or placebo, Control participants may have developed an implicit expectancy, after experiencing the drug on the first scan, of having a similar subjective experience on the subsequent scan. Midbrain DA neurons are hypothesized to encode reward prediction error by increasing firing in response to an expected reward and reducing firing in

response to a lack of an expected reward (Bayer & Glimcher, 2005; Glimcher, 2011; Schultz, Dayan, & Montague, 1997). Not experiencing subjective effects of the drug on the second (placebo) scan may have led the Controls to experience a negative prediction error (omission of an expected reward). The ADHD participants may not have developed this expectancy, which could point to an alteration in expectancy learning mechanisms, consistent with previous findings of altered neural correlates and behavioral measures of anticipation and prediction (Elbaz, 2000; O'Driscoll et al., 2005; Perchet et al., 2001; Pliszka et al., 2000).

The finding of greater ΔBP in the ADHD group than Controls is in agreement with a previous finding that higher scores on a behavioral measure of inattention and impulsivity were associated with greater MPH-induced DA responses in the ventral striatum in adolescents with ADHD (Rosa-Neto et al., 2005). The magnitude of MPH-induced ΔBP in the ADHD participants reported by that study (12 %) was within a standard deviation to that observed in our ADHD sample (10 %). However, our results are not consistent with a previous report of a blunted MPH-induced DA response in the caudate of adults with ADHD compared to healthy controls (Volkow et al., 2007b). This discrepancy could potentially be attributed to differences in the participant sample and the study design, as well as to the differences in the route of drug administration. All of our participants were male, whereas the study by Volkow et al. (2007) included males and females, with more females in the ADHD than Control group (ADHD: 52.6% women; Controls: 25% women). Given previous reports suggesting a less pronounced stimulant-induced striatal DA response in females than males (Munro et al., 2006; Riccardi et al., 2006b), their finding of a blunted MPH-induced DA response in ADHD

participants may be partly attributable to the higher proportion of women in the ADHD group. In addition, despite a large proportion of women in their sample, Volkow et al. do not report controlling for the phase of the menstrual cycle in their female participants. Given that sex steroids such as estradiol and progesterone affect DA transmission (Becker & Cha, 1989; Lévesque & Di Paolo, 1988; Pasqualini, Olivier, Guibert, Frain, & Leviel, 1995), as well as and subjective, sympathetic, and DAergic responses to stimulants (Becker, 1990a; Becker, 1990b; Evans & Foltin, 2005; Justice & de Wit, 2000; Lile, Kendall, Babalonis, Martin, & Kelly, 2007; Sofuoglu, Dudish-Poulsen, Nelson, Pentel, & Hatsukami, 1999), uncontrolled differences in menstrual cycle phase between placebo and drug could have affected their Volkow et al. results.

Another possible explanation for the difference between our findings and the Volkow et al. findings relates to previous drug exposure. While drug abuse and dependence were exclusion criteria in the Volkow et al. study, participants' lifetime recreational drug exposure (including stimulants) is not reported. Recent findings by our group suggest that the greater amounts of life-time recreational drug use in non-addicted individuals are associated with less pronounced *d*-AMPH-induced reductions in BP (Casey et al., Submitted). ADHD participants are likely to have had more previous recreational drug use than Controls, given that abuse rates are higher in ADHD (Sobanski, 2006), and more previous cumulative clinical exposure to stimulants (which is not reported in the study), either of which could have contributed to the blunted DAergic response.

4.5 Frontal Cortical Thickness in Relation to *d*-AMPH-Induced ΔBP

We found significant linear associations between frontal cortical thickness and % Δ BP in sensorimotor and associative ROIs. However, the direction of the association was opposite in ADHD participants and Controls. In the control group thicker cortex predicted smaller *d*-AMPH induced ΔBP, an association also observed in a different sample of control participants from another study by our group (Casey *et al.* in preparation). In the ADHD group, however, the relationship was reversed, with greater cortical thickness predicting greater *d*-AMPH induced ΔBP.

Studies in animals have provided convincing evidence that the frontal cortex modulates striatal DAergic transmission. PFC lesions have been found to enhance DA-mediated behaviours, such as amphetamine-induced hyper-locomotion and stereotypy (Adler, 1961; Jaskiw et al., 1990; Lynch, Ballantine Ii, & Campbell, 1971), and to result in elevated measures of subcortical DA transmission (Jaskiw et al., 1990; Pycock et al., 1980), suggesting that PFC might exert inhibitory influences on subcortical DA function. Likewise, there is evidence from clinical studies in humans that PFC dysfunction is associated with augmented striatal 6-flurodopa uptake and *d*-AMPH-induced reductions in [^{11}C]raclopride BP (Bertolino et al., 2000; Meyer-Lindenberg et al., 2002). Studies examining the effects of frontal stimulation on levels of striatal DA have shown that while chemical and high frequency (60-200 Hz) electrical stimulation produces increases in burst activity of midbrain DA neurons and striatal DA release (Karreman & Moghaddam, 1996; Murase et al., 1993; Nieoullon, Cheramy, & Glowinski, 1978; Taber & Fibiger, 1995; Taber & Fibiger, 1993; You et al., 1998), stimulation at frequencies naturally occurring during cognitive tasks (10 Hz) can inhibit striatal DA release (Jackson

et al., 2001). High frequency repetitive transcranial magnetic stimulation (rTMS) of prefrontal and motor regions in humans and non-human primates was also found to induce striatal DA release as measured by [^{11}C]raclopride PET (Ohnishi et al., 2004; Strafella, Paus, Barrett, & Dagher, 2001; Strafella, Paus, Fraraccio, & Dagher, 2003). Although these findings have been viewed as evidence of excitation of striatal DA transmission by frontal glutamatergic afferents, they could also be interpreted as resulting from interference with the inhibitory influence of frontal regions over subcortical DA, as high frequency rTMS has been reported to disrupt prefrontal functions, such as inhibition of over-learned responses (Jahanshahi et al., 1998; Knoch et al., 2006).

In Controls, given a negative association between frontal cortical thickness and the magnitude of *d*-AMPH induced DA responses, thicker frontal cortex could be postulated to provide a more powerful inhibitory influence over striatal DA function, resulting in more attenuated DAergic responses to the drug. The mechanism of inhibitory regulation of striatal DA function could involve glutamatergic projections from the PFC to the striatal medium spiny GABAergic neurons, which in turn project to and could inhibit the firing of the midbrain DA neurons (Doherty & Gratton, 1997; Morari, O'Connor, Ungerstedt, Bianchi, & Fuxe, 1996; Sesack & Pickel, 1992). Alternatively, it could involve glutamatergic projections from the PFC directly to the midbrain GABAergic neurons leading to the inhibition of midbrain DA neurons (Carr & Sesack, 2000; Morari et al., 1996). Indeed, disruption of glutamatergic transmission with ketamine in humans lead to an augmentation of *d*-AMPH-induced DA release as measured by [^{123}I]IBZM PET (Kegeles et al., 2000).

In ADHD participants, the direction of this association was reversed, with thicker cortex predicting more pronounced DA responses. Clearly this suggests there may be a different functional significance of frontal cortical thickness in ADHD participants as a group. Divergent associations between gray matter volume and thickness and cognitive function have been previously reported in clinical populations versus healthy controls (Duarte et al., 2006; Hartberg et al., 2010) and in different age groups of healthy adults (Gautam, Cherbuin, Sachdev, Wen, & Anstey, 2011). The relationship between brain structure and function is complex. For example, although many studies have found that larger gray matter volume and thickness of prefrontal regions were associated with better cognitive performance (Chee et al., 2009; Fjell et al., 2006; Gautam et al., 2011; Gunning-Dixon & Raz, 2003; Hartberg et al., 2010; Head, Kennedy, Rodrigue, & Raz, 2009; Head, Rodrigue, Kennedy, & Raz, 2008; Milad et al., 2005; Narr et al., 2007; Raz, Gunning-Dixon, Head, Dupuis, & Acker, 1998; Raz et al., 2008; Sowell et al., 2004; Walhovd et al., 2006; Westlye et al., 2011), others have found negative associations between prefrontal volume and cognitive performance in older adults (Duarte et al., 2006; Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; Gautam et al., 2011; Salat, Kaye, & Janowsky, 2002; Van Petten et al., 2004). While positive structure-function relationships have been usually explained in terms of the 'bigger is better' hypothesis, the negative relationships have been explained in terms of inadequate pruning (Chantome et al., 1999; Foster et al., 1999; Gautam et al., 2011), which (along with myelination) likely contributes to normal thinning of the frontal cortical grey matter during adolescence and early adulthood (Hensch, 2004; Huttenlocher & Dabholkar, 1997; Toga, Thompson, & Sowell, 2006). This thinning is preceded by initial thickening in

childhood and followed by stabilization in later adulthood (Shaw et al., 2006a; Shaw et al., 2008; Sowell et al., 2003a; Sowell et al., 2004). Trajectories of cortical development characterized by more rapid cortical thinning in the frontal regions in adolescence were found to be associated with higher intelligence scores (Shaw et al., 2006a). Likewise, frontal cortical thickness in adolescents was found to correlate inversely with executive function performance (Tamnes et al., 2010), as well as with task-related activations in the same regions (Lu et al., 2009), consistent with adolescent cortical thinning supporting cognitive development.

Trajectories of frontal cortical development in ADHD children have been found to lag behind those of typically developing controls (Shaw et al., 2007a). Typically developing children attained peak thickness in the middle, superior, and medial prefrontal cortex up to 5 years earlier than children with ADHD. The rate of adolescent cortical thinning was also slower for youths with ADHD, with more severe symptom scores predicting slower rates of thinning (Shaw et al., 2011). Notably, regions of association between cortical thickness and striatal DA responses in our data are contained within the more extensive frontal regions marked by a developmental delay in Shaw's *et al* (2007) ADHD participants. They also overlap with the regions whose thinning associated with symptom scores (Shaw et al., 2011). Because of the limited age range examined, that study was unable to investigate cortical developmental trajectories of the two groups at the stage where adolescent cortical thinning levels off and gives way to adult stabilization of cortical dimensions. However, the authors predicted that attainment of the static adult phase of cortical development would be delayed in those with ADHD (Shaw et al., 2007a). If this prediction is accurate, within a group of ADHD adults, thinner cortex may

be associated with more significant delays in cortical development. Thus, thicker cortex among ADHD participants may signify a less mature cortex with insufficient pruning and hence less effective inhibitory regulation of subcortical DA function explaining the direction of the association in our data.

Alternatively, the opposite relationships between cortical thickness and *d*-AMPH-induced DA responses in the ADHD participants and Controls could reflect different aspects of fronto-striatal connectivity. Since anatomical architecture exists that could support both excitatory and inhibitory influences of the PFC on striatal DAergic function, it is possible that the excitatory and inhibitory frontal influences are differentially apparent in the two groups. Specifically, prefrontal glutamatergic afferents to GABAergic striatal and midbrain neurons likely inhibit DA firing (Carr & Sesack, 2000; Sesack & Grace, 2010; Sesack & Pickel, 1992), but those that synapse directly on the DAergic midbrain neurons (Carr & Sesack, 2000; Sesack & Carr, 2002; Sesack & Pickel, 1992) likely excite DA neuron burst firing (Sesack & Carr, 2002). Prefrontal glutamatergic afferents also synapse on to the dendritic spines of striatal medium spiny neurons in close proximity to DA neuron terminals (Bouyer, Park, Joh, & Pickel, 1984; Sesack & Pickel, 1992), and application of glutamate to striatum promotes dopamine release (Cheramy, Romo, Godeheu, Baruch, & Glowinski, 1986; Keefe et al., 1992; Leviel, Gobert, & Guibert, 1990). Thus, negative association between cortical thickness and DA responses in Controls could preferentially reflect the inhibitory influences via afferents to striatal and midbrain GABAergic neurons, whereas the positive association in ADHD participants could preferentially reflect the excitatory influences via afferents to DAergic neurons.

Unlike, previous studies in adults (Almeida et al.; Makris et al., 2007) we did not find significant cortical thinning in frontal regions of our ADHD group relative to Controls, nor did we find thickening of any area in motor cortex as reported by Shaw and colleagues (2007). However, previous studies were larger making them more powerful to detect between group differences (Cohen, 1988). In addition, these studies included participants with psychiatric comorbidities, which may have resulted in more pathological ADHD samples.

CHAPTER 5

LIMITATIONS AND FUTURE DIRECTIONS

A number of limitations need to be considered in interpreting the finding of the present study. Probably the most the most significant of the limitations is the relatively small *d*-AMPH-induced decreases in [^{11}C]raclopride binding observed in our control group. Oral administrations of *d*-AMPH typically result in ≈10% decreases in BP (Boileau et al., 2006; Boileau et al., 2007; Clatworthy et al., 2009; Leyton et al., 2002; Narendran et al., 2010; Volkow et al., 2004; Volkow et al., 2007b; Volkow et al., 2001; Volkow et al., 2002b), which is higher than the ≈ 4.5% ΔBP across the 3 ROIs in our Controls, though our ΔBP is within or sometimes slightly beyond 1 standard deviation of the mean in the other studies (Table 5-1). However, our Control participants demonstrated both significant cardiovascular and subjective responses to the drug, and these were similar in magnitude to those observed in ADHD participants. As well, the plasma amphetamine levels were nearly identical in the two groups. Thus, the relatively small ΔBP in the controls is somewhat at odds with the other effects of the drug in the same individuals.

As can be seen from Table 5-1, there is considerable variability in stimulant-induced reductions in [^{11}C]raclopride BP values across studies, with some studies reporting ΔBP values almost twice as high as others. Although the ΔBP values in our Controls are at the low end of this distribution, values in this range are not unprecedented. An earlier study from our group using an identical protocol (Leyton et al., 2002) found a significant 11% *d*-AMPH-induced BP reduction in the ventral striatum of healthy adult males (with no significant BP decreases in other ROIs). Our ΔBP values of 6% in the ventral striatum are within one standard deviation of the mean of Leyton *et al.* (2002). Another study found that a lower dose of MPH (~.2mg/kg) did not produce

significant BP decreases on its own, but did so only when combined with a task requiring solving mathematical problems for a potential reward (Volkow et al., 2004).

The variability in ΔBP values across studies is not surprising given the substantial individual differences in stimulant-induced ΔBPs within studies with both oral and intravenous stimulant administrations (Table 5-1). Such inter-individual variability in [^{11}C]raclopride BP responses to stimulants is likely in large part due to individual differences in the characteristics of the striatal DA system and metabolic function. However, some of the variability may be also related to methodological factors.

The [^{11}C]raclopride PET method does not provide a direct measurement of endogenous DA levels in the striatum, and the competition model (described in the Introduction) does not fully describe the relationship between benzamide ligand binding and endogenous DA levels (Ginovart, 2005; Laruelle, 2000). Indeed, as mentioned earlier, the observed linear relationship between *d*-AMPH-induced changes in extracellular DA levels and tracer BP is not reliably present within individual subjects (Breier et al., 1997).

Study	N CTRLS	Challenge	Dose	Mode	ΔBP Controls
Volkow *et al,* 1994	15	MPH	0.5mg/kg	IV	-23 ±15%
Volkow *et al,* 1997	23	MPH	0.5mg/kg	IV	-21 ±13%
Wang *et al,* 1999	7	MPH	0.5mg/kg	IV	-18 ±9%
Volkow *et al,* 1999a	7	MPH	0.5mg/kg	IV	-18 ± 9% -13 ± 9%
Volkow *et al,* 1999b	14	MPH	.25mg/kg .5mg/kg	IV	~ 20%
Volkow *et al,* 2001	11	MPH	0.8±0.11 mg/kg	oral	-20 ± 12%
Volkow *et al,* 2002	10	MPH	60 mg (~ .8mg/kg)	oral	-16 ± 8%
Volkow *et al,* 2003	14	MPH	.5mg/kg .25mg/kg	IV	-22±9% -20±4%
Volkow *et al,* 2004	16	MPH	20 mg ~.2mg/kg	oral	Ns change
Volkow *et al,* 2007	19	MPH	.5mg/kg	oral	Caudate: -14% Putamen: - 23%
Clatworthy *et al,* 2009	10	MPH	60 mg (~ .8mg/kg)	oral	VS: -15 %; AC:-3%; PC:-12% AP:-9%; PP:-22%
Breier *et al,* 1997	12	*d*-Amph	0.2mg/kg	IV	-15.5 ± 6%
Drevets *et al,* 2001	7	*d*-Amph	.3 mg/kg	IV	Striatum: -11 ± 7% VS: -15 ± 11% DC:-4±8%; Mid Caud:-11±12% DP: -10 ± 10%; VP: -14 ± 10%
Martinez *et al,* 2003	14	*d*-Amph	.3 mg/kg	IV	Limbic: −15 ± 12% SM: −16 ± 10% Assoc: −8 ± 7%
Oswald *et al,* 2005	16	*d*-Amph	.3 mg/kg	IV	(L)VS -11±5 %; (R)VS -9 ± 6 % (L)DP -17±5 %; (R)DP -17 ±5% (L)DC -5±5 %; (R)DC -4 ± 3 %
Oswald *et al,* 2006	43	*d*-Amph	.3 mg/kg	IV	AP: -13 ± 6; PP: -20 ± 7 AC: -7 ± 6 ; PC: -10 ± 7 VS: -12 ± 6
Schneier *et al,* 2009	13	*d*-Amph	.3mg/kg	IV	Limbic : -13.06 ±7.04 Assoc: -5.15 ±4.61 SM : -15.78 ± 6.21
Leyton *et al,* 2002	8	*d*-Amph	.3 mg/kg	oral	VS: -10.7 ± 9.5%
Cardenas *et al,* 2004	12	*d*-Amph	.3mg/kg	IV	VS: 13 ± 5%
Boileau *et al,* 2006	10	*d*-Amph	.3 mg/kg	oral	VS:−17.7%±9% DPP:−7.3%±3%
Boileau *et al,* 2007	9	*d*-Amph	.3 mg/kg	oral	VS: -22.24 ±18% DPP:-11.48±10% DP: -11.42 ±7%
Narendran *et al,* 2010	10	*d*-Amph	.5 mg/kg	oral	VS: -9.7±4.4 Caud: -8.4 ± 4.2 Put: -14.7 ± 4.8
Cherkasova *et al*	15	d-Amph	.3 mg/kg	oral	Limbic: -6.09 ± 10.45% Assoc: -3.81 ± 10.5% SM: -3.5 ± 9.5%

Table 5-1. Methylphenidate (MPH) and *d*-amphetamine (*d*-Amph)-induced ΔBP in healthy controls. VS = ventral striatum; AC = anterior caudate; PC = posterior caudate; AP = anterior putamen; PP = posterior putamen; DC = dorsal caudate; DP = dorsal putamen; DPP = dorsal posterior putamen;VP = ventral putamen; SM = sensorimotor; Asscoc = Associative; (L) = left; (R) = right

Other factors besides changes in endogenous DA levels have been proposed to contribute to changes in [^{11}C]raclopride BP. One such factor, as mentioned earlier, is affinity state configuration of D2/D3 receptors, as raclopride binds to DA receptors in both affinity states, while dopamine only binds to receptors in the high affinity state (George et al., 1985; Richfield et al., 1989; Seeman & Grigoriadis, 1987; Sibley et al., 1982; Zahniser & Molinoff, 1978). DA receptors can convert between states of high and low affinity (Sibley et al., 1982), which could also contribute noise to the observed ΔBP values. Another potential factor contributing to variability in ΔBP values could be is G-protein-coupled receptor internalization in the presence of a DA receptor agonist (Sun et al., 2003; Vickery & von Zastrow, 1999), which makes a subset of receptors unavailable for binding.

A important methodological limitation of the present study is that measurement of specific activity of [^{11}C]raclopride was not possible for all participants on all scans due to technical constraints. Specific activity refers to radioactive yield of the radioligand per unit of mass. While the radioactivity level of the tracer delivered to a given participant was always measured, the total mass of the ligand over which the radioisotope was distributed was not determined for the majority of the scans. On the minority of scans where measurement of specific activity was taken, the specific activity values were in the desired range (injected mass 2.7 - 4μg or 0.02 - 0.06 μg/kg). Values reported in previous studies injected masses of around 2μg (Martinez et al., 2003; Narendran et al., 2010; Volkow et al., 1994; Volkow et al., 2007b; Volkow et al., 1999). Thus in the scans for which data were available, the specific activity is in the desired range.

The absence of measurement of the effect of the drug on neurocognitive function in our participants limited our ability to examine the functional significance of the DA system's response to the drug challenge. It may have been informative to investigate whether the magnitude of *d*-AMPH-induced decreases in BP was associated with changes in neurocognitive performance with the same drug dose. However, the cognitive battery in our study included tasks with large practice effects, such as the Trails A and B, the Tower of Hanoi, and the Antisaccade task (Beglinger et al., 2005; Ettinger et al., 2003; Ronnlund, Lovden, & Nilsson, 2008), which could confound the findings with repeated battery administrations. However, future studies could address this question using tasks that are relatively unsusceptible to practice effects, such as the SSRT (Logan et al., 1984).

Certain characteristics of our participant sample also limit our conclusions. We excluded participants with psychiatric comorbidities to ensure homogeneity and purity of our sample and maximize the likelihood of the observed findings being attributable to ADHD. However, comorbidities are a rule rather than an exception in adults with ADHD: 65 - 85 % of ADHD adults suffer from at least one additional comorbid disorder (Sobanski, 2006). Thus, our recruitment strategy may have resulted in an unusually well-adapted and high-functioning group of ADHD participants. This may render it difficult to generalize our finding to the majority of adults with ADHD who have psychiatric comorbidities. However, the inclusions of participants with comorbidities requires statistical controls that are not efficient given the wide variety of possible comorbidities. Our sample was also exclusively male. Future studies should examine amphetamine-induced dopamine responses in female ADHD participants. Finally, our sample comprised ADHD participants with the predominantly inattentive subtype and those with

the combined subtype, and our sample size did not permit separate analyses for each subtype. It is currently debated in the field whether ADHD subtypes are best conceptualized as components of a unitary construct or as diagnostically distinct categories, representing different sets of problems and different neural substrates (Diamond, 2005). Future studies on the effects of subtype on *d*-AMPH-induced DA release in ADHD could shed additional light on this issue.

One important area for future studies to examine is frontal dopaminergic function in ADHD. A wealth of both direct and indirect evidence points to the PFC as a significant locus of dysfunction in ADHD (see Introduction). Yet no studies to date have looked at prefrontal dopaminergic transmission in ADHD. A new high affinity D2/D3 receptror radioligand [^{18}F]fallypride has been recently successfully used to image D2/D3 receptor availability in extrastriatal regions both at baseline and with an amphetamine challenge (Mukherjee et al., 2002; Mukherjee et al., 2005; Riccardi et al., 2008; Riccardi et al., 2006a). Further, since stimulation of D1 receptors has been found especially important for executive functions such as working memory (Goldman-Rakic et al., 2000; Seamans & Yang, 2004), [^{18}F]fallypride could in the future be used in conjunction with D1 receptor ligands, such as SKF 82957, SCH 23390 to measure prefrontal DA function in ADHD.

REFERENCES

Ad-Dab'bagh, Y., Lyttelton, O., Muehlboeck, J.-S., Lepage, C., Einarson, D., Mok, K. (2006). *The CIVET Image-Processing Environment: A Fully Automated Comprehensive Pipeline for Anatomical Neuroimaging Research*. Paper presented at the 12th Annual Meeting of the Organization for Human Brain Mapping, Florence, Italy.

Ad-Dab'bagh, Y., Singh, V., Robbins, S., Lerch, J., Lyttelton, O., Fombonne, E. (2005). *Native space cortical thickness measurement and the absence of correlation to cerebral volume.* Paper presented at the 11th Annual Meeting of the Organization for Human Brain Mapping, Totonto.

Adler, M. W. (1961). Changes in sensitivity to amphetamine in rats with chronic brain lesions. *Journal of Pharmacology and Experimental Therapeutics, 134*, 214-221.

Aldridge, J. W., Anderson, R. J., & Murphy, J. T. (1980). Sensory-motor processing in the caudate nucleus and globus pallidus: a single-unit study in behaving primates. *Canadian Journal of Physiology and Pharmacology, 58*(10), 1192-1201.

Alexander, G. E., & Crutcher, M. D. (1990). Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends in Neurosciences, 13*(7), 266-271.

Alexander, G. E., DeLong, M. R., & Strick, P. L. (1986). Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neurosciences, 9*, 357-381.

Allman, A.-A., Benkelfat, C., Durand, F., Sibon, I., Dagher, A., Leyton, M. (2010). Effect of d-amphetamine on inhibition and motor planning as a function of baseline performance. *Psychopharmacology, 211*(4), 423-433.

Almeida, L. G., Ricardo-Garcell, J., Prado, H., Barajas, L., Fernández-Bouzas, A., Ávila, D. Reduced right frontal cortical thickness in children, adolescents and adults with ADHD and its correlation to clinical variables: A cross-sectional study. *Journal of Psychiatric Research, In Press, Corrected Proof*.

Amador, S. C., Hood, A. J., Schiess, M. C., Izor, R., & Sereno, A. B. (2006). Dissociating cognitive deficits involved in voluntary eye movement dysfunctions in Parkinson's disease patients. *Neuropsychologia, 44*(8), 1475-1482.

Amen, D. G., & Carmichael, B. D. (1997). High-resolution brain SPECT imaging in ADHD. *Annals of Clinical Psychiatry, 9*(2), 81-86.

Anckarsater, H., Stahlberg, O., Larson, T., Hakansson, C., Jutblad, S.-B., Niklasson, L. (2006). The impact of ADHD and autism spectrum disorders on temperament, character, and personality development. *American Journal of Psychiatry, 163*(7), 1239-1244.

APA. (1994). *Diagnostic and statistical manual of mental disorders - IV*. Washington, DC.

Archer, T., Danysz, W., Fredriksson, A., Jonsson, G., Luthman, J., Sundström, E. (1988). Neonatal 6-hydroxydopamine-induced dopamine depletions: Motor activity and performance in maze learning. *Pharmacology Biochemistry and Behavior, 31*(2), 357-364.

Arnsten, A. F. (2006). Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. *Journal of Clinical Psychiatry, 67 Suppl 8*, 7-12.

Arnsten, A. F., & Dudley, A. G. (2005). Methylphenidate improves prefrontal cortical cognitive function through alpha2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. *Behavioral and Brain Functions, 1*(1), 2.

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *The Neuroscientist, 13*(3), 214-228.

Aron, A. R., Dowson, J. H., Sahakian, B. J., & Robbins, T. W. (2003). Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 54*(12), 1465-1468.

Aron, A. R., & Poldrack, R. A. (2006). Cortical and subcortical contributions to stop signal response Inhibition: Role of the subthalamic nucleus. *Journal of Neuroscience, 26*(9), 2424-2433.

Asghar, S. J., Baker, G. B., Rauw, G. A., & Silverstone, P. H. (2002). A rapid method of determining amphetamine in plasma samples using pentafluorobenzenesulfonyl chloride and electron-capture gas chromatography. *Journal of Pharmacological and Toxicological Methods, 46*(2), 111-115.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., & Van Tol, H. H. (1995). Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *Journal of Neurochemistry, 65*(3), 1157-1165.

Aspide, R., Gironi Carnevale, U. A., Sergeant, J. A., & Sadile, A. G. (1998). Non-selective attention and nitric oxide in putative animal models of Attention-Deficit Hyperactivity Disorder. *Behavioural Brain Research, 95*(1), 123-133.

Aston-Jones, G., Rajkowski, J., & Cohen, J. (1999). Role of locus coeruleus in attention and behavioral flexibility. *Biological Psychiatry, 46*(9), 1309-1320.

Aston, J., Gunn, R., Worsley, K., Ma, Y., Evans, A. C., & Dagher, A. (2000). A statistical method for the analysis of positron emission tomopgraphy neuroreceptor ligand data. *Neuroimage, 12*(3), 245-256.

Aylward, E. H., Reiss, A. L., Reader, M. J., Singer, H. S., Brown, J. E., & Denckla, M. B. (1996). Basal ganglia volumes in children with attention-deficit hyperactivity disorder. *Journal of Child Neurology, 11*(2), 112-115.

Backman, L., Robins-Wahlin, T. B., Lundin, A., Ginovart, N., & Farde, L. (1997). Cognitive deficits in Huntington's disease are predicted by dopaminergic PET markers and brain volumes. *Brain, 120 (Pt 12)*, 2207-2217.

Baldo, J. V., Schwartz, S., Wilkins, D., & Dronkers, N. F. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society, 12*(6), 896-900.

Banaschewski, T., Brandeis, D., Heinrich, H., Albrecht, B., Brunner, E., & Rothenberger, A. (2003). Association of ADHD and conduct disorder--brain electrical evidence for the existence of a distinct subtype. *Journal of Child Psychology and Psychiatry, 44*(3), 356-376.

Bancroft, B. S. G. N., Morgan, B. S. K. A., Flietstra, P. D. R. J., & Levant, P. D. B. (1998). Binding of [3H]PD 128907, a putatively selective ligand for the D3 dopamine receptor, in rat brain: A receptor binding and quantitative autoradiographic study. *Neuropsychopharmacology, 18*(4), 305-316.

Barbeau, A., Murphy, G. F., & Sourkes, T. L. (1961). Excretion of dopamine in diseases of basal ganglia. *Science, 133*, 1706-1707.
Barkley, R., Murphy, K. R., & Fischer, M. (2008). *ADHD in Adults: What the Science Says*. New York: Guilford Press.
Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin, 121*(1), 65-94.
Barkley, R. A., & Murphy, K. R. (1998). *Attention deficit hyperactivity disorder: a clinical workbook* (2 ed.). New York: Guilford Publications.
Barrett, S. P., Boileau, I., Okker, J., Pihl, R. O., & Dagher, A. (2004). The hedonic response to cigarette smoking is proportional to dopamine release in the human striatum as measured by positron emission tomography and [11C]raclopride. *Synapse, 54*(2), 65-71.
Batty, M. J., Liddle, E. B., Pitiot, A., Toro, R., Groom, M. J., Scerif, G. (2010). Cortical gray matter in attention-deficit/hyperactivity disorder: a structural magnetic resonance imaging study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(3), 229-238.
Bayer, H. M., & Glimcher, P. W. (2005). Midbrain dopamine neurons encode a quantitative reward prediction error signal. *Neuron, 47*(1), 129-141.
Beck, A. T., & Steer, R. A. (1987). Manual for the Revised Beck Depression Inventory: Psychological Corporation.
Becker, J. B. (1990a). Direct effect of 17 beta-estradiol on striatum: sex differences in dopamine release. *Synapse, 5*(2), 157-164.
Becker, J. B. (1990b). Estrogen rapidly potentiates amphetamine-induced striatal dopamine release and rotational behavior during microdialysis. *Neuroscience Letters, 118*(2), 169-171.
Becker, J. B., & Cha, J.-H. (1989). Estrous cycle-dependent variation in amphetamine-induced behaviors and striatal dopamine release assessed with microdialysis. *Behavioural Brain Research, 35*(2), 117-125.
Beglinger, L. J., Gaydos, B., Tangphao-Daniels, O., Duff, K., Kareken, D. A., Crawford, J. (2005). Practice effects and the use of alternate forms in serial neuropsychological testing. *Archives of Clinical Neuropsychology, 20*(4), 517-529.
Beninger, R. J. (1983). The role of dopamine in locomotor activity and learning. *Brain Research Reviews, 6*(2), 173-196.
Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., & Hamer, D. H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics, 12*(1), 81-84.
Bentivoglio, M., & Morelli, M. (2005). The organization of circuits of mesencephalic dopaminergic neurons and the distribution of dopamine receptors in the brain. In S. B. Dunnett, M. Bentivoglio, A. Bjorklund & T. Hokfelt (Eds.), *Handbook of Chemical Neuroanatomy* (Vol. 21). Amsterdam: Elsevier.
Berquin, P. C., Giedd, J. N., Jacobsen, L. K., Hamburger, S. D., Krain, A. L., Rapoport, J. L. (1998). Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. *Neurology, 50*(4), 1087-1093.
Berridge, C. W., Devilbiss, D. M., Andrzejewski, M. E., Arnsten, A. F. T., Kelley, A. E., Schmeichel, B. (2006). Methylphenidate preferentially increases catecholamine

neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biological Psychiatry, 60*(10), 1111-1120.

Berridge, K. C., Aldridge, J. W., Houchard, K. R., & Zhuang, X. (2005). Sequential super-stereotypy of an instinctive fixed action pattern in hyper-dopaminergic mutant mice: a model of obsessive compulsive disorder and Tourette's. *BMC Biology, 3*, 4.

Berridge, K. C., & Robinson, T. E. (1998). What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Research. Brain Research Reviews, 28*(3), 309-369.

Bertolino, A., Breier, A., Callicott, J. H., Adler, C., Mattay, V. S., Shapiro, M. (2000). The relationship between dorsolateral prefrontal neuronal N-acetylaspartate and evoked release of striatal dopamine in schizophrenia. *Neuropsychopharmacology, 22*(2), 125-132.

Biederman, J., Faraone, S., Spencer, T., Wilens, T., Norman, D., Lapey, K. (1993). Patterns of psychiatric comorbidity, cognition, and psychosocial functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 150*(12), 1792-1798.

Biederman, J., Mick, E., & Faraone, S. V. (2000). Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *American Journal of Psychiatry, 157*(5), 816-818.

Biederman, J., Monuteaux, M. C., Mick, E., Spencer, T., Wilens, T. E., Silva, J. M. (2006). Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. *Psychological Medicine, 36*(02), 167-179.

Björklund, A., & Dunnett, S. B. (2007). Dopamine neuron systems in the brain: an update. *Trends in Neurosciences, 30*(5), 194-202.

Boileau, I., Assaad, J. M., Pihl, R. O., Benkelfat, C., Leyton, M., Diksic, M. (2003). Alcohol promotes dopamine release in the human nucleus accumbens. *Synapse, 49*(4), 226-231.

Boileau, I., Dagher, A., Leyton, M., Gunn, R. N., Baker, G. B., Diksic, M. (2006). Modeling sensitization to stimulants in humans: an [11C]raclopride/positron emission tomography study in healthy men. *Archives of General Psychiatry, 63*(12), 1386-1395.

Boileau, I., Dagher, A., Leyton, M., Welfeld, K., Booij, L., Diksic, M. (2007). Conditioned dopamine release in humans: a positron emission tomography [11C]raclopride study with amphetamine. *Journal of Neuroscience, 27*(15), 3998-4003.

Boonstra, A. M., Kooij, J. J., Oosterlaan, J., Sergeant, J. A., Buitelaar, J. K., & Van Someren, E. J. (2007). Hyperactive night and day? Actigraphy studies in adult ADHD: a baseline comparison and the effect of methylphenidate. *Sleep, 30*(4), 433-442.

Booth, J. R., Burman, D. D., Meyer, J. R., Lei, Z., Trommer, B. L., Davenport, N. D. (2005). Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry, 46*(1), 94-111.

Borcherding, B. G., Keysor, C. S., Cooper, T. B., & Rapoport, J. L. (1989). Differential effects of methylphenidate and dextroamphetamine on the motor activity level of hyperactive children. *Neuropsychopharmacology, 2*(4), 255-263.

Bouthenet, M.-L., Souil, E., Martres, M.-P., Sokoloff, P., Giros, B., & Schwartz, J.-C. (1991). Localization of dopamine D3 receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine D2 receptor mRNA. *Brain Research, 564*(2), 203-219.

Bouyer, J. J., Park, D. H., Joh, T. H., & Pickel, V. M. (1984). Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals in rat neostriatum. *Brain Research, 302*(2), 267-275.

Braaten, E. B., & Rosén, L. A. (1997). Emotional reactions in adults with symptoms of attention deficit hyperactivity disorder. *Personality and Individual Differences, 22*(3), 355-361.

Breier, A., Adler, C. M., Weisenfeld, N., Su, T. P., Elman, I., Picken, L. (1998). Effects of NMDA antagonism on striatal dopamine release in healthy subjects: application of a novel PET approach. *Synapse, 29*(2), 142-147.

Breier, A., Su, T. P., Saunders, R., Carson, R. E., Kolachana, B. S., de Bartolomeis, A. (1997). Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proceeding of the National Academy of Sciences, 94*(6), 2569-2574.

Briand, K. A., Strallow, D., Hening, W., Poizner, H., & Sereno, A. B. (1999). Control of voluntary and reflexive saccades in Parkinson's disease. *Experimental Brain Research, 129*(1), 38-48.

Bridgett, D. J., & Walker, M. E. (2006). Intellectual functioning in adults with ADHD: a meta-analytic examination of full scale IQ differences between adults with and without ADHD. *Psychological Assessment, 18*(1), 1-14.

Brody, A. L., Mandelkern, M. A., Olmstead, R. E., Scheibal, D., Hahn, E., Shiraga, S. (2006). Gene variants of brain dopamine pathways and smoking-induced dopamine release in the ventral caudate/nucleus accumbens. *Archives of General Psychiatry, 63*(7), 808-816.

Brown, T. E., & Gammon, G. D. (1995). Differential diagnosis of ADD versus ADHD in adults. In K. G. Nadeau (Ed.), *Comprehensive guide to attention deficit disorder in adults* (pp. 93-107). New York: Brunner/Mazel.

Brozoski, T. J., Brown, R. M., Rosvold, H. E., & Goldman, P. S. (1979). Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. *Science, 205*(31), 929-931.

Bruno, K. J., Freet, C. S., Twining, R. C., Egami, K., Grigson, P. S., & Hess, E. J. (2007). Abnormal latent inhibition and impulsivity in coloboma mice, a model of ADHD. *Neurobiology of Disease, 25*(1), 206-216.

Buckholtz, J. W., Treadway, M. T., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S. (2010). Dopaminergic network differences in human impulsivity. *Science, 329*(5991), 532-.

Buitelaar, J. K., Van der Gaag, R. J., Swaab-Barneveld, H., & Kuiper, M. (1995). Prediction of clinical response to methylphenidate in children with attention-deficit hyperactivity disorder. *Journal of the Americam Academy of Child and Adolescent Psychiatry, 34*(8), 1025-1032.

Bull, E., Reavill, C., Hagan, J. J., Overend, P., & Jones, D. N. C. (2000). Evaluation of the spontaneously hypertensive rat as a model of attention deficit hyperactivity disorder: acquisition and performance of the DRL-60s test. *Behavioural Brain Research, 109*(1), 27-35.

Bunney, B. S., Walters, J. R., Roth, R. H., & Aghajanian, G. K. (1973). Dopaminergic neurons: effect of antipsychotic drugs and amphetamine on single cell activity. *Journal of Pharmacology and Experimental Therapeutics, 185*(3), 560-571.

Burd, L., Klug, M. G., Coumbe, M. J., & Kerbeshian, J. (2003). Children and adolescents with attention defitic-hyperactivity disorder: 1. Prevalence and cost of care. *Journal of Child Neurology, 18*(8), 555-561.

Burk, J. A., & Mair, R. G. (2001). Effects of dorsal and ventral striatal lesions on delayed matching trained with retractable levers. *Behavioural Brain Research, 122*(1), 67-78.

Bush, G., Frazier, J. A., Rauch, S. L., Seidman, L. J., Whalen, P. J., Jenike, M. A. (1999). Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. *Biological Psychiatry, 45*(12), 1542-1552.

Bush, G., Spencer, T. J., Holmes, J., Shin, L. M., Valera, E. M., Seidman, L. J. (2008). Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Archives of General Psychiatry, 65*(1), 102-114.

Bussing, R., Grudnik, J., Mason, D., Wasiak, M., & Leonard, C. (2002). ADHD and conduct disorder: an MRI study in a community sample. *The World Journal of Biological Psychiatry, 3*(4), 216-220.

Cadoret, R. J., Langbehn, D., Caspers, K., Troughton, E. P., Yucuis, R., Sandhu, H. K. (2003). Associations of the serotonin transporter promoter polymorphism with aggressivity, attention deficit, and conduct disorder in an adoptee population. *Comprehensive Psychiatry, 44*(2), 88-101.

Camus, A., Javoy-Agid, F., Dubois, A., & Scatton, B. (1986). Autoradiographic localization and quantification of dopamine D2 receptors in normal human brain with [3H]N-n-propylnorapomorphine. *Brain Research, 375*(1), 135-149.

Cantwell, D. P. (1975). Genetics of hyperactivity. *Journal of Child Psychology and Psychiatry, 16*(3), 261-264.

Carboni, E., Imperato, A., Perezzani, L., & Di Chiara, G. (1989). Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. *Neuroscience, 28*(3), 653-661.

Carboni, E., Tanda, G. L., Frau, R., & Di Chiara, G. (1990). Blockade of the noradrenaline carrier increases extracellular dopamine concentrations in the prefrontal cortex: evidence that dopamine is taken up in vivo by noradrenergic terminals. *Journal of Neurochemistry, 55*(3), 1067-1070.

Carey, M. P., Diewald, L. M., Esposito, F. J., Pellicano, M. P., Gironi Carnevale, U. A., Sergeant, J. A. (1998). Differential distribution, affinity and plasticity of dopamine D-1 and D-2 receptors in the target sites of the mesolimbic system in an animal model of ADHD. *Behavioural Brain Research, 94*(1), 173-185.

Carlsson, A. (2001). A paradigm shift in brain research. *Science, 294*(5544), 1021-1024.

Carmona, S., Vilarroya, O., Bielsa, A., Trèmols, V., Soliva, J. C., Rovira, M. (2005). Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. *Neuroscience Letters, 389*(2), 88.

Caron, M. G., & Gainetdinov, R. R. (2010). Role of dopamine transporters in neuronal homeostasis. In L. Iversen, S. D. Iversen, S. B. Dunnett & A. Bjorklund (Eds.), *Dopamine Handbook* (pp. 88-99). Oxford: Oxford University Press.

Carr, D. B., & Sesack, S. R. (2000). Projections from the rat prefrontal cortex to the ventral tegmental area: Target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *The Journal of Neuroscience, 20*(10), 3864-3873.

Carr, L. A., Nigg, J. T., & Henderson, J. M. (2006). Attentional versus motor inhibition in adults with attention-deficit/hyperactivity disorder. *Neuropsychology, 20*(4), 430-441.

Casey, K. F., Benkelfat, C., Cherkasova, M. V., Baker, G. B., Dagher, A., & Leyton, M. (Submitted). Reduced dopamine response to amphetamine in subjects at familial risk for addiction.

Castaneda, E., Whishaw, I. Q., Lermer, L., & Robinson, T. E. (1990). Dopamine depletion in neonatal rats: effects on behavior and striatal dopamine release assessed by intracerebral microdialysis during adulthood. *Brain Research, 508*(1), 30-39.

Castellanos, F. X., Elia, J., Kruesi, M. J., Gulotta, C. S., Mefford, I. N., Potter, W. Z. (1994a). Cerebrospinal fluid monoamine metabolites in boys with attention-deficit hyperactivity disorder. *Psychiatry Research, 52*(3), 305-316.

Castellanos, F. X., Elia, J., Kruesi, M. J., Marsh, W. L., Gulotta, C. S., Potter, W. Z. (1996a). Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention deficit/hyperactivity disorder. *Neuropsychopharmacology, 14*(2), 125-137.

Castellanos, F. X., Giedd, J. N., Berquin, P. C., Walter, J. M., Sharp, W., Tran, T. (2001). Quantitative brain magnetic resonance imaging in girls with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry, 58*(3), 289-295.

Castellanos, F. X., Giedd, J. N., Eckburg, P., Marsh, W. L., Vaituzis, A. C., Kaysen, D. (1994b). Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. *American Journal of Psychiatry, 151*(12), 1791-1796.

Castellanos, F. X., Giedd, J. N., Marsh, W. L., Hamburger, S. D., Vaituzis, A. C., Dickstein, D. P. (1996b). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Archives of General Psychiatry, 53*(7), 607-615.

Castellanos, F. X., Lee, P. P., Sharp, W., Jeffries, N. O., Greenstein, D. K., Clasen, L. S. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Jounal of the American Medical Association, 288*, 1740 - 1748.

Castellanos, F. X., Sharp, W. S., Gottesman, R. F., Greenstein, D. K., Giedd, J. N., & Rapoport, J. L. (2003). Anatomic brain abnormalities in monozygotic twins discordant for attention deficit hyperactivity disorder. *American Journal of Psychiatry, 160*(9), 1693-1696.

Castellanos, F. X., & Tannock, R. (2002). Neuroscience of attention-deficit/hyperactivity disorder: the search for endophenotypes. *Nature Reviews. Neuroscience, 3*, 617 - 628.

Chan, F., Armstrong, I. T., Pari, G., Riopelle, R. J., & Munoz, D. P. (2005). Deficits in saccadic eye-movement control in Parkinson's disease. *Neuropsychologia, 43*(5), 784-796.

Chantome, M., Perruchet, P., Hasboun, D., Dormont, D., Sahel, M., Sourour, N. (1999). Is there a negative correlation between explicit memory and hippocampal volume? *NeuroImage, 10*(5), 589-595.

Chee, M. W. L., Chen, K. H. M., Zheng, H., Chan, K. P. L., Isaac, V., Sim, S. K. Y. (2009). Cognitive function and brain structure correlations in healthy elderly East Asians. *NeuroImage, 46*(1), 257-269.

Cheon, K., Ryu, Y., Kim, Y., Namkoong, K., Kim, C., & Lee, J. (2003). Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. *European Journal of Nuclear Medicine and Molecular Imaging, 30*, 306 - 311.

Cheramy, A., Romo, R., Godeheu, G., Baruch, P., & Glowinski, J. (1986). In vivo presynaptic control of dopamine release in the cat caudate nucleus--II. Facilitatory or inhibitory influence of L-glutamate. *Neuroscience, 19*(4), 1081-1090.

Cherkasova, M. V., Ponde, M. P., & Hechtman, L. (In Press). Adolescent and adult outcome of attention deficit hyperactivity disorder: presentation and predictors. *Minerva Psichiatrica*.

Chudasama, Y., & Robbins, T. W. (2006). Functions of frontostriatal systems in cognition: Comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biological Psychology, 73*(1), 19-38.

Chung, M. K., & Taylor, J. (2004). *Diffusion smoothing on brain surface via finite element method*. Paper presented at the IEEE International Symposium on Biomedical Imaging: Macro to Nano, Arlington, VA.

Chung, M. K., Worsley, K. J., Taylor, J., Ramsay, J. O., Robbins, S., & Evans, A. C. (2001). Diffusion smoothing on the cortical surface. *NeuroImage, 13S*, 95.

Clatworthy, P. L., Lewis, S. J. G., Brichard, L., Hong, Y. T., Izquierdo, D., Clark, L. (2009). Dopamine release in dissociable striatal subregions predicts the different effects of oral methylphenidate on reversal learning and spatial eorking memory. *Journal of Neuroscience, 29*(15), 4690-4696.

Cloninger, C. R. (1987). A systematic method for clinical description and classification of personality variants: A proposal. *Archives of General Psychiatry, 44*(6), 573-588.

Cloninger, C. R., Przybeck, T. R., & Svrakic, D. M. (1991). The Tridimensional Personality Questionnaire: U.S. normative data. *Psychological reports, 69*(3), 1047-1057.

Cohen, D. J., Caparulo, B. K., Shaywitz, B. A., & Bowers, M. B., Jr. (1977). Dopamine and serotonin metabolism in neuropsychiatrically disturbed children. CSF homovanillic acid and 5-hydroxyindoleacetic acid. *Archvies of General Psychiatry, 34*(5), 545-550.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*.

Cohen, M. X., Young, J., Baek, J.-M., Kessler, C., & Ranganath, C. (2005). Individual differences in extraversion and dopamine genetics predict neural reward responses. *Cognitive Brain Research, 25*(3), 851-861.

Collins, D., Peters, T., & Evans, A. (1995). Automatic 3D model-based neuroanatomical segmentation. *Human Brain Mapping, 3*(3), 190-208.

Collins, D. L., & Evans, A. C. (1997). Animal: validation and applications of nonlinear registration-based segmentation. *International Journal of Pattern Recognition and Artificial Intelligence, 11*(8), 1271-1294.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Journal of Computer Assisted Tomography, 18*(2), 192-205.

Conners, C. K., Erhart, D., & Sparrow, E. (1999). *Conners' Adult ADHD Rating Scales. Technical manual*. New York: Multi-Health Systems.

Cools, R. (2006). Dopaminergic modulation of cognitive function-implications for l-DOPA treatment in Parkinson's disease. *Neuroscience & Biobehavioral Reviews, 30*(1), 1-23.

Cooper, J. (2003). *Biochemical Basis of Neuropharmacology, The - 8th Ed. (2003)*.

Corkum, P., Moldofsky, H., Hogg-Johnson, S., Humphries, T. O. M., & Tannock, R. (1999). Sleep Problems in Children With Attention[hyphen (true graphic)]Deficit/Hyperactivity Disorder: Impact of Subtype, Comorbidity, and Stimulant Medication. *Journal of the American Academy of Child & Adolescent Psychiatry, 38*(10), 1285-1293.

Cortese, S., Konofal, E., Yateman, N., Mouren, M. C., & Lecendreux, M. (2006). Sleep and alertness in children with attention-deficit/hyperactivity disorder: a systematic review of the literature. *Sleep, 29*(4), 504-511.

Costa, E., Groppetti, A., & Naimzada, M. K. (1972). Effects of amphetamine on the turnover rate of brain catecholamines and motor activity. *British Journal of Pharmacology, 44*(4), 742-751.

Costa, P. T., & McCrae, R. R. (1992). Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI) Professional Manual. *Psychological Assessment Resources*. Odessa, FL.

Costes, N., Dagher, A., Larcher, K., Evans, A. C., Collins, D. L., & Reilhac, A. (2009). Motion correction of multi-frame PET data in neuroreceptor mapping: Simulation based validation. *NeuroImage, 47*(4), 1496-1505.

Cox, S. M. L., Benkelfat, C., Dagher, A., Delaney, J. S., Durand, F., McKenzie, S. A. (2009). Striatal dopamine responses to intranasal cocaine self-administration in humans. *Biological Psychiatry, 65*(10), 846-850.

Cropley, V. L., Innis, R. B., Nathan, P. J., Brown, A. K., Sangare, J. L., Lerner, A. (2008). Small effect of dopamine release and no effect of dopamine depletion on [18F]fallypride binding in healthy humans. *Synapse, 62*(6), 399-408.

Cumyn, L., French, L., & Hechtman, L. (2009). Comorbidity in adults with attention-deficit hyperactivity disorder. *Canadian Journal of Psychiatry, 54*(10), 673-683.

Dane, A. V., Schachar, R. J., & Tannock, R. (2000). Does actigraphy differentiate ADHD subtypes in a clinical research setting? *Journal of the American Academy of Child and Adolescent Psychiatry, 39*(6), 752-760.

Darlington, R. B. (1968). Multiple regression in psychological research and practice. *Psychological Bulletin, 69*(3), 161-182.
Davids, E., Zhang, K., Kula, N. S., Tarazi, F. I., & Baldessarini, R. J. (2002). Effects of norepinephrine and serotonin transporter inhibitors on hyperactivity induced by neonatal 6-hydroxydopamine lesioning in rats. *Journal of Pharmacology and Experimental Therapeutics, 301*(3), 1097-1102.
Davis, G. D. (1957). Effects of central excitant and depressant drugs on locomotor activity in the monkey. *American Journal of Physiology, 188*(3), 619-623.
Davis, H. P., & Keller, F. R. (1998). Colorado assessment test manual. Colorado Springs: Colorado Assessment Tests.
de Villiers, A. S., Russell, V. A., Sagvolden, T., Searson, A., Jaffer, A., & Taljaard, J. J. (1995). Alpha 2-adrenoceptor mediated inhibition of [3H]dopamine release from nucleus accumbens slices and monoamine levels in a rat model for attention-deficit hyperactivity disorder. *Neurochemical Research, 20*(4), 427-433.
Decamp, E., & Schneider, J. S. (2004). Attention and executive function deficits in chronic low-dose MPTP-treated non-human primates. *European Journal of Neuroscience, 20*(5), 1371-1378.
Dennis, M., Francis, D. J., Cirino, P. T., Schachar, R., Barnes, M. A., & Fletcher, J. M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *Journal of the International Neuropsychological Society, 15*(3), 331-343.
Depue, R. A., & Collins, P. F. (1999). Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. *Behavioral and Brain Sciences, 22*(03), 491-517.
Depue, R. A., Luciana, M., Arbisi, P., Collins, P., & Leon, A. (1994). Dopamine and the structure of personality: Relation of agonist-induced dopamine activity to positive emotionality. *Journal of Personality and Social Psychology, 67*(3), 485-498.
Descarries, L., Soghomonian, J. J., Garcia, S., Doucet, G., & Bruno, J. P. (1992). Ultrastructural analysis of the serotonin hyperinnervation in adult rat neostriatum following neonatal dopamine denervation with 6-hydroxydopamine. *Brain Research, 569*(1), 1-13.
Devilbiss, D. M., & Berridge, C. W. (2006). Low-dose methylphenidate actions on tonic and phasic locus coeruleus discharge. *Journal of Pharmacology and Experimental Therapeutics, 319*(3), 1327-1335.
DeVito, E., Blackwell, A., Clark, L., Kent, L., Dezsery, A., Turner, D. (2009). Methylphenidate improves response inhibition but not reflection–impulsivity in children with attention deficit hyperactivity disorder (ADHD). *Psychopharmacology, 202*(1), 531-539.
Di Chiara, G., Bassareo, V., Fenu, S., De Luca, M. A., Spina, L., Cadoni, C. (2004). Dopamine and drug addiction: the nucleus accumbens shell connection. *Neuropharmacology, 47*(Supplement 1), 227-241.
Di Chiara, G., & Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proceedings of the National Academy of Sciences, 85*(14), 5274-5278.
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). *Development and Psychopathology, 17*(3), 807-825.
Dickerson, B. C., Fenstermacher, E., Salat, D. H., Wolk, D. A., Maguire, R. P., Desikan, R. (2008). Detection of cortical thickness correlates of cognitive performance: Reliability across MRI scan sessions, scanners, and field strengths. *NeuroImage, 39*(1), 10-18.
Dimoska, A., Johnstone, S. J., Barry, R. J., & Clarke, A. R. (2003). Inhibitory motor control in children with attention-deficit/hyperactivity disorder: event-related potentials in the stop-signal paradigm. *Biological Psychiatry, 54*(12), 1345-1354.
Dixon, W., & Yuen, K. (1974). Trimming and winsorization: A review. *Statistical Papers, 15*(2), 157-170.
Doherty, M. D., & Gratton, A. (1997). NMDA receptors in nucleus accumbens modulate stress-induced dopamine release in nucleus accumbens and ventral tegmental area. *Synapse, 26*(3), 225-234.
Donnelly, M., Rapoport, J. L., Potter, W. Z., Oliver, J., Keysor, C. S., & Murphy, D. L. (1989). Fenfluramine and dextroamphetamine treatment of childhood hyperactivity. Clinical and biochemical findings. *Archives of General Psychiatry, 46*(3), 205-212.
Dougherty, D. D., Bonab, A. A., Spencer, T. J., Rauch, S. L., Madras, B. K., & Fischman, A. J. (1999). Dopamine transporter density in patients with attention deficit hyperactivity disorder. *Lancet, 354*, 2132 - 2133.
Douglas, V. I. (1983). Attention and cognitive problems. In M. Rutter (Ed.), *Developmental Neuropsychiatry* (pp. 239-280). New York: Guilford Press.
Douglas, V. I. (1988). Cognitive deficits in children with attention deficit disorder with hyperactivity. In L. M. Bloomingdale & J. A. Sergeant (Eds.), *Attention deficit disorder: Critetia, cognition, intervention* (pp. 65-82). London: Pergamon.
Downey, K. K., Stelson, F. W., Pomerleau, O. F., & Giordani, B. (1997). Adult attention deficit hyperactivity disorder: Psychological test profiles in a clinical population. *The Journal of Nervous and Mental Disease, 185*(1), 32-38.
Drabant, E. M., Hariri, A. R., Meyer-Lindenberg, A., Munoz, K. E., Mattay, V. S., Kolachana, B. S. (2006). Catechol O-methyltransferase val158met genotype and neural mechanisms related to affective arousal and regulation. *Archives of General Psychiatry, 63*(12), 1396-1406.
Dreher, J. C., Kohn, P., Kolachana, B., Weinberger, D. R., & Berman, K. F. (2009). Variation in dopamine genes influences responsivity of the human reward system. *Proceedings of the National Academy of Sciences 106*(2), 617-622.
Dresel, S., Krause, J., Krause, K. H., LaFougere, C., Brinkbäumer, K., Kung, H. F. (2000). Attention deficit hyperactivity disorder: binding of [99mTC]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. *European Journal of Nuclear Medicine and Molecular Imaging, 27*(10), 1518-1524.
Drevets, W. C., Gautier, C., Price, J. C., Kupfer, D. J., Kinahan, P. E., Grace, A. A. (2001). Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry, 49*(2), 81-96.
Duarte, A., Hayasaka, S., Du, A., Schuff, N., Jahng, G. H., Kramer, J. (2006). Volumetric correlates of memory and executive function in normal elderly, mild cognitive impairment and Alzheimer's disease. *Neuroscience Letters, 406*(1-2), 60-65.

Duka, T., & Lupp, A. (1997). The effects of incentive on antisaccades: is a dopaminergic mechanism involved? *Behavioural Pharmacology, 8*(5), 373-382.

Durston, S., Davidson, M. C., Mulder, M. J., Spicer, J. A., Galvan, A., Tottenham, N. (2007). Neural and behavioral correlates of expectancy violations in attention-deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry, 48*(9), 881-889.

Durston, S., Hulshoff Pol, H. E., Schnack, H. G., Buitelaar, J. K., Steenhuis, M. P., Minderaa, R. B. (2004). Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*, 332 - 340.

Durston, S., Mulder, M., Casey, B. J., Ziermans, T., & van Engeland, H. (2006). Activation in Ventral Prefrontal Cortex is Sensitive to Genetic Vulnerability for Attention-Deficit Hyperactivity Disorder. *Biological Psychiatry, 60*(10), 1062-1070.

Durston, S., Tottenham, N. T., Thomas, K. M., Davidson, M. C., Eigsti, I. M., Yang, Y. (2003). Differential patterns of striatal activation in young children with and without ADHD. *Biological Psychiatry, 53*(10), 871-878.

Ebstein, R. P., & Belmaker, R. H. (1997). Saga of an adventure gene: novelty seeking, substance abuse and the dopamine D4 receptor (D4DR) exon III repeat polymorphism. *Molecular Psychiatry, 2*(5), 381-384.

Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics, 12*(1), 78-80.

Elbaz, Z. K. (2000). *Cognitive Control Processes in Attention Deficit Hyperactivity Disorder: Behavioural and Cardiovascular Measures*. Doctoral Dissertation. McGill University Library, Montreal.

Elderkin-Thompson, V., Ballmaier, M., Hellemann, G., Pham, D., & Kumar, A. (2008). Executive function and MRI prefrontal volumes among healthy older adults. *Neuropsychology, 22*(5), 626-637.

Ellison-Wright, I., Ellison-Wright, Z., & Bullmore, E. (2008). Structural brain change in Attention Deficit Hyperactivity Disorder identified by meta-analysis. *BMC Psychiatry, 8*(1), 51.

Epstein, J. N., Casey, B. J., Tonev, S. T., Davidson, M. C., Reiss, A. L., Garrett, A. (2007). ADHD- and medication-related brain activation effects in concordantly affected parent-child dyads with ADHD. *Journal of Child Psychology and Psychiatry, 48*(9), 899-913.

Erinoff, L., MacPhail, R. C., Heller, A., & Seiden, L. S. (1979). Age-dependent effects of 6-hydroxydopamine on locomotor activity in the rat. *Brain Research, 164*, 195-205.

Ernst, M., Zametkin, A., Matochik, J., Pascualvaca, D., Jons, PH. (1999). High midbrain [18F]DOPA accumulation in children with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 156*, 1209 - 1215.

Ernst, M., Zametkin, A. J., Matochik, J. A., Jons, P. H., & Cohen, R. M. (1998). DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18]fluorodopa positron emission tomographic study. *Journal of Neroscience, 18*, 5901 - 5907.

Ernst, M., Zametkin, A. J., Matochik, J. A., Liebenauer, L., Fitzgerald, G. A., & Cohen, R. M. (1994). Effects of intravenous dextroamphetamine on brain metabolism in adults with attention-deficit hyperactivity disorder (ADHD). Preliminary findings. *Psychopharmacology Bulletin, 30*(2), 219-225.

Ettinger, U., Kumari, V., Crawford, T. J., Davis, R. E., Sharma, T., & Corr, P. J. (2003). Reliability of smooth pursuit, fixation, and saccadic eye movements. *Psychophysiology, 40*, 1-9.

Evans, A. C., Marrett, S., Neelin, P., Collins, L., Worsley, K. J., Dai, W. (1992). Anatomical mapping of functional activation in stereotactic coordinate space. *Neuroimage, 1*(1), 43-53.

Evans, S. M., & Foltin, R. W. (2005). Exogenous progesterone attenuates the subjective effects of smoked cocaine in women, but not in men. *Neuropsychopharmacology, 31*(3), 659-674.

Everling, S., & Fischer, B. (1998). The antisaccade: A review of basic research and clinical studies. *Neuropsychologia, 36*(9), 885-899.

Faraone, S. V. (2000). Genetics of childhood disorders: XX. ADHD, Part 4: is ADHD genetically heterogeneous? *Jurnal of the American Academy of Child and Adolescent Psychiatry, 39*(11), 1455-1457.

Faraone, S. V., & Biederman, J. (1998). Neurobiology of attention-deficit hyperactivity disorder. *Biological Psychiatry, 44*(10), 951-958.

Faraone, S. V., Biederman, J., & Mick, E. (2006). The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychological Medicine, 36*(2), 159-165.

Faraone, S. V., Doyle, A. E., Mick, E., & Biederman, J. (2001). Meta-analysis of the association between the 7-repeat allele of the dopamine D(4) receptor gene and attention deficit hyperactivity disorder. *American Journal of Psychiatry, 158*(7), 1052-1057.

Faraone, S. V., & Mick, E. (2010). Molecular genetics of attention deficit hyperactivity disorder. *Psychiatric Clinics of North America, 33*(1), 159-180.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A. (2005a). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1313.

Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A. (2005b). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 1313 - 1323.

Faraone, S. V., Sergeant, J., Gillberg, C., & Biederman, J. (2003). The worldwide prevalence of ADHD: is it an American condition? *World Psychiatry, 2*(2), 104-113.

Feifel, D., Farber, R. H., Clementz, B. A., Perry, W., & Anllo-Vento, L. (2004). Inhibitory deficits in ocular motor behavior in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 56*(5), 333-339.

Fellows, L. K. (2007). Advances in understanding ventromedial prefrontal function: the accountant joins the executive. *Neurology, 68*(13), 991-995.

Filipek, P. A., Semrud-Clikeman, M., Steingard, R. J., Renshaw, P. F., Kennedy, D. N., & Biederman, J. (1997). Volumetric MRI analysis comparing subjects having

attention-deficit hyperactivity disorder with normal controls. *Neurology, 48*(3), 589-601.
Finn, I. B., Iuvone, P. M., & Holtzman, S. G. (1990). Depletion of catecholamines in the brain of rats differentially affects stimulation of locomotor activity by caffeine, D-amphetamine, and methylphenidate. *Neuropharmacology, 29*(7), 625-631.
First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders.* New York: Biometrics Research Department, New York State Psychiatric Institute.
Fjell, A. M., Walhovd, K. B., Reinvang, I., Lundervold, A., Salat, D., Quinn, B. T. (2006). Selective increase of cortical thickness in high-performing elderly--structural indices of optimal cognitive aging. *NeuroImage, 29*(3), 984-994.
Flaherty, A., & Graybiel, A. (1994). Input-output organization of the sensorimotor striatum in the squirrel monkey. *The Journal of Neuroscience, 14*(2), 599-610.
Floor, E., & Meng, L. (1996). Amphetamine releases dopamine from synaptic vesicles by dual mechanisms. *Neuroscience Letters, 215*(1), 53-56.
Florin, S. M., Kuczenski, R., & Segal, D. S. (1994). Regional extracellular norepinephrine responses to amphetamine and cocaine and effects of clonidine pretreatment. *Brain Research, 654*(1), 53-62.
Ford, T., Goodman, R., & Meltzer, H. (2003). The British child and adolescent mental health survey 1999: the prevalence of DSM-IV disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(10), 1203-1211.
Forssberg, H., Fernell, E., Waters, S., Waters, N., & Tedroff, J. (2006). Altered pattern of brain dopamine synthesis in male adolescents with attention deficit hyperactivity disorder. *Behavioral and Brain Functions, 2*(1), 40.
Foster, J. K., Meikle, A., Goodson, G., Mayes, A. R., Howard, M., Sunram, S. I. (1999). The hippocampus and delayed recall: bigger is not necessarily better? *Memory, 7*(5-6), 715-732.
Franklin, T. R., Lohoff, F. W., Wang, Z., Sciortino, N., Harper, D., Li, Y. (2009). DAT genotype modulates brain and behavioral responses elicited by cigarette cues. *Neuropsychopharmacology, 34*(3), 717-728.
Frazier, T. W., Demaree, H. A., & Youngstrom, E. A. (2004). Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology, 18*(3), 543-555.
Freedman, L. R., Rock, D., Roberts, S. A., Cornblatt, B. A., & Erlenmeyer-Kimling, L. (1998). The New York High-Risk Project: attention, anhedonia and social outcome. *Schizophr Res, 30*(1), 1-9.
Friedman, D. P., Aggleton, J. P., & Saunders, R. C. (2002). Comparison of hippocampal, amygdala, and perirhinal projections to the nucleus accumbens: Combined anterograde and retrograde tracing study in the Macaque brain. *The Journal of Comparative Neurology, 450*(4), 345-365.
Fudge, J. L., Kunishio, K., Walsh, P., Richard, C., & Haber, S. N. (2002). Amygdaloid projections to ventromedial striatal subterritories in the primate. *Neuroscience, 110*(2), 257-275.
Fuke, S., Suo, S., Takahashi, N., Koike, H., Sasagawa, N., & Ishiura, S. (2001). The VNTR polymorphism of the human dopamine transporter (DAT1) gene affects gene expression. *Pharmacogenomics Journal, 1*(2), 152-156.

Fuster, J. M. (1999). Synopsis of function and dysfunction of the frontal lobe. *Acta Psychiatrica Scandinavica, 99*, 51-57.
Gainetdinov, R. R. (2010). Strengths and limitations of genetic models of ADHD. *Attention Deficit Hyperactivity Disorder: from genes to animal models to patients, 2*(1), 21-30.
Gainetdinov, R. R., & Caron, M. G. (2000). An animal model of attention deficit hyperactivity disorder. *Molecular Medicine Today, 6*(1), 43-44.
Gainetdinov, R. R., & Caron, M. G. (2001). Genetics of childhood disorders: XXIV. ADHD, part 8: hyperdopaminergic mice as an animal model of ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(3), 380-382.
Gainetdinov, R. R., Jones, S. R., & Caron, M. G. (1999a). Functional hyperdopaminergia in dopamine transporter knock-out mice. *Biological Psychiatry, 46*(3), 303-311.
Gainetdinov, R. R., Wetsel, W. C., Jones, S. R., Levin, E. D., Jaber, M., & Caron, M. G. (1999b). Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. *Science, 283*(5400), 397-401.
Garris, P. A., & Wightman, R. M. (1994). Different kinetics govern dopaminergic transmission in the amygdala, prefrontal cortex, and striatum: An in vivo voltammetric study. *Journal of Neuroscience, 14*(1), 442-450.
Gautam, P., Cherbuin, N., Sachdev, P. S., Wen, W., & Anstey, K. J. (2011). Relationships between cognitive function and frontal grey matter volumes and thickness in middle aged and early old-aged adults: The PATH Through Life Study. *NeuroImage, 55*(3), 845-855.
George, S. R., Watanabe, M., Di Paolo, T., Falardeau, P., Labrie, F., & Seeman, P. (1985). The functional state of the dopamine receptor in the anterior pituitary is in the high affinity form. *Endocrinology, 117*(2), 690-697.
Gerfen, C., Herkenham, M., & Thibault, J. (1987). The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *The Journal of Neuroscience, 7*(12), 3915-3934.
Geurts, H. M., Verté, S., Oosterlaan, J., Roeyers, H., & Sergeant, J. A. (2004). How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? *Journal of Child Psychology and Psychiatry, 45*(4), 836-854.
Giedd, J. N., Castellanos, F. X., Casey, B. J., Kozuch, P., King, A. C., Hamburger, S. D. (1994). Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. *American Journal of Psychiatry, 151*(5), 665-669.
Ginovart, N. (2005). Imaging the dopamine system with in vivo [11C]raclopride displacement studies: Understanding the true mechanism. *Molecular Imaging and Biology, 7*(1), 45-52.
Ginovart, N., Farde, L., Halldin, C., & Swahn, C. G. (1997). Effect of reserpine-induced depletion of synaptic dopamine on [11C]raclopride binding to D2-dopamine receptors in the monkey brain. *Synapse, 25*(4), 321-325.
Giros, B., Jaber, M., Jones, S. R., Wightman, R. M., & Caron, M. G. (1996). Hyperlocomotion and indifference to cocaine and amphetamine in mice lacking the dopamine transporter. *Nature, 379*(6566), 606-612.

Glimcher, P. W. (2011). Understanding dopamine and reinforcement learning: The dopamine reward prediction error hypothesis. *Proceedings of the National Academy of Sciences, 108*(Supplement 3), 15647-15654.
Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron, 14*(3), 477-485.
Goldman-Rakic, P. S., Muly, I., E C, & Williams, G. V. (2000). D1 receptors in prefrontal cells and circuits. *Brain Research Reviews, 31*(2-3), 295-301.
Goto, Y., Hatakeyama, K., Kitama, T., Sato, Y., Kanemura, H., Aoyagi, K. (2010). Saccade eye movements as a quantitative measure of frontostriatal network in children with ADHD. \ *Brain and Development, 32*(5), 347-355.
Gourovitch, M. L., Kirkby, B. S., Goldberg, T. E., Weinberger, D. R., Gold, J. M., Esposito, G. (2000). A comparison of rCBF patterns during letter and semantic fluency. *Neuropsychology, 14*(3), 353-360.
Grace, A. A. (1991). Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience, 41*(1), 1-24.
Grace, A. A. (2001). Psychostimulant actions on dopamine and limbic system function: relevance to the pathophysiology and treatment of ADHD. In M. Solanto, A. F. Arnsten & F. X. Castellanos (Eds.), *Stimulant drugs and ADHD: basic and clinical neuroscience*. New York: Oxford University Press.
Grace, A. A., & Bunney, B. S. (1979). Paradoxical GABA excitation of nigral dopaminergic cells: Indirect mediation through reticulata inhibitory neurons. *European Journal of Pharmacology, 59*(3-4), 211-218.
Grace, A. A., & Bunney, B. S. (1984a). The control of firing pattern in nigral dopamine neurons: burst firing. *Journal of Neuroscience, 4*(11), 2877-2890.
Grace, A. A., & Bunney, B. S. (1984b). The control of firing pattern in nigral dopamine neurons: single spike firing. *Journal of Neuroscience, 4*(11), 2866-2876.
Graham, A. W., & Aghajanian, G. K. (1971). Effects of amphetamine on single cell activity in a catecholamine nucleus, the locus coeruleus. [10.1038/234100b0]. *Nature, 234*(5324), 100-102.
Greenwood, T. A., Alexander, M., Keck, P. E., McElroy, S., Sadovnick, A. D., Remick, R. A. (2002). Segmental linkage disequilibrium within the dopamine transporter gene. *Molecular Psychiatry, 7*(2), 165-173.
Grilly, D. M., & Gowans, G. C. (1988). Effects of naltrexone, and d-amphetamine, and their interaction on the stimulus control of choice behavior of rats. *Psychopharmacology (Berl), 96*(1), 73-80.
Grilly, D. M., Gowans, G. C., McCann, D. S., & Grogan, T. W. (1989). Effects of cocaine and d-amphetamine on sustained and selective attention in rats. *Pharmacol Biochem Behav, 33*(4), 733-739.
Grilly, D. M., & Simon, B. B. (1994). Differential effects of d-amphetamine on vigilance in younger and older male rats. *Pharmacol Biochem Behav, 49*(3), 497-502.
Groves, P. M., Fenster, G. A., Tepper, J. M., Nakamura, S., & Young, S. J. (1981). Changes in dopaminergic terminal excitability induced by amphetamine and haloperidol. *Brain Research, 221*(2), 425-431.

Gruber, R., Sadeh, A. V. I., & Raviv, A. (2000). Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry, 39*(4), 495-501.

Gunn, R. N., Lammertsma, A. A., Hume, S. P., & Cunningham, V. J. (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage, 6*(4), 279-287.

Gunning-Dixon, F. M., & Raz, N. (2003). Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. *Neuropsychologia, 41*(14), 1929-1941.

Haber, S. N. (2010). Convergence of limbic, cognitive, and motor cortico-striatal circuits with dopamine pathways in the primate brain. In L. Iversen, S. D. Iversen, S. B. Dunnett & A. Bjorklund (Eds.), *Dopamine Handbook*. Oxford: Oxford University Press.

Haber, S. N., Fudge, J. L., & McFarland, N. R. (2000). Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *The Journal of Neuroscience, 20*(6), 2369-2382.

Haber, S. N., Lynd, E., Klein, C., & Groenewegen, H. J. (1990). Topographic organization of the ventral striatal efferent projections in the rhesus monkey: An anterograde tracing study. *The Journal of Comparative Neurology, 293*(2), 282-298.

Haber, S. N., & McFarland, N. R. (1999). The concept of the ventral striatum in nonhuman primates. *Annals of the New York Academy of Sciences, 877*(1), 33-48.

Haertzen, C. A., Hill, H. E., & Belleville, R. E. (1963). Development of the Addiction Research Center Inventory (Arci): Selection of Items That Are Sensitive to the Effects of Various Drugs. *Psychopharmacologia, 4*, 155-166.

Hall, H., Farde, L., & Sedvall, G. (1988). Human dopamine receptor subtypes--in vitro binding analysis using 3H-SCH 23390 and 3H-raclopride. *Journal of Neural Transmission, 73*(1), 7-21.

Hall, H., Sedvall, G., Magnusson, O., Kopp, J., Halldin, C., & Farde, L. (1994). Distribution of D1- and D2-dopamine receptors, and dopamine and its metabolites in the human brain. *Neuropsychopharmacology, 11*(4), 245-256.

Hallett, P. E. (1978). Primary and secondary saccades to goals defined by instructions. *Vision Research, 18*(10), 1279-1296.

Halperin, J. M., Matier, K., Bedi, G., Sharma, V., & Newcorn, J. H. (1992). Specificity of inattention, impulsivity, and hyperactivity to the diagnosis of attention-deficit hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*(2), 190-196.

Halperin, J. M., Newcorn, J. H., Matier, K., Sharma, V., McKay, K. E., & Schwartz, S. (1993). Discriminant validity of attention-deficit hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 32*(5), 1038-1043.

Hart, E. L., Lahey, B. B., Loeber, R., Applegate, B., & Frick, P. J. (1995). Developmental change in attention-deficit hyperactivity disorder in boys: A four-year longitudinal study. *Journal of Abnormal Child Psychology, 23*(6), 729-749.

Hartberg, C. B., Lawyer, G., Nyman, H., Jönsson, E. G., Haukvik, U. K., Saetre, P. (2010). Investigating relationships between cortical thickness and cognitive

performance in patients with schizophrenia and healthy adults. *Psychiatry Research: Neuroimaging, 182*(2), 123-133.
Hassani, O.-K., François, C., Yelnik, J., & Féger, J. (1997). Evidence for a dopaminergic innervation of the subthalamic nucleus in the rat. *Brain Research, 749*(1), 88-94.
Haycock, J. W., Buskirk, R., & Gold, P. E. (1977). Effects on retention of posttraining amphetamine injections in mice: Interaction with pretraining experience. *Psychopharmacology, 54*(1), 21-24.
Head, D., Kennedy, K. M., Rodrigue, K. M., & Raz, N. (2009). Age differences in perseveration: Cognitive and neuroanatomical mediators of performance on the Wisconsin Card Sorting Test. *Neuropsychologia, 47*(4), 1200-1203.
Head, D., Rodrigue, K. M., Kennedy, K. M., & Raz, N. (2008). Neuroanatomical and cognitive mediators of age-related differences in episodic memory. *Neuropsychology, 22*(4), 491-507.
Heal, D. J., Cheetham, S. C., & Smith, S. L. (2009). The neuropharmacology of ADHD drugs in vivo: Insights on efficacy and safety. *Neuropharmacology, 57*(7-8), 608-618.
Heal, D. J., Smith, S. L., Kulkarni, R. S., & Rowley, H. L. (2008). New perspectives from microdialysis studies in freely-moving, spontaneously hypertensive rats on the pharmacology of drugs for the treatment of ADHD. *Pharmacology Biochemistry and Behavior, 90*(2), 184-197.
Hedreen, J. C., & Delong, M. R. (1991). Organization of striatopallidal, striatonigral, and nigrostriatal projections in the macaque. *The Journal of Comparative Neurology, 304*(4), 569-595.
Heinz, A., Goldman, D., Jones, D. W., Palmour, R., Hommer, D., Gorey, J. G. (2000). Genotype influences in vivo dopamine transporter availability in human striatum. *Neuropsychopharmacology, 22*(2), 133-139.
Helmeste, D. M., & Seeman, P. (1982). Amphetamine-induced hypolocomotion in mice with more brain D2 dopamine receptors. *Psychiatry Research, 7*(3), 351-359.
Henry, J. D., & Crawford, J. R. (2004). A meta-analytic review of verbal fluency performance following focal cortical lesions. *Neuropsychology, 18*(2), 284-295.
Hensch, T. K. (2004). Critical period regulation. *Annual Review of Neuroscience, 27*(1), 549-579.
Hervey, A. S., Epstein, J. N., & Curry, J. F. (2004). Neuropsychology of adults with attention-deficit/hyperactivity disorder: a meta-analytic review. *Neuropsychology, 18*(3), 485-503.
Hess, E. J., Collins, K. A., & Wilson, M. C. (1996). Mouse model of hyperkinesis implicates SNAP-25 in behavioral regulation. *Journal of Neuroscience, 16*(9), 3104-3111.
Hesse, S., Ballaschke, O., Barthel, H., & Sabri, O. (2009). Dopamine transporter imaging in adult patients with attention-deficit/hyperactivity disorder. *Psychiatry Research, 171*(2), 120-128.
Hikosaka, O., Takikawa, Y., & Kawagoe, R. (2000). Role of the basal ganglia in the control of purposive saccadic eye movements. *Physiological Reviews, 80*(3), 953-978.

Hill, D. E., Yeo, R. A., Campbell, R. A., Hart, B., Vigil, J., & Brooks, W. M. (2003). Magnetic resonance imaging correlates of attention-deficit/ hyperactivity disorder in children. *Neuropsychology, 17*(3), 496-506.

Hooks, M. S., Jones, G. H., Smith, A. D., Neill, D. B., & Justice, J. B., Jr. (1991). Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. *Synapse, 9*(2), 121-128.

Howell, D. C. (2010). *Statistical methods for psychology*. Belmont, CA: Thomson Wadsworth.

Huang-Pollock, C. L., Nigg, J. T., & Carr, T. H. (2005). Deficient attention is hard to find: applying the perceptual load model of selective attention to attention deficit hyperactivity disorder subtypes. *Journal of Child Psychology and Psychiatry, 46*(11), 1211-1218.

Hurks, P. P. M., Hendriksen, J. G. M., Vles, J. S. H., Kalff, A. C., Feron, F. J. M., Kroes, M. (2004). Verbal fluency over time as a measure of automatic and controlled processing in children with ADHD. *Brain and Cognition, 55*(3), 535-544.

Husain, M., & Mehta, M. A. (2011). Cognitive enhancement by drugs in health and disease. *Trends in Cognitive Sciences, 15*(1), 28-36.

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology, 387*(2), 167-178.

Hutton, S. B., & Ettinger, U. (2006). The antisaccade task as a research tool in psychopathology: a critical review. *Psychophysiology, 43*(3), 302-313.

Hynd, G. W., Hern, K. L., Novey, E. S., Eliopulos, D., Marshall, R., Gonzalez, J. J. (1993). Attention deficit hyperactivity disorder and asymmetry of the caudate nucleus. *Journal of Child Neurology, 8*(4), 339-347.

Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., Novey, E. S., & Eliopulos, D. (1990). Brain morphology in developmental dyslexia and attention deficit disorder/ hyperactivity. *Archives of Neurology, 47*(8), 919-926.

Iaboni, F., Douglas, V. I., & Baker, A. G. (1995). Effects of reward and response costs on inhibition in ADHD children. *Journal of Abnormal Psychology, 104*(1), 232-240.

Ichise, M., Ballinger, J. R., Tanaka, F., Moscovitch, M., St. George-Hyslop, P. H., Raphael, D. (1998). Age-related changes in D2 receptor binding with Iodine-123-Iodobenzofuran SPECT. *Journal of Nuclear Medicine, 39*(9), 1511-1518.

Ihalainen, J. A., Riekkinen Jr, P., & Feenstra, M. G. P. (1999). Comparison of dopamine and noradrenaline release in mouse prefrontal cortex, striatum and hippocampus using microdialysis. *Neuroscience Letters, 277*(2), 71-74.

Ilgin, N., Senol, S., Gucuyener, K., Gokcora, N., Atavci, S., & Sener, S. (2001). Is increased D2 receptor availability associated with response to stimulant medication in ADHD. *Developmental Medicine & Child Neurology, 43*(11), 755-760.

Ilinsky, I. A., Jouandet, M. L., & Goldman-Rakic, P. S. (1985). Organization of the nigrothalamocortical system in the rhesus monkey. *The Journal of Comparative Neurology, 236*(3), 315-330.

Jackson, M. E., Frost, A. S., & Moghaddam, B. (2001). Stimulation of prefrontal cortex at physiologically relevant frequencies inhibits dopamine release in the nucleus accumbens. *Journal of Neurochemistry, 78*(4), 920-923.

Jacob, C., Romanos, J., Dempfle, A., Heine, M., Windemuth-Kieselbach, C., Kruse, A. (2007). Co-morbidity of adult attention-deficit/hyperactivity disorder with focus on personality traits and related disorders in a tertiary referral center. *European Archives of Psychiatry and Clinical Neuroscience, 257*(6), 309-317.

Jacobsen, L. K., Staley, J. K., Zoghbi, S. S., Seibyl, J. P., Kosten, T. R., Innis, R. B. (2000). Prediction of dopamine transporter binding availability by genotype: a preliminary report. *American Journal of Psychiatry, 157*(10), 1700-1703.

Jahanshahi, M., Profice, P., Brown, R. G., Ridding, M. C., Dirnberger, G., & Rothwell, J. C. (1998). The effects of transcranial magnetic stimulation over the dorsolateral prefrontal cortex on suppression of habitual counting during random number generation. *Brain, 121 (Pt 8)*, 1533-1544.

Jaskiw, G. E., Karoum, F., Freed, W. J., Phillips, I., Kleinman, J. E., & Weinberger, D. R. (1990). Effect of ibotenic acid lesions of the medial prefrontal cortex on amphetamine-induced locomotion and regional brain catecholamine concentrations in the rat. *Brain Research, 534*(1-2), 263-272.

Jones, M. D., Williams, M. E., & Hess, E. J. (2001). Abnormal presynaptic catecholamine regulation in a hyperactive SNAP-25-deficient mouse mutant. *Pharmacology Biochemistry and Behavior, 68*(4), 669-676.

Joober, R., Grizenko, N., Sengupta, S., Amor, L. B., Schmitz, N., Schwartz, G. (2006). Dopamine transporter 3[prime]-UTR VNTR genotype and ADHD: a pharmaco-behavioural genetic study with methylphenidate. *Neuropsychopharmacology, 32*(6), 1370-1376.

Joober, R., Toulouse, A., Benkelfat, C., Lal, S., Bloom, D., Labelle, A. (2000). DRD3 and DAT1 genes in schizophrenia: an association study. *Journal Psychiatric Research, 34*(4-5), 285-291.

Joyce, J. N., Frohna, P. A., & Neal-Beliveau, B. S. (1996). Functional and molecular differentiation of the dopamine system induced by neonatal denervation. *Neuroscience and Biobehavioral Reviews, 20*(3), 453-486.

Jucaite, A., Fernell, E., Halldin, C., Forssberg, H., & Farde, L. (2005). Reduced midbrain dopamine transporter binding in male adolescents with attention-deficit/hyperactivity disorder: Association between striatal dopamine markers and motor hyperactivity. *Biological Psychiatry, 57*(3), 229.

Justice, A. J. H., & de Wit, H. (2000). Acute effects of estradiol pretreatment on the response to d-amphetamine in women. *Neuroendocrinology, 71*(1), 51-59.

Kamal, L. A., Arbilla, S., Galzin, A. M., & Langer, S. Z. (1983). Amphetamine inhibits the electrically evoked release of [3H]dopamine from slices of the rabbit caudate. *Journal of Pharmacology and Experimental Therapeutics, 227*(2), 446-458.

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry, 160*(1), 13-23.

Karatekin, C. (2006). Improving antisaccade performance in adolescents with attention-deficit/hyperactivity disorder (ADHD). *Experimental Brain Research, 174*(2), 324-341.

Karreman, M., & Moghaddam, B. (1996). The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: An effect mediated by ventral tegmental area. *Journal of Neurochemistry, 66*(2), 589-598.

Kates, W. R., Frederikse, M., Mostofsky, S. H., Folley, B. S., Cooper, K., Mazur-Hopkins, P. (2002). MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. *Psychiatry Research: Neuroimaging, 116*(1-2), 63.

Katz, J. L. (1988). Effects of drugs on stimulus control of behavior. III. Analysis of effects of pentobarbital and d-amphetamine. *Journal of Pharmacology and Experimental Therapeutics, 246*(1), 76-83.

Kebabian, J. W., & Greengard, P. (1971). Dopamine-sensitive adenyl cyclase: Possible role in synaptic transmission. *Science, 174*(4016), 1346-1349.

Keefe, K. A., Zigmond, M. J., & Abercrombie, E. D. (1992). Extracellular dopamine in striatum: influence of nerve impulse activity in medial forebrain bundle and local glutamatergic input. *Neuroscience, 47*(2), 325-332.

Kegeles, L. S., Abi-Dargham, A., Zea-Ponce, Y., Rodenhiser-Hill, J., Mann, J. J., Van Heertum, R. L. (2000). Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biological Psychiatry, 48*(7), 627-640.

Kempton, S., Vance, A., Maruff, P., Luk, E., Costin, J., & Pantelis, C. (1999). Executive function and attention deficit hyperactivity disorder: stimulant medication and better executive function performance in children. *Psychological Medicine, 29*(3), 527-538.

Kent, L., Doerry, U., Hardy, E., Parmar, R., Gingell, K., Hawi, Z. (2002). Evidence that variation at the serotonin transporter gene influences susceptibility to attention deficit hyperactivity disorder (ADHD): analysis and pooled analysis. *Molecular Psychiatry, 7*(8), 908-912.

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O. (2006). The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *American Journal of Psychiatry, 163*(4), 716-723.

Khan, Z. U., Gutiérrez, A., Martín, R., Peñafiel, A., Rivera, A., & de la Calle, A. (2000). Dopamine D5 receptors of rat and human brain. *Neuroscience, 100*(4), 689-699.

Kim, B.-N., Lee, J.-S., Shin, M.-S., Cho, S.-C., & Lee, D.-S. (2002). Regional cerebral perfusion abnormalities in attention deficit/hyperactivity disorder. *European Archives of Psychiatry and Clinical Neuroscience, 252*(5), 219-225.

Kim, B. N., Lee, J. S., Cho, S. C., & Lee, D. S. (2001). Methylphenidate increased regional cerebral blood flow in subjects with attention deficit/ hyperactivity disorder. *Yonsei Medical Journal, 42*, 19-29.

Kim, J. S., Singh, V., Lee, J. K., Lerch, J., Ad-Dab'bagh, Y., MacDonald, D. (2005). Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. *NeuroImage, 27*(1), 210-221.

Kimura, M. (1986). The role of primate putamen neurons in the association of sensory stimuli with movement. *Neuroscience Research, 3*(5), 436-443.

Klein-Schwartz, W., & McGrath, J. (2003). Poison centers' experience with methylphenidate abuse in pre-teens and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry, 42*(3), 288-294.

Klein, C. (2001). Developmental functions for saccadic eye movement parameters derived from pro- and antisaccade tasks. *Experimental Brain Research, 139*(1), 1-17.

Klein, C., Fischer, B., Jr, Fischer, B., & Hartnegg, K. (2002). Effects of methylphenidate on saccadic responses in patients with ADHD. *Experimental Brain Research, 145*(1), 121-125.

Klein, C. H., Raschke, A., & Brandenbusch, A. (2003). Development of pro- and antisaccades in children with attention-deficit hyperactivity disorder (ADHD) and healthy controls. *Psychophysiology, 40*(1), 17-28.

Kluger, A. N., Siegfried, Z., & Ebstein, R. P. (2002). A meta-analysis of the association between DRD4 polymorphism and novelty seeking. *Molecular Psychiatry, 7*(7), 712-717.

Knoch, D., Treyer, V., Regard, M., Muri, R. M., Buck, A., & Weber, B. (2006). Lateralized and frequency-dependent effects of prefrontal rTMS on regional cerebral blood flow. *Neuroimage, 31*(2), 641-648.

Koepp, M. J., Gunn, R. N., Lawrence, A. D., Cunningham, V. J., Dagher, A., Jones, T. (1998). Evidence for striatal dopamine release during a video game. *Nature, 393*(6682), 266-268.

Köhler, C., Hall, H., Ögren, S.-O., & Gawell, L. (1985). Specific in vitro and in vivo binding of 3H-raclopride a potent substituted benzamide drug with high affinity for dopamine D-2 receptors in the rat brain. *Biochemical Pharmacology, 34*(13), 2251-2259.

Kolachana, B. S., Saunders, R. C., & Weinberger, D. R. (1995). Augmentation of prefrontal cortical monoaminergic activity inhibits dopamine release in the caudate nucleus: an in vivo neurochemical assessment in the rhesus monkey. *Neuroscience, 69*(3), 859-868.

Kollins, S. H., MacDonald, E. K., & Rush, C. R. (2001). Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. *Pharmacology Biochemistry and Behavior, 68*(3), 611-627.

Konofal, E., Lecendreux, M., Bouvard, M. P., & Mouren-Simeoni, M. C. (2001). High levels of nocturnal activity in children with attention-deficit hyperactivity disorder: a video analysis. *Psychiatry and Clinical Neurosciences, 55*(2), 97-103.

Konrad, K., Gunther, T., Hanisch, C., & Herpertz-Dahlmann, B. (2004). Differential effects of methylphenidate on attentional functions in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 43*(2), 191-198.

Konrad, K., Neufang, S., Hanisch, C., Fink, G. R., & Herpertz-Dahlmann, B. (2006). Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: evidence from an event-related functional magnetic resonance imaging study. *Biological Psychiatry, 59*(7), 643-651.

Koob, G. F. (1996). Hedonic valence, dopamine and motivation. *Molecular Psychiatry, 1*(3), 186-189.

Kooij, J. J., Middelkoop, H. A., van Gils, K., & Buitelaar, J. K. (2001). The effect of stimulants on nocturnal motor activity and sleep quality in adults with ADHD: an open-label case-control study. *Journal of Clinical Psychiatry, 62*(12), 952-956.

Kostrzewa, R. M., Reader, T. A., & Descarries, L. (1998). Serotonin neural adaptations to ontogenetic loss of dopamine neurons in rat brain. *Journal of Neurochemistry, 70*(3), 889-898.

Koziol, L. F., & Stout, C. E. (1991). The use of a verbal fluency measure in understanding and evaluating ADHD as an exucutive function disorder. *Archives of Clinical Neuropsychology, 6*(3), 201-.

Krause, K. H., Dresel, S. H., Krause, J., Kung, H. F., & Tatsch, K. (2000). Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. *Neuroscience Letters, 285*(2), 107-110.

Kuczenski, R. (1975). Effects of catecholamine releasing agents on synaptosomal dopamine biosynthesis: multiple pools of dopamine or multiple forms of tyrosine hydroxylase. *Neuropharmacology, 14*(1), 1-10.

Kuczenski, R., & Segal, D. (1989). Concomitant characterization of behavioral and striatal neurotransmitter response to amphetamine using in vivo microdialysis. *Journal of Neuroscience, 9*(6), 2051-2065.

Kuczenski, R., Segal, D., & Aizenstein, M. (1991). Amphetamine, cocaine, and fencamfamine: relationship between locomotor and stereotypy response profiles and caudate and accumbens dopamine dynamics. *Journal of Neuroscience, 11*(9), 2703-2712.

Kuczenski, R., & Segal, D. S. (1992). Differential effects of amphetamine and dopamine uptake blockers (cocaine, nomifensine) on caudate and accumbens dialysate dopamine and 3-methoxytyramine. *Journal of Pharmacology and Experimental Therapeutics, 262*(3), 1085-1094.

Kuczenski, R., & Segal, D. S. (1997). Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *Journal of Neurochemistry, 68*(5), 2032-2037.

Kuczenski, R., & Segal, D. S. (2001). Locomotor effects of acute and repeated threshold doses of amphetamine and methylphenidate: relative roles of dopamine and norepinephrine. *Journal of Pharmacology and Experimental Therapeutics, 296*(3), 876-883.

Kuczenski, R., & Segal, D. S. (2002). Exposure of adolescent rats to oral methylphenidate: Preferential effects on extracellular norepinephrine and absence of sensitization and cross-sensitization to methamphetamine. *Journal of Neuroscience, 22*(16), 7264-7271.

Kuntsi, J., Andreou, P., Ma, J., Borger, N. A., & van der Meere, J. J. (2005). Testing assumptions for endophenotype studies in ADHD: reliability and validity of tasks in a general population sample. *BMC Psychiatry, 5*, 40.

Kuntsi, J., Oosterlaan, J., & Stevenson, J. (2001). Psychological mechanisms in hyperactivity: I. Response inhibition deficit, working memory impairment, delay aversion, or something else? *Journal of Child Psychology and Psychiatry, 42*, 199 - 210.

Kuo, J.-S., & Carpenter, M. B. (1973). Organization of pallidothalamic projections in the rhesus monkey. *The Journal of Comparative Neurology, 151*(3), 201-235.

Labbe, C., Froment, J. C., Kennedy, A., Ashburner, J., & Cinotti, L. (1996). Positron emission tomography metabolic data corrected for cortical atrophy using

magnetic resonance imaging. *Alzheimer Disease and Associated Disorders, 10*(3), 141-170.
Lacroix, D., & Ferron, A. (1988). Electrophysiological effects of methylphenidate on the coeruleo-cortical noradrenergic system in the rat. *European Journal of Pharmacology, 149*(3), 277-285.
Lammertsma, A. A., & Hume, S. P. (1996). Simplified reference tissue model for PET receptor studies. *Neuroimage, 4*(3 Pt 1), 153-158.
Langleben, D. D., Austin, G., Krikorian, G., Ridlehuber, H. W., & Strauss, H. W. (2001). Interhemispheric assymmetry of regional recebral blood flow in prepubescent boys with attention deficit hyperactivity disorder. *Nuclear Medicine Communications, 22*(12), 1333-1340.
Lanska, D. J. (2010). Chapter 33: the history of movement disorders. *Handbok of Clinical Neurology, 95*, 501-546.
Larisch, R., Sitte, W., Antke, C., Nikolaus, S., Franz, M., Tress, W. (2006). Striatal dopamine transporter density in drug naive patients with attention-deficit/hyperactivity disorder. *Nuclear Medicine Communications, 27*(3), 267-270.
Laruelle, M. (2000). Imaging synaptic neurotransmission with in vivo binding competition techniques: A critical review. *Journal of Cerebral Blood Flow and Metabolism, 20*(3), 423-451.
Laruelle, M., Iyer, R. N., al-Tikriti, M. S., Zea-Ponce, Y., Malison, R., Zoghbi, S. S. (1997). Microdialysis and SPECT measurements of amphetamine-induced dopamine release in nonhuman primates. *Synapse, 25*(1), 1-14.
Lavoie, B., Smith, Y., & Parent, A. (1989). Dopaminergic innervation of the basal ganglia in the squirrel monkey as revealed by tyrosine hydroxylase immunohistochemistry. *The Journal of Comparative Neurology, 289*(1), 36-52.
Lawrence, A., Weeks, R., Brooks, D., Andrews, T., Watkins, L., Harding, A. (1998). The relationship between striatal dopamine receptor binding and cognitive performance in Huntington's disease. *Brain, 121*(7), 1343-1355.
Le Moal, M. (1996). Mesocorticolimbic dopaminergic neurons: Functional and regulatory roles. In B. F.E. & D. J. Kupfer (Eds.), *Psychopharmacology: The Fourth Generation of Progress* (pp. 283-284). New York: Raven Press.
Lee, B., London, E. D., Poldrack, R. A., Farahi, J., Nacca, A., Monterosso, J. R. (2009). Striatal dopamine D2/D3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *Journal of Neuroscience, 29*(47), 14734-14740.
Lee, Y. S., Han, D. H., Lee, J. H., & Choi, T. Y. (2010). The Effects of Methylphenidate on Neural Substrates Associated with Interference Suppression in Children with ADHD: A Preliminary Study Using Event Related fMRI. *Psychiatry Investigation, 7*(1), 49-54.
Leigh, R. J., & Kennard, C. (2004). Using saccades as a research tool in the clinical neurosciences. *Brain, 127*(Pt 3), 460-477.
Lerch, J. P., & Evans, A. C. (2005). Cortical thickness analysis examined through power analysis and a population simulation. *NeuroImage, 24*(1), 163-173.

Lesch, K. P., Bengel, D., Heils, A., Sabol, S. Z., Greenberg, B. D., Petri, S. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*(5292), 1527-1531.

Levant, B., Grigoriadis, D. E., & DeSouza, E. B. (1992). Characterization of [3H]quinpirole binding to D2-like dopamine receptors in rat brain. *Journal of Pharmacology and Experimental Therapeutics, 262*(3), 929-935.

Lévesque, D., & Di Paolo, T. (1988). Rapid conversion of high into low striatal D2-dopamine receptor agonist binding states after an acute physiological dose of 17[beta]-estradiol. *Neuroscience Letters, 88*(1), 113-118.

Lévesque, D., Diaz, J., Pilon, C., Martres, M. P., Giros, B., Souil, E. (1992). Identification, characterization, and localization of the dopamine D3 receptor in rat brain using 7-[3H]hydroxy-N,N-di-n-propyl-2-aminotetralin. *Proceedings of the National Academy of Sciences, 89*(17), 8155-8159.

Levey, A. I., Hersch, S. M., Rye, D. B., Sunahara, R. K., Niznik, H. B., Kitt, C. A. (1993). Localization of D1 and D2 dopamine receptors in brain with subtype-specific antibodies. *Proceedings of the National Academy of Sciences, 90*(19), 8861-8865.

Leviel, V., Gobert, A., & Guibert, B. (1990). The glutamate-mediated release of dopamine in the rat striatum: further characterization of the dual excitatory-inhibitory function. *Neuroscience, 39*(2), 305-312.

Leyton, M. (2007). Conditioned and sensitized responses to stimulant drugs in humans. *Progress Neuro-Psychopharmacology and Biological Psychiatry, 31*(8), 1601-1613.

Leyton, M., aan het Rot, M., Booij, L., Baker, G. B., Young, S. N., & Benkelfat, C. (2007). Mood-elevating effects of d-amphetamine and incentive salience: the effect of acute dopamine precursor depletion. *Journal of Psychiatry and Neuroscience, 32*(2), 129-136.

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., & Dagher, A. (2002). Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. *Neuropsychopharmacology, 27*(6), 1027-1035.

Leyton, M., Dagher, A., Boileau, I., Casey, K., Baker, G. B., Diksic, M. (2004). Decreasing amphetamine-induced dopamine release by acute phenylalanine/tyrosine depletion: A PET/[11C]raclopride study in healthy men. *Neuropsychopharmacology, 29*(2), 427-432.

Leyton, M., Okazawa, H., Diksic, M., Paris, J., Rosa, P., Mzengeza, S. (2001). Brain regional α-[11C]methyl-l-tryptophan trapping in impulsive subjects with borderline personality disorder. *American Journal of Psychiatry, 158*(5), 775-782.

Li, D., Sham, P., Owen, M., & He, L. (2006). Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Human Molecular Genetics, 15*, 2276 - 2284.

Lichter, D. G., & Cummings, J. L. (2001). Cognitive Abilities Mediated by Frontal-Subcortical Circuits. In D. G. Lichter & J. L. Cummings (Eds.), *Frontal-Subcortical Circuits in Psychiatric and Neurological Disorders* (pp. 114-150). New York: Guilford.

Lijffijt, M., Kenemans, J. L., Verbaten, M. N., & van Engeland, H. (2005). A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: Deficient inhibitory motor control? *Journal of Abnormal Psychology, 114*(2), 216-222.

Lijffijt, M., Kenemans, J. L., Wal, A. t., Quik, E. H., Kemner, C., Westenberg, H. (2006). Dose-related effect of methylphenidate on stopping and changing in children with attention-deficit/hyperactivity disorder. *European Psychiatry, 21*(8), 544-547.

Lile, J. A., Kendall, S. L., Babalonis, S., Martin, C. A., & Kelly, T. H. (2007). Evaluation of estradiol administration on the discriminative-stimulus and subject-rated effects of d-amphetamine in healthy pre-menopausal women. *Pharmacology Biochemistry and Behavior, 87*(2), 258-266.

Lindvall, O., & Björklund, A. (1979). Dopaminergic innervation of the globus pallidus by collaterals from the nigrostriatal pathway. *Brain Research, 172*(1), 169-173.

Ljungberg, T., & Enquist, M. (1987). Disruptive effects of low doses of d-amphetamine on the ability of rats to organize behaviour into functional sequences. *Psychopharmacology (Berl), 93*(2), 146-151.

Loe, I. M., Feldman, H. M., Yasui, E., & Luna, B. (2009). Oculomotor performance identifies underlying cognitive deficits in attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(4), 431-440.

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

Logan, G. D. (2004). Working memory, task switching, and executive control in the task span procedure. *Journal of Experimental Psychology General, 133*(2), 218-236.

Logan, G. D., Cowan, W. B., & Davis, K. A. (1984). On the ability to inhibit simple and choice reaction time responses: a model and method. *Journal of Experimental Psychology: Human Perception and Performance, 10*(2), 276-291.

Lorr, M., McNair, D. M., & Fisher, S. U. (1982). Evidence for bipolar mood states. *Journal of Personality Assessment, 46*(4), 432-436.

Lott, D. C., Kim, S.-J., Cook, E. H., Jr., & de Wit, H. (2004). Dopamine transporter gene associated with diminished subjective response to amphetamine. *Neuropsychopharmacology, 30*(3), 602-609.

Lou, H. C., Henriksen, L., & Bruhn, P. (1984). Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. *Archives of Neurology, 41*(8), 825-829.

Lou, H. C., Henriksen, L., & Bruhn, P. (1990). Focal cerebral dysfunction in developmental learning disabilities. *Lancet, 335*(8680), 8-11.

Lou, H. C., Henriksen, L., Bruhn, P., Borner, H., & Bieber Nielson, J. (1989). Striatal dysfunction in attention deficit and hyperkinetic disorder. *Archives of Neurology, 46*(1), 48-52.

Lou, H. C., Rosa, Pedro, Pryds, O., Karrebaek, H., Lunding, J. (2004). ADHD: increased dopamine receptor availability linked to attention deficit and low neonatal cerebral blood flow. *Developmental Medicine & Child Neurology, 46*(3), 179-183.

Lu, L. H., Dapretto, M., O'Hare, E. D., Kan, E., McCourt, S. T., Thompson, P. M. (2009). Relationships between brain activation and brain structure in normally developing children. *Cereb Cortex, 19*(11), 2595-2604.

Luthman, J., Bassen, M., Fredriksson, A., & Archer, T. (1997). Functional changes induced by neonatal cerebral 6-hydroxydopamine treatment: effects of dose levels on behavioral parameters. *Behavioural Brain Research, 82*(2), 213-221.

Luthman, J., Brodin, E., Sundstrom, E., & Wiehager, B. (1990). Studies on brain monoamine and neuropeptide systems after neonatal intracerebroventricular 6-hydroxydopamine treatment. *International Journal of Developmental Neuroscience, 8*(5), 549-560.

Luthman, J., Fredriksson, A., Lewander, T., Jonsson, G., & Archer, T. (1989). Effects of *d*-amphetamine and methylphenidate on hyperactivity produced by neonatal 6-hydroxydopamine treatment. *Psychopharmacology, 99*(4), 550-557.

Lynch, G., Ballantine Ii, P., & Campbell, B. A. (1971). Differential rates of recovery following frontal cortical lesions in rats. *Physiology & Behavior, 7*(5), 737-741.

Lynd-Balta, E., & Haber, S. N. (1994a). The organization of midbrain projections to the striatum in the primate: Sensorimotor-related striatum versus ventral striatum. *Neuroscience, 59*(3), 625-640.

Lynd-Balta, E., & Haber, S. N. (1994b). Primate striatonigral projections: A comparison of the sensorimotor-related striatum and the ventral striatum. *The Journal of Comparative Neurology, 345*(4), 562-578.

MacDonald, D., Kabani, N., Avis, D., & Evans, A. C. (2000). Automated 3-D extraction of Inner and outer surfaces of cerebral cortex from MRI. *NeuroImage, 12*(3), 340-356.

Mack, F., & Bonisch, H. (1979). Dissociation constants and lipophilicity of catecholamines and related compounds. *Naunyn-Schmiedebergs Archives of Pharmacology, 310*(1), 1-9.

Maisonneuve, I. M., Keller, R. W., & Glick, S. D. (1990). Similar effects ofd-amphetamine and cocaine on extracellular dopamine levels in medial prefrontal cortex of rats. *Brain Research, 535*(2), 221-226.

Makris, N., Biederman, J., Valera, E. M., Bush, G., Kaiser, J., Kennedy, D. N. (2007). Cortical thinning of the attention and executive function networks in adults with attention-deficit/hyperactivity disorder. *Cerebral Cortex, 17*(6), 1364-1375.

Malloy-Diniz, L., Fuentes, D., Leite , W. B., Correa, H., & Bechara, A. (2007). Impulsive behavior in adults with attention deficit/ hyperactivity disorder: Characterization of attentional, motor and cognitive impulsiveness. *Journal of the International Neuropsychological Society, 13*(04), 693-698.

Mannuzza, S., Klein, R. G., Bessler, A., Malloy, P., & LaPadula, M. (1993). Adult outcome of hyperactive boys: educational achievement, occupational rank, and psychiatric status. *Archives of General Psychiatry, 50*(7), 565-576.

Mannuzza, S., Klein, R. G., Bessler, A., Malloy, P., & LaPadula, M. (1998). Adult psychiatric status of hyperactive boys grown up. *American Journal of Psychiatry, 155*(4), 493-498.

Manor, I., Eisenberg, J., Tyano, S., Sever, Y., Cohen, H., Ebstein, R. P. (2001). Family-based association study of the serotonin transporter promoter region

polymorphism (5-HTTLPR) in attention deficit hyperactivity disorder. *American Journal of Medical Genetics, 105*(1), 91-95.

Mansour, A., Meador-Woodruff, J. H., Zhou, Q., Civelli, O., Akil, H., & Watson, S. J. (1992). A comparison of D1 receptor binding and mRNA in rat brain using receptor autoradiographic and in situ hybridization techniques. *Neuroscience, 46*(4), 959-971.

Marinelli, M., & White, F. J. (2000). Enhanced vulnerability to cocaine self-administration is associated with elevated impulse activity of midbrain dopamine neurons. *Journal of Neuroscience, 20*(23), 8876-8885.

Martinez, D., Slifstein, M., Broft, A., Mawlawi, O., Hwang, D. R., Huang, Y. (2003). Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *Journal of Cerebral Blood Flow and Metabolism, 23*(3), 285-300.

Marzocchi, G. M., Oosterlaan, J., Zuddas, A., Cavolina, P., Geurts, H., Redigolo, D. (2008). Contrasting deficits on executive functions between ADHD and reading disabled children. *Journal of Child Psychology and Psychiatry, 49*(5), 543-552.

Mataro, M., Garcia-Sanchez, C., Junque, C., Estevez-Gonzalez, A., & Pujol, J. (1997). Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. *Archives of Neurology, 54*(8), 963-968.

Mattay, V. S., Callicott, J. H., Bertolino, A., Heaton, I., Frank, J. A., Coppola, R. (2000). Effects of dextroamphetamine on cognitive performance and cortical activation. *Neuroimage, 12*(3), 268-275.

Mattay, V. S., Goldberg, T. E., Fera, F., Hariri, A. R., Tessitore, A., Egan, M. F. (2003). Catechol O-methyltransferase val158-met genotype and individual variation in the brain response to amphetamine. *Proceedings of the National Academy of Sciences, 100*(10), 6186-6191.

Mattay, V. S., Tessitore, A., Callicott, J. H., Bertolino, A., Goldberg, T. E., Chase, T. N. (2002). Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Annals of Neurology, 51*(2), 156-164.

Mattes, J. A. (1980). The role of frontal lobe dysfunction in childhood hyperkinesis. *Comparative Psychiatry, 21*(5), 358-369.

Mawlawi, O., Martinez, D., Slifstein, M., Broft, A., Chatterjee, R., Hwang, D. R. (2001). Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D(2) receptor parameter measurements in ventral striatum. *Journal of Cerebral Blood Flow and Metabolism, 21*(9), 1034-1057.

Mazziotta, J. C., Toga, A. W., Evans, A., Fox, P., & Lancaster, J. (1995). A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). *Neuroimage, 2*(2), 89-101.

McAlonan, G. M., Cheung, V., Cheung, C., Chua, S. E., Murphy, D. G. M., Suckling, J. (2007). Mapping brain structure in attention deficit-hyperactivity disorder: A voxel-based MRI study of regional grey and white matter volume. *Psychiatry Research: Neuroimaging, 154*(2), 171-180.

McGaughy, J., & Sarter, M. (1995). Behavioral vigilance in rats: task validation and effects of age, amphetamine, and benzodiazepine receptor ligands. *Psychopharmacology (Berl), 117*(3), 340-357.

McNair, D. M., Lorr, M., & Droppleman, L. F. (1988). Manual for the Profile of Mood States. San Diego: Educational and Industrial Testing Service.

Meador-Woodruff, J. H., Damask, S. P., Wang, J., Haroutunian, V., Davis, K. L., & Watson, S. J. (1996). Dopamine receptor mRNA expression in human striatum and neocortex. *Neuropsychopharmacology, 15*(1), 17-29.

Meador-Woodruff, J. H., Mansour, A., Bunzow, J. R., Van Tol, H. H., Watson, S. J., & Civelli, O. (1989). Distribution of D2 dopamine receptor mRNA in rat brain. *Proceedings of the National Academy of Sciences, 86*(19), 7625-7628.

Mehta, M. A., Sahakian, B. J., & Robbins, T. W. (2001). Comparative pharmacology of methylphenidate and related drugs in human volunteers, patients with ADHD, and experimental animals. In M. Solanto, A. F. Arnsten & F. X. Castellanos (Eds.), *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience* (pp. 303-331). New York: Oxford University Press.

Meltzer, C. C., Leal, J. P., Mayberg, H. S., Wagner, H. N., Jr., & Frost, J. J. (1990). Correction of PET data for partial volume effects in human cerebral cortex by MR imaging. *Journal of Computer Assisted Tomography, 14*(4), 561-570.

Meyer-Lindenberg, A., Miletich, R. S., Kohn, P. D., Esposito, G., Carson, R. E., Quarantelli, M. (2002). Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nature Neuroscience, 5*(3), 267-271.

Middleton, F. A., & Strick, P. L. (2002). Basal-ganglia 'projections' to the prefrontal cortex of the primate. *Cerebral Cortex, 12*(9), 926-935.

Milad, M. R., Quinn, B. T., Pitman, R. K., Orr, S. P., Fischl, B., & Rauch, S. L. (2005). Thickness of ventromedial prefrontal cortex in humans is correlated with extinction memory. *Proceedings of the National Academy of Sciences, 102*(30), 10706-10711.

Mill, J., Xu, X., Ronald, A., Curran, S., Price, T., Knight, J. (2005). Quantitative trait locus analysis of candidate gene alleles associated with attention deficit hyperactivity disorder (ADHD) in five genes: DRD4, DAT1, DRD5, SNAP-25, and 5HT1B. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 133B*(1), 68-73.

Miller, C. J., Miller, S. R., Newcorn, J. H., & Halperin, J. M. (2008). Personality characteristics associated with persistent ADHD in late adolescence. *Journal of Abnormal Child Psychology, 36*(2), 165-173.

Miller, G. A., & Chapman, J. P. (2001). Misunderstanding analysis of covariance. *Journal of Abnormal Psychology, 110*(1), 40-48.

Millstein, R. B., Wilens, T. E., Biederman, J., & Spencer, T. J. (1997). Presenting ADHD symptoms and subtypes in clinically referred adults with ADHD. *Journal of Attention Disorders, 2*(3), 159-166.

Monuteaux, M. C., Seidman, L. J., Faraone, S. V., Makris, N., Spencer, T., Valera, E. (2008). A preliminary study of dopamine D4 receptor genotype and structural brain alterations in adults with ADHD. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 147B*(8), 1436-1441.

Morari, M., O'Connor, W. T., Ungerstedt, U., Bianchi, C., & Fuxe, K. (1996). Functional neuroanatomy of the nigrostriatal and striatonigral pathways as studied with dual probe microdialysis in the awake rat--II. Evidence for striatal N-methyl-D-aspartate receptor regulation of striatonigral GABAergic transmission and motor function. *Neuroscience, 72*(1), 89-97.

Morrison, J. R., & Stewart, M. A. (1973). The psychiatric status of the legal families of adopted hyperactive children. *Archives of General Psychiatry, 28*(6), 888-891.

Mostofsky, S. H., Cooper, K. L., Kates, W. R., Denckla, M. B., & Kaufmann, W. E. (2002). Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 52*(8), 785.

Mostofsky, S. H., Lasker, A. G., Cutting, L. E., Denckla, M. B., & Zee, D. S. (2001). Oculomotor abnormalities in attention deficit hyperactivity disorder: a preliminary study. *Neurology, 57*(3), 423-430.

Mostofsky, S. H., Reiss, A. L., Lockhart, P., & Denckla, M. B. (1998). Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *Journal of Child Neurology, 13*(9), 434-439.

Mrzljak, L., Bergson, C., Pappy, M., Huff, R., Levenson, R., & Goldman-Rakic, P. S. (1996). Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. [10.1038/381245a0]. *Nature, 381*(6579), 245-248.

Mukherjee, J., Christian, B. T., Dunigan, K. A., Shi, B., Narayanan, T. K., Satter, M. (2002). Brain Imaging of 18F-Fallypride in Normal Volunteers: Blood Analysis, Distribution, Test-Retest Sudies and Preliminary Assessment of Sensitivity to Aging Effects on Dopamine D-2/D-3 Receptors. *Synapse, 46*, 170-188.

Mukherjee, J., Christian, B. T., Narayanan, T. K., Shi, B., & Collins, D. (2005). Measurement of d-amphetamine-induced effects on the binding of dopamine D-2/D-3 receptor radioligand, 18F-fallypride in extrastriatal brain regions in non-human primates using PET. *Brain Research, 1032*(1-2), 77.

Mulder, M. J., Baeyens, D., Davidson, M. C., Casey, B. J., van den Ban, E., van Engeland, H. (2008). Familial vulnerability to ADHD affects activity in the cerebellum in addition to the prefrontal systems. *Journal of te American Academy of Child and Adolescent Psychiatry, 47*(1), 68-75.

Munakata, Y., Herd, S. A., Chatham, C. H., Depue, B. E., Banich, M. T., & O'Reilly, R. C. (2011). A unified framework for inhibitory control. *Trends in Cognitive Sciences, 15*(10), 453-459.

Munoz, D. P., Armstrong, I. T., Hampton, K. A., & Moore, K. D. (2003). Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. *Journal of Neurophysiology, 90*(1), 503-514.

Munoz, D. P., & Everling, S. (2004). Look away: the anti-saccade task and the voluntary control of eye movement. *Nature Reviews Neuroscience, 5*(3), 218-228.

Munro, C. A., McCaul, M. E., Wong, D. F., Oswald, L. M., Zhou, Y., Brasic, J. (2006). Sex differences in striatal dopamine release in healthy adults. *Biological Psychiatry, 59*(10), 966-974.

Murase, S., Grenhoff, J., Chouvet, G., Gonon, F. G., & Svensson, T. H. (1993). Prefrontal cortex regulates burst firing and transmitter release in rat mesolimbic dopamine neurons studied in vivo. *Neuroscience Letters, 157*(1), 53-56.

Murphy, K. J., & Barkley, R. A. (1996). Prevalence of DSM-IV symptoms of ADHD in adult licensed drivers: Implications for clinical diagnosis *Journal of Attention Disorders, 1*(3), 147-161.

Murphy, K. R., Barkley, R. A., & Bush, T. (2002). Young adults with attention deficit hyperactivity disorder: subtype differences in comorbidity, educational, and clinical history. *Journal of Nervous and Mental Disease, 190*(3), 147-157.

Myers, M. M., Musty, R. E., & Hendley, E. D. (1982). Attenuation of hyperactivity in the spontaneously hypertensive rat by amphetamine. *Behavioral and Neural Biology, 34*(1), 42-54.

Narendran, R., Frankle, W. G., Mason, N. S., Rabiner, E. A., Gunn, R. N., Searle, G. E. (2009). Positron emission tomography imaging of amphetamine-induced dopamine release in the human cortex: A comparative evaluation of the high affinity dopamine D2/3 radiotracers [11C]FLB 457 and [11C]fallypride. *Synapse, 63*(6), 447-461.

Narendran, R., Mason, N. S., Laymon, C. M., Lopresti, B. J., Velasquez, N. D., May, M. A. (2010). A comparative evaluation of the dopamine D(2/3) agonist radiotracer [11C](-)-N-propyl-norapomorphine and antagonist [11C]raclopride to measure amphetamine-induced dopamine release in the human striatum. *Journal of Pharmacology and Experimental Therapeutics 333*(2), 533-539.

Narr, K. L., Woods, R. P., Thompson, P. M., Szeszko, P., Robinson, D., Dimtcheva, T. (2007). Relationships between IQ and regional cortical gray matter thickness in healthy adults. *Cerebral Cortex, 17*(9), 2163-2171.

Neef, N. A., Bicard, D. F., & Endo, S. (2001). Assessment of impulsivity and the development of self-control in students with attention deficit hyperactivity disorder. *Journal of Applied Behavioural Analysis, 34*(4), 397-408.

Newman, J. P. (1987). Reaction to punishment in extraverts and psychopaths: Implications for the impulsive behavior of disinhibited individuals. *Journal of Research in Personality, 21*(4), 464-480.

Newman, J. P., & Kosson, D. S. (1986). Passive avoidance learning in psychopathic and nonpsychopathic offenders. *J Abnorm Psychol, 95*(3), 252-256.

Newman, J. P., Patterson, C. M., Howland, E. W., & Nichols, S. L. (1990). Passive avoidance in psychopaths: The effects of reward. *Personality and Individual Differences, 11*(11), 1101-1114.

Newman, J. P., Widom, C. S., & Nathan, S. (1985). Passive avoidance in syndromes of disinhibition: Psychopathy and extraversion. *Journal of Personality and Social Psychology, 48*(5), 1316-1327.

Nieoullon, A., Cheramy, A., & Glowinski, J. (1978). Release of dopamine evoked by electrical stimulation of the motor and visual areas of the cerebral cortex in both caudate nuclei and in the substantia nigra in the cat. *Brain Research, 145*(1), 69-83.

Nigg, J. T. (2001). Is ADHD a disinhibitory disorder? *Psychological Bulletin, 127*(5), 571-598.

Nigg, J. T. (2005). Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: the sate of the field and salient challenges for the coming decade. *Biological Psychiatry, 57*(11), 1424.

Nigg, J. T. (2006). Temperament and developmental psychopathology. *Journal of Child Psychology and Psychiatry, 47*(3-4), 395-422.

Nigg, J. T., Butler, K. M., Huang-Pollock, C. L., & Henderson, J. M. (2002a). Inhibitory processes in adults with persistent childhood onset ADHD. *Journal of Consulting and Clinical Psychology, 70*(1), 153-157.

Nigg, J. T., John, O. P., Blaskey, L. G., Huang-Pollock, C. L., Willicut, E. G., Hinshaw, S. P. (2002b). Big Five dimensions and ADHD symptoms: Links between personality traits and clinical symptoms. *Journal of Personality and Social Psychology, 83*(2), 451-469.

O'Driscoll, G. A., Depatie, L., Holahan, A. L., Savion-Lemieux, T., Barr, R. G., Jolicoer, C. (2005). Executive functions and methylphenidate response in subtypes of Attention Deficit/Hyperactivity Disorder. *Biological Psychiatry, 57*, 1452-1460.

Ohnishi, T., Hayashi, T., Okabe, S., Nonaka, I., Matsuda, H., Iida, H. (2004). Endogenous dopamine release induced by repetitive transcranial magnetic stimulation over the primary motor cortex: an [11C]raclopride positron emission tomography study in anesthetized macaque monkeys. *Biological Psychiatry, 55*(5), 484-489.

Okuyama, Y., Ishiguro, H., Nankai, M., Shibuya, H., Watanabe, A., & Arinami, T. (2000). Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. *Molecular Psychiatry, 5*(1), 64-69.

Oswald, L. M., Wong, D. F., McCaul, M., Zhou, Y., Kuwabara, H., Choi, L. (2005). Relationships among ventral striatal dopamine release, cortisol secretion, and subjective responses to amphetamine. *Neuropsychopharmacology, 30*(4), 821-832.

Overmeyer, S., Bullmore, E. T., Suckling, J., Simmons, A., Williams, S. C., Santosh, P. J. (2001). Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. *Psychological Medicine, 31*, 1425 - 1435.

Paladini, C. A., Fiorillo, C. D., Morikawa, H., & Williams, J. T. (2001). Amphetamine selectively blocks inhibitory glutamate transmission in dopamine neurons. *Nature Neuroscience, 4*(3), 275-281.

Papa, M., Sellitti, S., & Sadile, A. G. (2000). Remodeling of neural networks in the anterior forebrain of an animal model of hyperactivity and attention deficits as monitored by molecular imaging probes. *Neuroscience & Biobehavioral Reviews, 24*(1), 149-156.

Pasqualini, C., Olivier, V., Guibert, B., Frain, O., & Leviel, V. (1995). Acute stimulatory effect of estradiol on striatal dopamine synthesis. *Journal of Neurochemistry, 65*(4), 1651-1657.

Patterson, C. M., Kosson, D. S., & Newman, J. P. (1987). Reaction to punishment, reflectivity, and passive avoidance learning in extraverts. *Journal of Persnality and Socical Psychology, 52*(3), 565-575.

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology, 51*(6), 768-774.

Pennington, B. F., & Ozonoff, S. (1996). Executive functions and developmental psychopathology. *Journal of Child Psychology and Psychiatry, 37*(1), 51-87.

Perchet, C., Revol, O., Fourneret, P., Mauguiere, F., & Garcia-Larrea, L. (2001). Attention shifts and anticipatory mechanisms in hyperactive children: an ERP study using the Posner paradigm. *Biological Psychiatry, 50*, 44 - 57.

Perlov, E., Philipsen, A., Matthies, S., Drieling, T., Maier, S., Bubl, E. (2009). Spectroscopic findings in attention-deficit/hyperactivity disorder: review and meta-analysis. *World Journal of Biological Psychiatry, 10*(4 Pt 2), 355-365.

Petrides, M., & Milner, B. (1982). Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia, 20*(3), 249-262.

Philipsen, A., Feige, B., Hesslinger, B., Ebert, D., Carl, C., Hornyak, M. (2005). Sleep in adults with attention-deficit/hyperactivity disorder: a controlled polysomnographic study including spectral analysis of the sleep EEG. *Sleep, 28*(7), 877-884.

Phillips, A. G., Pfaus, J. G., & Blaha, C. D. (1991). Dopamine and motivated behavior: insights provided by in vivo analyses. In P. Willner & J. Scheel-Krüger (Eds.), *The Mesolimbic Dopamine System: From Motivation to Action* (pp. 199-224). Chichester: Wiley & Sons Ltd.

Piazza, P. V., Deminiere, J. M., Le Moal, M., & Simon, H. (1989). Factors that predict individual vulnerability to amphetamine self-administration. *Science, 245*(4925), 1511-1513.

Pierce, R. C., Crawford, C. A., Nonneman, A. J., Mattingly, B. A., & Bardo, M. T. (1990). Effect of forebrain dopamine depletion on novelty-induced place preference behavior in rats. *Pharmacology, Biochemistry, and Behavior, 36*(2), 321-325.

Pilgrim, B. M., Meyers, J. E., Bayless, J., & Whetstone, M. M. (1999). Validity of the Ward seven-subtest WAIS-III short form in a neuropsychological population. *Applied Neuropsychology, 6*(4), 243-246.

Pliszka, S. R., Glahn, D. C., Semrud-Clikeman, M., Franklin, C., Perez Iii, R., Xiong, J. (2006). Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. *American Journal of Psychiatry, 163*(6), 1052-1060.

Pliszka, S. R., Liotti, M., & Woldorff, M. G. (2000). Inhibitory control in children with attention-deficit/hyperactivity disorder: event-related potentials identify the processing component and timing of an impaired right-frontal response-inhibition mechanism. *Biological Psychiatry, 48*(3), 238-246.

Polli, F. E., Barton, J. J. S., Cain, M. S., Thakkar, K. N., Rauch, S. L., & Manoach, D. S. (2005). Rostral and dorsal anterior cingulate cortex make dissociable contributions during antisaccade error commission. *Proceedings of the National Academy of Sciences of the United States of America, 102*(43), 15700-15705.

Porrino, L. J., Rapoport, J. L., Behar, D., Sceery, W., Ismond, D. R., & Bunney, W. E., Jr. (1983). A naturalistic assessment of the motor activity of hyperactive boys. I. Comparison with normal controls. *Archives of General Psychiatry, 40*(6), 681-687.

Prehn-Kristensen, A., Krauel, K., Hinrichs, H., Fischer, J., Malecki, U., Schuetze, H. (2011). Methylphenidate does not improve interference control during a working memory task in young patients with attention-deficit hyperactivity disorder. *Brain Research, 1388*, 56-68.

Prensa, L. a., & Parent, A. (2001). The nigrostriatal pathway in the rat: A single-axon study of the relationship between dorsal and ventral tier nigral neurons and the striosome/matrix striatal compartments. *The Journal of Neuroscience, 21*(18), 7247-7260.

Prou, D., Gu, W. J., Le Crom, S., Vincent, J. D., Salamero, J., & Vernier, P. (2001). Intracellular retention of the two isoforms of the D(2) dopamine receptor promotes endoplasmic reticulum disruption. *Journal of Cell Science, 114*(Pt 19), 3517-3527.

Pruessner, J. C., Champagne, F., Meaney, M. J., & Dagher, A. (2004). Dopamine release in response to a psychological stress in humans and its relationship to early life maternal care: a positron emission tomography study using [11C]raclopride. *Journal of Neuroscience, 24*(11), 2825-2831.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology, 28*(7), 916-931.

Pycock, C. J., Kerwin, R. W., & Carter, C. J. (1980). Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. *Nature, 286*(5768), 74-76.

Raber, J., Mehta, P. P., Kreifeldt, M., Parsons, L. H., Weiss, F., Bloom, F. E. (1997). Coloboma hyperactive mutant mice exhibit regional and transmitter-specific deficits in neurotransmission. *Journal of Neurochemistry, 68*(1), 176-186.

Ranseen, J. D., Campbell, D. A., & Baer, R. A. (1998). NEO PI-R profiles of adults with attention deficit disorder. *Assessment, 5*(1), 19-24.

Rapoport, J., Buchsbaum, M., Zahn, T., Weingartner, H., Ludlow, C., & Mikkelsen, E. (1978). Dextroamphetamine: cognitive and behavioral effects in normal prepubertal boys. *Science, 199*(4328), 560-563.

Rasmussen, J. L. (1987). Estimating correlation coefficients: Bootstrap and parametric approaches. *Psychological Bulletin, 101*(1), 136-139.

Raz, N., Gunning-Dixon, F. M., Head, D., Dupuis, J. H., & Acker, J. D. (1998). Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging. *Neuropsychology, 12*(1), 95-114.

Raz, N., Lindenberger, U., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Acker, J. D. (2008). Neuroanatomical correlates of fluid intelligence in healthy adults and persons with vascular risk factors. *Cerebral Cortex, 18*(3), 718-726.

Reichenbach, L. C., Halperin, J. M., Sharma, V., & Newcorn, J. H. (1992). Children's motor activity: Reliability and relationship to attention and behavior. *Developmental Neuropsychology, 8*(1), 87-97.

Reimherr, F. W., Wender, P. H., Ebert, M. H., & Wood, D. R. (1984). Cerebrospinal fluid homovanillic acid and 5-hydroxy-indoleacetic acid in adults with attention deficit disorder, residual type. *Psychiatry Research, 11*(1), 71-78.

Reitan, R. M. (1958). The validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motror Skills, 8*, 271-276.

Retz, W., Thome, J., Blocher, D., Baader, M., & Rösler, M. (2002). Association of attention deficit hyperactivity disorder-related psychopathology and personality

traits with the serotonin transporter promoter region polymorphism. *Neuroscience Letters, 319*(3), 133-136.
Reynolds, C. R., Willson, V. L., & Clark, P. L. (1983). A four-test short-form of the WAIS-R for clinical screening. *Clinical Neuropsychology, 5*, 111-116.
Riccardi, P., Baldwin, R., Salomon, R., Anderson, S., Ansari, M. S., Li, R. (2008). Estimation of baseline dopamine D2 receptor occupancy in striatum and extrastriatal regions in humans with positron emission tomography with [18F] fallypride. *Biological Psychiatry, 63*(2), 241.
Riccardi, P., Li, R., Ansari, M. S., Zald, D., Park, S., Dawant, B. (2006a). Amphetamine-induced displacement of [18F] fallypride in striatum and extrastriatal regions in humans. *Neuropsychopharmacology, 31*(5), 1016-1026.
Riccardi, P., Park, S., Anderson, S., Doop, M., Ansari, M. S., Schmidt, D. (2011). Sex differences in the relationship of regional dopamine release to affect and cognitive function in striatal and extrastriatal regions using positron emission tomography and [18F]fallypride. *Synapse, 65*(2), 99-102.
Riccardi, P., Zald, D., Li, R., Park, S., Ansari, M. S., Dawant, B. (2006b). Sex differences in amphetamine-induced displacement of [18F]fallypride in striatal and extrastriatal regions: A PET study. *American Journal of Psychiatry, 163*(9), 1639-1641.
Ricci, A., Vega, J. A., Mammola, C. L., & Amenta, F. (1995). Localisation of dopamine D3 receptor in the rat cerebellar cortex: a light microscope autoradiographic study. *Neuroscience Letters, 190*(3), 163-166.
Richfield, E. K., Penney, J. B., & Young, A. B. (1989). Anatomical and affinity state comparisons between dopamine D1 and D2 receptors in the rat central nervous system. *Neuroscience, 30*(3), 767-777.
Rinne, J. O., Lönnberg, P., & Marjamäki, P. (1990). Age-dependent decline in human brain dopamine D1 and D2 receptors. *Brain Research, 508*(2), 349-352.
Riordan, H., Flashman, L., Saykin, A., Frutiger, S., Carrol, K., & Huey, L. (1999). Neuropsychological correlates of methylphenidate treatment in adult ADHD with and without depresson. *Archives of Clinical Neuropsychology, 14*, 217 - 233.
Robbins, T. W. (2000). Chemical neuromodulation of frontal-executive functions in humans and other animals. *Experimental Brain Research, 133*(1), 130-138.
Robbins, T. W., & Arnsten, A. F. T. (2009). The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. *Annual Review of Neuroscience, 32*(1), 267-287.
Robbins, T. W., & Sahakian, B. J. (1979). "Paradoxical" effects of psychomotor stimulant drugs in hyperactive children from the standpoint of behavioural pharmacology. *Neuropharmacology, 18*(12), 931-950.
Robinson, T. E., & Camp, D. M. (1990). Does amphetamine preferentially increase the extracellular concentration of dopamine in the mesolimbic system of freely moving rats? *Neuropsychopharmacology, 3*(3), 163-173.
Roeltgen, D. P., & Schneider, J. S. (1991). Chronic low-dose MPTP in nonhuman primates: a possible model for attention deficit disorder. *Journal of Child Neurology, 6 Suppl*, S82-89.

Roeltgen, D. P., & Schneider, J. S. (1994). Task persistence and learning ability in normal and chronic low dose MPTP-treated monkeys. *Behavioural Brain Research, 60*(2), 115-124.

Ronnlund, M., Lovden, M., & Nilsson, L. G. (2008). Cross-sectional versus longitudinal age gradients of tower of Hanoi performance: the role of practice effects and cohort differences in education. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology, and Cognition, 15*(1), 40-67.

Rosa-Neto, P., Lou, H. C., Cumming, P., Pryds, O., Karrebaek, H., Lunding, J. (2005). Methylphenidate-evoked changes in striatal dopamine correlate with inattention and impulsivity in adolescents with attention deficit hyperactivity disorder. *NeuroImage, 25*(3), 868.

Rosen, V. M., & Engle, R. W. (1997). The role of working memory capacity in retrieval. *Journal of Experimental Psychology: General, 126*(3), 211-227.

Rousset, O. G., Ma, Y., & Evans, A. C. (1998). Correction for partial volume effects in PET: principle and validation. *Journal of Nuclear Medicine, 39*(5), 904-911.

Rubia, K., Halari, R., Cubillo, A., Smith, A. B., Mohammad, A. M., Brammer, M. (2011a). Methylphenidate normalizes fronto-striatal underactivation during interference inhibition in medication-naive boys with attention-deficit hyperactivity disorder. *Neuropsychopharmacology, 36*(8), 1575-1586.

Rubia, K., Halari, R., Mohammad, A. M., Taylor, E., & Brammer, M. (2011b). Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 70*(3), 255-262.

Rubia, K., Halari, R., Smith, A. B., Mohammed, M., Scott, S., Giampietro, V. (2008). Dissociated Functional Brain Abnormalities of Inhibition in Boys With Pure Conduct Disorder and in Boys With Pure Attention Deficit Hyperactivity Disorder. *Am J Psychiatry, 165*(7), 889-897.

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S., Simmons, A. (1999). Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. *American Journal of Psychiatry, 156*, 891 - 896.

Rubia, K., Smith, A. B., Brammer, M. J., Toone, B., & Taylor, E. (2005). Abnormal Brain Activation During Inhibition and Error Detection in Medication-Naive Adolescents With ADHD. *Am J Psychiatry, 162*(6), 1067-1075.

Russell, V., de Villiers, A., Sagvolden, T., Lamm, M., & Taljaard, J. (1998). Differences between electrically-, ritalin- and -amphetamine-stimulated release of [3H]dopamine from brain slices suggest impaired vesicular storage of dopamine in an animal model of Attention-Deficit Hyperactivity Disorder. [*Behavioural Brain Research, 94*(1), 163-171.

Russell, V. A. (2011). Overview of animal models of attention deficit hyperactivity disorder (ADHD). *Current Protocols in Neuroscience, Chapter 9*, Unit9 35.

Russell, V. A., Sagvolden, T., & Johansen, E. B. (2005). Animal models of attention-deficit hyperactivity disorder. *Behavioral and Brain Functions, 1*, 9.

Sagvolden, T. (2000). Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). *Neuroscience and Biobehavioral Reviews, 24*, 31 - 39.

Sagvolden, T., Hendley, E. D., & Knardahl, S. (1992a). Behavior of hypertensive and hyperactive rat strains: Hyperactivity is not unitarily determined. *Physiology & Behavior, 52*(1), 49-57.

Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences, 28*(3), 397-419.

Sagvolden, T., Metzger, M. A., Schiorbeck, H. K., Rugland, A.-L., Spinnangr, I., & Sagvolden, G. (1992b). The spontaneously hypertensive rat (SHR) as an animal model of childhood hyperactivity (ADHD): changed reactivity to reinforcers and to psychomotor stimulants. *Behavioral and Neural Biology, 58*(2), 103-112.

Sagvolden, T., & Sergeant, J. A. (1998). Attention deficit/hyperactivity disorder--from brain dysfunctions to behaviour. *Behavioural Brain Research, 94*(1), 1-10.

Salat, D. H., Kaye, J. A., & Janowsky, J. S. (2002). Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults. *Cerebral Cortex, 12*(5), 494-505.

Sara, S. J., & Deweer, B. (1982). Memory retrieval enhanced by amphetamine after a long retention interval. *Behavioral and Neural Biology, 36*(2), 146-160.

Sara, S. J., & Segal, M. (1991). Plasticity of sensory responses of locus coeruleus neurons in the behaving rat: implications for cognition. *Progress in Brain Research, 88*, 571-585.

Saunders, C., Ferrer, J. V., Shi, L., Chen, J., Merrill, G., Lamb, M. E. (2000). Amphetamine-induced loss of human dopamine transporter activity: an internalization-dependent and cocaine-sensitive mechanism. *Proceedings of the National Academy of Sciences, 97*(12), 6850-6855.

Sawaguchi, T., & Goldman-Rakic, P. S. (1991). D1 dopamine receptors in prefrontal cortex: involvement in working memory. *Science, 251*(4996), 947-950.

Scheres, A., Milham, M. P., Knutson, B., & Castellanos, F. X. (2007). Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. *Biological Psychiatry, 61*(5), 720-724.

Scheres, A., Oosterlaan, J., Geurts, H., Morein-Zamir, S., Meiran, N., Schut, H. (2004). Executive functioning in boys with ADHD: primarily an inhibition deficit? *Archives of Clinical Neuropsychology, 19*(4), 569-594.

Schiffer, W. K., Volkow, N. D., Fowler, J. S., Alexoff, D. L., Logan, J., & Dewey, S. L. (2006). Therapeutic doses of amphetamine or methylphenidate differentially increase synaptic and extracellular dopamine. *Synapse, 59*(4), 243-251.

Schinka, J., Letsch, E., & Crawford, F. (2002). DRD4 and novelty seeking: Results of meta-analyses. *American Journal of Medical Genetics, 114*(6), 643-648.

Schlaepfer, T., Pearlson, G., Wong, D., Marenco, S., & Dannals, R. (1997). PET study of competition between intravenous cocaine and [11C]raclopride at dopamine receptors in human subjects. *American Journal of Psychiatry, 154*(9), 1209-1213.

Schneier, F. R., Abi-Dargham, A., Martinez, D., Slifstein, M., Hwang, D. R., Liebowitz, M. R. (2009). Dopamine transporters, D2 receptors, and dopamine release in generalized social anxiety disorder. *Depression and Anxiety, 26*(5), 411-418.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science, 275*(5306), 1593-1599.

Schwartz, S., Baldo, J., Graves, R. E., & Brugger, P. (2003). Pervasive influence of semantics in letter and category fluency: A multidimensional approach. *Brain and Language, 87*(3), 400-411.

Schweitzer, J. B., & Sulzer-Azaroff, B. (1995). Self-control in boys with attention deficit hyperactivity disorder: effects of added stimulation and time. *Journal of Child Psychology and Psychiatry, 36*(4), 671-686.

Seamans, J. K., & Yang, C. R. (2004). The principal features and mechanisms of dopamine modulation in the prefrontal cortex. *Progress in Neurobiology, 74*(1), 1-58.

Seeger, G., Schloss, P., & Schmidt, M. H. (2001). Functional polymorphism within the promotor of the serotonin transporter gene is associated with severe hyperkinetic disorders. *Molecular Psychiatry, 6*(2), 235-238.

Seeman, P., & Grigoriadis, D. (1987). Dopamine receptors in brain and periphery. *Neurochem Int, 10*(1), 1-25.

Seeman, P., Guan, H. C., & Niznik, H. B. (1989). Endogenous dopamine lowers the dopamine D2 receptor density as measured by [3H]raclopride: implications for positron emission tomography of the human brain. *Synapse, 3*(1), 96-97.

Seeman, P., & Madras, B. (2002). Methylphenidate elevates resting dopamine which lowers the impulse-triggered release of dopamine: a hypothesis. *Behavioural Brain Research, 130*(1-2), 79-83.

Seidman, L. J. (2006). Neuropsychological functioning in people with ADHD across the lifespan. *Clinical Psychology Review, 26*(4), 466-485.

Seidman, L. J., Valera, E. M., & Makris, N. (2005). Structural brain imaging of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1263-1272.

Semrud-Clikeman, M., Filipek, P. A., Biederman, J., Steingard, R., Kennedy, D., Renshaw, P. (1994). Attention-deficit hyperactivity disorder: magnetic resonance imaging morphometric analysis of the corpus callosum. *Journal of the American Academy of Child & Adolescent Psychiatry, 33*(6), 875-881.

Semrud-Clikeman, M., Steingard, R. J., Filipek, P., Biederman, J., Bekken, K., & Renshaw, P. F. (2000). Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. *Jounal of the American Academy of Child & Adolescent Psychiatry, 39*(4), 477-484.

Sergeant, J. A. (2005). Modeling attention-deficit/hyperactivity disorder: A critical appraisal of the cognitive-energetic model. *Biological Psychiatry, 57*(11), 1248-1255.

Sergeant, J. A., Oosterlaan, J., & Van der Meere, J. J. (1999). Information processing and energetic factors in attention-deficit/hyperactivity disorder. In H. C. Quay & A. Hogan (Eds.), *Handbook of Disruptive Behaviour Disorders* (pp. 75-104). New York: Plenum Press.

Sesack, S. R., & Carr, D. B. (2002). Selective prefrontal cortex inputs to dopamine cells: implications for schizophrenia. *Physiology & Behavior, 77*(4-5), 513-517.

Sesack, S. R., & Grace, A. A. (2010). Cortico-Basal Ganglia reward network: microcircuitry. *Neuropsychopharmacology, 35*(1), 27-47.

Sesack, S. R., Hawrylak, V. A., Matus, C., Guido, M. A., & Levey, A. I. (1998). Dopamine axon varicosities in the prelimbic division of the rat prefrontal cortex

exhibit sparse immunoreactivity for the dopamine transporter. *The Journal of Neuroscience, 18*(7), 2697-2708.
Sesack, S. R., & Pickel, V. M. (1992). Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. *Journal of Comparative Neurology, 320*(2), 145-160.
Shafer, R. A., & Levant, B. (1998). The D3 dopamine receptor in cellular and organismal function. *Psychopharmacology, 135*(1), 1-16.
Shafritz, K. M., Marchione, K. E., Gore, J. C., Shaywitz, S. E., & Shaywitz, B. A. (2004). The Effects of Methylphenidate on Neural Systems of Attention in Attention Deficit Hyperactivity Disorder. *Am J Psychiatry, 161*(11), 1990-1997.
Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 298*(1089), 199-209.
Sharp, T., Zetterström, T., Ljungberg, T., & Ungerstedt, U. (1987). A direct comparison of amphetamine-induced behaviours and regional brain dopamine release in the rat using intracerebral dialysis. *Brain Research, 401*(2), 322-330.
Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D. (2007a). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*(49), 19649-19654.
Shaw, P., Gilliam, M., Liverpool, M., Weddle, C., Malek, M., Sharp, W. (2011). Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention deficit hyperactivity disorder. *American Journal of Psychiatry, 168*(2), 143-151.
Shaw, P., Gornick, M., Lerch, J., Addington, A., Seal, J., Greenstein, D. (2007b). Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry, 64*(8), 921-931.
Shaw, P., Greenstein, D., Lerch, J., Clasen, L., Lenroot, R., Gogtay, N. (2006a). Intellectual ability and cortical development in children and adolescents. [10.1038/nature04513]. *Nature, 440*(7084), 676-679.
Shaw, P., Kabani, N. J., Lerch, J. P., Eckstrand, K., Lenroot, R., Gogtay, N. (2008). Neurodevelopmental trajectories of the human cerebral cortex. *Journal of Neuroscience, 28*(14), 3586-3594.
Shaw, P., Lerch, J., Greenstein, D., Sharp, W., Clasen, L., Evans, A. (2006b). Longitudinal mapping of cortical thickness and clinical outcome in children and adolescents with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry, 63*(5), 540-549.
Shaywitz, B. A., Cohen, D. J., & Bowers, M. B., Jr. (1977). CSF monoamine metabolites in children with minimal brain dysfunction: evidence for alteration of brain dopamine. A preliminary report. *Journal of Pediatrics, 90*(1), 67-71.
Shaywitz, B. A., Klopper, J. H., Yager, R. D., & Gordon, J. W. (1976a). Paradoxical response to amphetamine in developing rats treated with 6-hydroxydopamine. *Nature, 261*(5556), 153-155.

Shaywitz, B. A., Yager, R. D., & Klopper, J. H. (1976b). Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. *Science, 191*(4224), 305-308.
Shea, T., & Fisher, B. E. (1996). Self ratings of mood levels and mood variability as predictors of Junior I-6 impulsivity and ADHD classroom behaviors. *Personality and Individual Differences, 20*(2), 209-214.
Shetty, T., & Chase, T. N. (1976). Central monoamines and hyperkinase of childhood. *Neurology, 26*(10), 1000-1002.
Shi, W. X., Pun, C. L., Smith, P. L., & Bunney, B. S. (2000). Endogenous DA-mediated feedback inhibition of DA neurons: involvement of both D(1)- and D(2)-like receptors. *Synapse, 35*(2), 111-119.
Sibley, D. R., De Lean, A., & Creese, I. (1982). Anterior pituitary dopamine receptors. Demonstration of interconvertible high and low affinity states of the D-2 dopamine receptor. *Journal of Biological Chemistry, 257*(11), 6351-6361.
Sieg, K. G., Gaffney, G. R., Preston, D. F., & Hellings, J. A. (1995). SPECT brain imaging abnormalities in attention deficit hyperactivity disorder. *Clinical Nuclear Medicine, 20*(1), 55-60.
Siesser, W. B., Zhao, J., Miller, L. R., Cheng, S. Y., & McDonald, M. P. (2006). Transgenic mice expressing a human mutant β1 thyroid receptor are hyperactive, impulsive, and inattentive. *Genes, Brain and Behavior, 5*(3), 282-297.
Skirboll, L., Grace, A., & Bunney, B. (1979). Dopamine auto- and postsynaptic receptors: electrophysiological evidence for differential sensitivity to dopamine agonists. *Science, 206*(4414), 80-82.
Sled, J. G., Zijdenbos, A. P., & Evans, A. C. (1998). A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Transactions of Medical Imaging, 17*(1), 87-97.
Slifstein, M., Kegeles, L. S., Xu, X., Thompson, J. L., Urban, N., Castrillon, J. (2010). Striatal and extrastriatal dopamine release measured with PET and [18F] fallypride. *Synapse, 64*(5), 350-362.
Slifstein, M., Narendran, R., Hwang, D. R., Sudo, Y., Talbot, P., Huang, Y. (2004). Effect of amphetamine on [18F] fallypride in vivo binding to D2 receptors in striatal and extrastriatal regions of the primate brain: Single bolus and bolus plus constant infusion studies. *Synapse, 54*, 46-63.
Small, D. M., Jones-Gotman, M., & Dagher, A. (2003). Feeding-induced dopamine release in dorsal striatum correlates with meal pleasantness ratings in healthy human volunteers. *Neuroimage, 19*(4), 1709-1715.
Smith, A. B., Taylor, E., Brammer, M., Toone, B., & Rubia, K. (2006). Task-specific hypoactivation in prefrontal and temporoparietal brain regions during motor Inhibition and task switching in medication-naive children and adolescents with attention deficit hyperactivity disorder. *American Journal of Psychiatry, 163*(6), 1044-1051.
Smith, M. E., & Farah, M. J. (2011). Are prescription stimulants "smart pills"? The epidemiology and cognitive neuroscience of prescription stimulant use by normal healthy individuals. *Psychological Bulletin, 137*(5), 717-741.
Smith, T. F. (2010). Meta-analysis of the heterogeneity in association of DRD4 7-repeat allele and AD/HD: stronger association with AD/HD combined type. *American*

Journal of Medical Genetenetics, B Neuropsychiatric Genetics, 153B(6), 1189-1199.
Smith, Y., Lavoie, B., Dumas, J., & Parent, A. (1989). Evidence for a distinct nigropallidal dopaminergic projection in the squirrel monkey. *Brain Research, 482*(2), 381-386.
Smoller, J. W., Biederman, J., Arbeitman, L., Doyle, A. E., Fagerness, J., Perlis, R. H. (2006). Association between the 5HT1B receptor gene (HTR1B) and the inattentive subtype of ADHD. *Biological Psychiatry, 59*(5), 460-467.
Sobanski, E. (2006). Psychiatric comorbidity in adults with attention-deficit/hyperactivity disorder (ADHD). *European Archives of Psychiatry and Clinical Neuroscience, 256*, i26-i31.
Sofuoglu, M., Dudish-Poulsen, S., Nelson, D., Pentel, P. R., & Hatsukami, D. K. (1999). Sex and menstrual cycle differences in the subjective effects from smoked cocaine in humans. *Experimental and Clinical Psychopharmacology, 7*(3), 274-283.
Solanto, M. V. (1998). Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. *Behavioural Brain Research, 94*(1), 127-152.
Sontag, T. A., Tucha, O., Walitza, S., & Lange, K. W. (2010). Animal models of attention deficit/hyperactivity disorder (ADHD): a critical review. *Attention Deficit Hyperactivity Disorder: from genes to animal models to patients 2*(1), 1-20.
Sonuga-Barke, E. J. (2002). Psychological heterogeneity in AD/HD--a dual pathway model of behaviour and cognition. *Behavioural Brain Research, 130*(1-2), 29-36.
Sonuga-Barke, E. J. (2005). Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biological Psychiatry, 57*, 1231 - 1238.
Sonuga-Barke, E. J., Williams, E., Hall, M., & Saxton, T. (1996). Hyperactivity and delay aversion. III: The effect on cognitive style of imposing delay after errors. *Journal of Child Psychology and Psychiatry, 37*(2), 189-194.
Sowell, E. R., Peterson, B. S., Thompson, P. M., Welcome, S. E., Henkenius, A. L., & Toga, A. W. (2003a). Mapping cortical change across the human life span. *Nature Neuroscience, 6*(3), 309-315.
Sowell, E. R., Thompson, P. M., Leonard, C. M., Welcome, S. E., Kan, E., & Toga, A. W. (2004). Longitudinal mapping of cortical thickness and brain growth in normal children. *Journal of Neuroscience, 24*(38), 8223-8231.
Sowell, E. R., Thompson, P. M., Welcome, S. E., Henkenius, A. L., Toga, A. W., & Peterson, B. S. (2003b). Cortical abnormalities in children and adolescents with attention deficit hyperactivity disorder (ADHD). *The Lancet, 362*, 1699-1707.
Spencer, T., Biederman, J., Wilens, T., Harding, M., O'Donnell, D., & Griffin, S. (1996). Pharmacotherapy of attention-deficit hyperactivity disorder across the life cycle. *Journal of the American Academy of Child and Adolescent Psychiatry, 35*(4), 409-432.
Spencer, T. J., Biederman, J., Madras, B. K., Faraone, S. V., Dougherty, D. D., Bonab, A. A. (2005). In vivo neuroreceptor Imaging in attention-deficit/hyperactivity

disorder: A focus on the dopamine transporter. *Biological Psychiatry, 57*, 1293 - 1300.
Sprich, S., Biederman, J., Crawford, M. H., Mundy, E., & Faraone, S. V. (2000). Adoptive and biological families of children and adolescents with ADHD. *Journal of the American Academy of Child & Adolescent Psychiatry, 39*(11), 1432-1437.
Stachowiak, M. K., Bruno, J. P., Snyder, A. M., Stricker, E. M., & Zigmond, M. J. (1984). Apparent sprouting of striatal serotonergic terminals after dopamine-depleting brain lesions in neonatal rats. *Brain Research, 291*(1), 164-167.
Stein, M. A., Waldman, I. D., Sarampote, C. S., Seymour, K. E., Robb, A. S., Conlon, C. (2005). Dopamine transporter genotype and methylphenidate dose response in children with ADHD. *Neuropsychopharmacology, 30*(7), 1374-1382.
Stewart, J. (1983). Conditioned and unconditioned drug effects in relapse to opiate and stimulant drug self-adminstration. *Progress in Neuropsychopharmacology and Biological Psychiatry, 7*(4-6), 591-597.
Stewart, J., de Wit, H., & Eikelboom, R. (1984). Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychological Review, 91*(2), 251-268.
Strafella, A. P., Paus, T., Barrett, J., & Dagher, A. (2001). Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *Journal of Neuroscience, 21*(15), RC157.
Strafella, A. P., Paus, T., Fraraccio, M., & Dagher, A. (2003). Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain, 126*(Pt 12), 2609-2615.
Strick, P. L. (1976). Anatomical analysis of ventrolateral thalamic input to primate motor cortex. *Journal of Neurophysiology, 39*(5), 1020-1031.
Strobel, A., Wehr, A., Michel, A., & Brocke, B. (1999). Association between the dopamine D4 receptor (DRD4) exon III polymorphism and measures of Novelty Seeking in a German population. *Molecular Psychiatry, 4*(4), 378-384.
Ströhle, A., Stoy, M., Wrase, J., Schwarzer, S., Schlagenhauf, F., Huss, M. (2008). Reward anticipation and outcomes in adult males with attention-deficit/hyperactivity disorder. *NeuroImage, 39*(3), 966-972.
Stromberg, U., & Svensson, T. H. (1975). Differences between (+)- and (-)-amphetamine in effects on locomotor activity and L-dopa potentiating action in mice. *Naunyn-Schmiedebergs Archives of Pharmacology (Berlin), 287*(2), 171-179.
Sulzer, D., & Rayport, S. (1990). Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. *Neuron, 5*(6), 797-808.
Sulzer, D., Sonders, M. S., Poulsen, N. W., & Galli, A. (2005). Mechanisms of neurotransmitter release by amphetamines: A review. *Progress in Neurobiology, 75*(6), 406-433.
Sun, W., Ginovart, N., Ko, F., Seeman, P., & Kapur, S. (2003). In vivo evidence for dopamine-mediated internalization of D2-receptors after amphetamine: differential findings with [3H]raclopride versus [3H]spiperone. *Molecular Pharmacology, 63*(2), 456-462.

Suskauer, S. J., Simmonds, D. J., Fotedar, S., Blankner, J. G., Pekar, J. J., Denckla, M. B. (2008). Functional Magnetic Resonance Imaging Evidence for Abnormalities in Response Selection in Attention Deficit Hyperactivity Disorder: Differences in Activation Associated with Response Inhibition but Not Habitual Motor Response. *Journal of Cognitive Neuroscience, 20*(3), 478-493.

Taber, M., & Fibiger, H. (1995). Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: modulation by metabotropic glutamate receptors. *The Journal of Neuroscience, 15*(5), 3896-3904.

Taber, M. T., & Fibiger, H. C. (1993). Electrical stimulation of the medial prefrontal cortex increases dopamine release in the striatum. *Neuropsychopharmacology, 9*(4), 271-275.

Talairach, J., & Tournoux, P. (1988). *Co-Planar Stereotactic Atlas of the Human Brain*. Stuttgart: Thieme.

Tamm, L., Menon, V., Ringel, J., & Reiss, A. L. (2004). Event-related fMRI evidence of frontotemporal involvement in aberrant response inhibition and task-switching in attention-deficit/hyperactivity disorder. *Jounral of the American Academy of Child and Adolescent Psychiatry, 43*(11), 1430-1440.

Tamnes, C. K., Østby, Y., Walhovd, K. B., Westlye, L. T., Due-Tønnessen, P., & Fjell, A. M. (2010). Neuroanatomical correlates of executive functions in children and adolescents: A magnetic resonance imaging (MRI) study of cortical thickness. *Neuropsychologia, 48*(9), 2496-2508.

Teicher, M. H. (1995). Actigraphy and motion analysis: new tools for psychiatry. *Harvard Review of Psychiatry, 3*(1), 18-35.

Teicher, M. H., Anderson, C. M., Polcari, A., Gold, C. A., Maas, L. C., & Renshaw, P. F. (2000). Functional deficits in basal ganglia of children with attention deficit. hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. *Nature Medicine, 6*(4), 470-473.

Tillman, R., Geller, B., Craney, J. L., Bolhofner, K., Williams, M., Zimerman, B. (2003). Temperament and character factors in a prepubertal and early adolescent bipolar disorder phenotype compared to attention deficit hyperactive and normal controls. *Journal of Child and Adolescent Psychopharmacology, 13*(4), 531-543.

Toga, A. W., Thompson, P. M., & Sowell, E. R. (2006). Mapping brain maturation. *Trends in Neurosciences, 29*(3), 148-159.

Tohka, J., Zijdenbos, A., & Evans, A. (2004). Fast and robust parameter estimation for statistical partial volume models in brain MRI. *NeuroImage, 23*(1), 84-97.

Tripp, G., & Alsop, B. (2001). Sensitivity to reward delay in children with attention deficit hyperactivity disorder (ADHD). *Journal of Child Psychology and Psychiatry, 42*(5), 691-698.

Tripp, G., Ryan, J., & Peace, K. (2002). Neuropsychological functioning in children with DSM-IV combined type Attention Deficit Hyperactivity Disorder. *Australian and New Zeland Journal of Psychiatry, 36*(6), 771-779.

Tröster, A. I., Woods, S. P., & Fields, J. A. (2003). Verbal Fluency Declines After Pallidotomy: An Interaction Between Task and Lesion Laterality. *Applied Neuropsychology, 10*(2), 69 - 75.

Troyer, A. K., Moscovitch, M., Winocur, G., Alexander, M. P., & Stuss, D. (1998). Clustering and switching on verbal fluency: the effects of focal frontal- and temporal-lobe lesions. *Neuropsychologia, 36*(6), 499-504.

Tryon, W. W. (1993). The role of motor excess and instrumented activity measurement in attention deficit hyperactivity disorder. *Behavior Modification, 17*(4), 371-406.

Tsukada, H., Nishiyama, S., Kakiuchi, T., Ohba, H., Sato, K., & Harada, N. (1999). Is synaptic dopamine concentration the exclusive factor which alters the in vivo binding of [11C]raclopride?: PET studies combined with microdialysis in conscious monkeys. *Brain Research, 841*(1-2), 160-169.

Tukey, J. W. (1962). The future of data analysis. *The Annals of Mathematical Statistics, 33*(1), 1-67.

Uebel, H., Albrecht, B., Kirov, R., Heise, A., Dopfner, M., Freisleder, F. J. (2010). What can actigraphy add to the concept of labschool design in clinical trials? *Current Pharmaceutical Design, 16*(22), 2434-2442.

Vaidya, C. J., Austin, G., Kirkorian, G., Ridlehuber, H. W., Desmond, J. E., Glover, G. H. (1998). Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study. *Proceedings of the National Academy of Sciences, 95*(24), 14494-14499.

Vaidya, C. J., Bunge, S. A., Dudukovic, N. M., Zalecki, C. A., Elliott, G. R., & Gabrieli, J. D. E. (2005). Altered Neural Substrates of Cognitive Control in Childhood ADHD: Evidence From Functional Magnetic Resonance Imaging. *Am J Psychiatry, 162*(9), 1605-1613.

van den Bergh, F. S., Bloemarts, E., Chan, J. S. W., Groenink, L., Olivier, B., & Oosting, R. S. (2006). Spontaneously hypertensive rats do not predict symptoms of attention-deficit hyperactivity disorder. *Pharmacology Biochemistry and Behavior, 83*(3), 380-390.

van der Meere, J., Vreeling, H. J., & Sergeant, J. (1992). A motor presetting dtudy in hyperactive, learning disabled and control children. *Journal of Child Psychology and Psychiatry, 33*(8), 1347-1351.

Van Dyck, C., Quinlan, D., Cretella, L., Staley, J., Malison, R., Baldwin, R. (2002). Unaltered dopamine transporter availability in adult attention deficit hyperactivity disorder. *American Journal of Psychiatry, 159*, 309 - 312.

Van Petten, C., Plante, E., Davidson, P. S. R., Kuo, T. Y., Bajuscak, L., & Glisky, E. L. (2004). Memory and executive function in older adults: relationships with temporal and prefrontal gray matter volumes and white matter hyperintensities. *Neuropsychologia, 42*(10), 1313-1335.

Van Tol, H. H., Wu, C. M., Guan, H. C., Ohara, K., Bunzow, J. R., Civelli, O. (1992). Multiple dopamine D4 receptor variants in the human population. *Nature, 358*(6382), 149-152.

Vance, A., Silk, T. J., Casey, M., Rinehart, N. J., Bradshaw, J. L., Bellgrove, M. A. (2007). Right parietal dysfunction in children with attention deficit hyperactivity disorder, combined type: a functional MRI study. *Mol Psychiatry, 12*(9), 826-832.

VanNess, S., Owens, M., & Kilts, C. (2005). The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. *BMC Genetics, 6*(1), 55.

Vernaleken, I., Buchholz, H. G., Kumakura, Y., Siessmeier, T., Stoeter, P., Bartenstein, P. (2007). 'Prefrontal' cognitive performance of healthy subjects positively correlates with cerebral FDOPA influx: An exploratory [18F]-fluoro-L-DOPA-PET investigation. *Human Brain Mapping, 28*(10), 931-939.

Vickery, R. G., & von Zastrow, M. (1999). Distinct dynamin-dependent and -independent mechanisms target structurally homologous dopamine receptors to different endocytic membranes. *Journal of Cell Biology, 144*(1), 31-43.

Viggiano, D., Grammatikopoulos, G., & Sadile, A. G. (2002). A morphometric evidence for a hyperfunctioning mesolimbic system in an animal model of ADHD. *Behavioural Brain Research, 130*(1-2), 181-189.

Viggiano, D., Ruocco, L. A., Arcieri, S., & Sadile, A. G. (2004). Involvement of norepinephrine in the control of activity and attentive processes in animal models of attention deficit hyperactivity disorder. *Neural Plasticity 11*(1-2), 133-149.

Viggiano, D., & Sadile, A. G. (2000). Hypertrophic A10 dopamine neurones in a rat model of attention-deficit hyperactivity disorder (ADHD). *Neuroreport, 11*(17), 3677-3680.

Vles, J. S., Feron, F. J., Hendriksen, J. G., Jolles, J., van Kroonenburgh, M. J., & Weber, W. E. (2003). Methylphenidate down-regulates the dopamine receptor and transporter system in children with attention deficit hyperkinetic disorder (ADHD). *Neuropediatrics, 34*(2), 77-80.

Volkow, N., Wang, G., Fowler, J., & Ding, Y. (2005a). Imaging the effects of methylphenidate on brain dopamine: new model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 1410 - 1415.

Volkow, N., Wang, G., Fowler, J., Telang, F., Maynard, L., Logan, J. (2004). Evidence that methylphenidate enhances the saliency of a mathematical task by increasing dopamine in the human brain. *American Journal of Psychiatry, 161*, 1173 - 1180.

Volkow, N. D., Fowler, J. S., Wang, G. J., Ding, Y. S., & Gatley, S. J. (2002a). Role of dopamine in the therapeutic and reinforcing effects of methylphenidate in humans: results from imaging studies. *European Neuropsychopharmacology, 12*(6), 557-566.

Volkow, N. D., Wang, G.-J., Fowler, J. S., & Ding, Y.-S. (2005b). Imaging the effects of methylphenidate on brain dopamine: New model on its therapeutic actions for attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*(11), 1410.

Volkow, N. D., Wang, G.-J., Fowler, J. S., Logan, J., Schlyer, D., Hitzemann, R. (1994). Imaging endogenous dopamine competition with [11C]raclopride in the human brain. *Synapse, 16*(4), 255-262.

Volkow, N. D., Wang, G.-J., Newcorn, J., Fowler, J. S., Telang, F., Solanto, M. V. (2007a). Brain dopamine transporter levels in treatment and drug naïve adults with ADHD. *NeuroImage, 34*(3), 1182.

Volkow, N. D., Wang, G.-J., Newcorn, J., Telang, F., Solanto, M. V., Fowler, J. S. (2007b). Depressed dopamine activity in caudate and preliminary evidence of limbic involvement in adults with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry, 64*(8), 932-940.

Volkow, N. D., Wang, G., Fowler, J. S., Logan, J., Gerasimov, M., Maynard, L. (2001). Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *Journal of Neuroscience, 21*(2), RC121.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Franceschi, D., Maynard, L. (2002b). Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications. *Synapse, 43*(3), 181-187.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., Gifford, A. (1999). Prediction of reinforcing responses to psychostimulants in humans by brain dopamine D2 receptor levels. *American Journal of Psychiatry, 156*(9), 1440-1443.

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Gatley, S. J., MacGregor, R. R. (1996a). Measuring age-related changes in dopamine D2 receptors with 11C-raclopride and 18F-N-methylspiroperidol. *Psychiatry Research, 67*(1), 11-16.

Volkow, N. D., Wang, G. J., Fowler, J. S., Molina, P. E., Logan, J., Gatley, S. J. (2003). Cardiovascular effects of methylphenidate in humans are associated with increases of dopamine in brain and of epinephrine in plasma. *Psychopharmacology (Berl), 166*(3), 264-270.

Volkow, N. D., Wang, G. J., Gatley, S. J., Fowler, J. S., Ding, Y. S., Logan, J. (1996b). Temporal relationships between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects. *Psychopharmacology (Berl), 123*(1), 26-33.

Volkow, N. D., Wang, G. J., Kollins, S. H., Wigal, T. L., Newcorn, J. H., Telang, F. (2009). Evaluating dopamine reward pathway in ADHD: clinical implications. *Journal of the American Medical Association, 302*(10), 1084-1091.

Volkow, N. D., Wang, G. J., Newcorn, J. H., Kollins, S. H., Wigal, T. L., Telang, F. (2010). Motivation deficit in ADHD is associated with dysfunction of the dopamine reward pathway. *Mol Psychiatry*.

Wade, T. R., de Wit, H., & Richards, J. B. (2000). Effects of dopaminergic drugs on delayed reward as a measure of impulsive behavior in rats. *Psychopharmacology (Berl), 150*(1), 90-101.

Walhovd, K. B., Fjell, A. M., Dale, A. M., Fischl, B., Quinn, B. T., Makris, N. (2006). Regional cortical thickness matters in recall after months more than minutes. *NeuroImage, 31*(3), 1343-1351.

Wang, J., Jiang, T., Cao, Q., & Wang, Y. (2007). Characterizing anatomic differences in boys with attention-deficit/hyperactivity disorder with the use of deformation-based morphometry. *AJNR American Journal of Neuroradiology, 28*(3), 543-547.

Ward, M. F., Wender, P. H., & Reimherr, F. W. (1993). The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder *American Journal of Psychiatry, 150*(6), 885-890.

Watanabe, Y., Fujita, M., Ito, Y., Okada, T., Kusuoka, H., & Nishimura, T. (1997). Brain dopamine transporter in spontaneously hypertensive rats. *Journal of Nuclear Medicine, 38*(3), 470-474.

Weiner, D. M., Levey, A. I., Sunahara, R. K., Niznik, H. B., O'Dowd, B. F., Seeman, P. (1991). D1 and D2 dopamine receptor mRNA in rat brain. *Proceedings of the National Academy of Sciences, 88*(5), 1859-1863.

Weiss, G. (1993). *Hyperactive children grown up : ADHD in children, adolescents, and adults*.

Weiss, G., Hechtman, L., Milroy, T., & Perlman, T. (1985). Psychiatric Status of Hyperactives as Adults: A Controlled Prospective 15-Year Follow-up of 63 Hyperactive Children. *Journal of the American Academy of Child Psychiatry, 24*(2), 211-220.

Wender, P. (1987). *The hyperactive child, adolescent, and adult : attention deficit disorder through the lifespan*.

Wender, P. H. (1995). *Attention-deficit hyperactivity disorder in adults.* New York: Oxford University Press.

Westlye, L. T., Grydeland, H., Walhovd, K. B., & Fjell, A. M. (2011). Associations between regional cortical thickness and attentional networks as measured by the attention network test. *Cerebral Cortex, 21*(2), 345-356.

Wilens, T. E., Faraone, S. V., Biederman, J., & Gunawardene, S. (2003). Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. *Pediatrics, 111*(1), 179-185.

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/hyperactivity disorder: A meta-analytic review. *Biological Psychiatry, 57*(11), 1336-1346.

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*(1), 205-213.

Williams, G. V., & Goldman-Rakic, P. S. (1995). Modulation of memory fields by dopamine Dl receptors in prefrontal cortex. *Nature, 376*(6541), 572-575.

Wilson, M. C. (2000). Coloboma mouse mutant as an animal model of hyperkinesis and attention deficit hyperactivity disorder. *Neuroscience & Biobehavioral Reviews, 24*(1), 51-57.

Wise, R. A. (2004). Dopamine, learning and motivation. *Nature Reviews. Neuroscience, 5*(6), 483-494.

Wood, A. C., Asherson, P., Rijsdijk, F., & Kuntsi, J. (2009). Is overactivity a core feature in ADHD? Familial and receiver operating characteristic curve analysis of mechanically assessed activity level. *Journal of the American Academy of Child and Adolescent Psychiatry, 48*(10), 1023-1030.

Wool, R. S., Weldon, D. A., Shaywitz, B. A., Anderson, G. M., Cohen, D. J., & Teicher, M. H. (1987). Amphetamine reverses learning deficits in 6-hydroxydopamine-treated rat pups. *Developmental Psychobiology, 20*(2), 219-232.

Worsley, K., Andermann, M., Koulis, T., MacDonald, D., & Evans, A. (1999). Detecting changes in nonisotropic images. *Human Brain Mapping, 8*(2-3), 98-101.

Worsley, K. J., Marrett, S., Neelin, P., Vandal, A. C., Friston, K. J., & Evans, A. C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. *Human Brain Mapping, 4*, 58-73.

Yamamoto, B. K., & Novotney, S. (1998). Regulation of extracellular dopamine by the norepinephrine transporter. *Journal of Neurochemistry, 71*(1), 274-280.

Yang, B., Chan, R. C. K., Jing, J., Li, T., Sham, P., & Chen, R. Y. L. (2007). A meta-analysis of association studies between the 10-repeat allele of a VNTR polymorphism in the 3′-UTR of dopamine transporter gene and attention deficit hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144B*(4), 541-550.

You, Z. B., Tzschentke, T. M., Brodin, E., & Wise, R. A. (1998). Electrical stimulation of the prefrontal cortex increases cholecystokinin, glutamate, and dopamine release in the nucleus accumbens: an in vivo microdialysis study in freely moving rats. *Journal of Neuroscience, 18*(16), 6492-6500.

Zaczek, R., Culp, S., & De Souza, E. B. (1991). Interactions of [3H]amphetamine with rat brain synaptosomes. II. Active transport. *Journal of Pharmacology and Experimental Therapeutics, 257*(2), 830-835.

Zahniser, N. R., & Doolen, S. (2001). Chronic and acute regulation of Na+/Cl--dependent neurotransmitter transporters: drugs, substrates, presynaptic receptors, and signaling systems. *Pharmacology & Therapeutics, 92*(1), 21-55.

Zahniser, N. R., & Molinoff, P. B. (1978). Effect of guanine nucleotides on striatal dopamine receptors. *Nature, 275*(5679), 453-455.

Zald, D. H., Boileau, I., El-Dearedy, W., Gunn, R., McGlone, F., Dichter, G. S. (2004). Dopamine transmission in the human striatum during monetary reward tasks. *Journal of Neuroscience, 24*(17), 4105-4112.

Zametkin, A., Liebenauer, L., Fitzgerald, G., King, A., Minkunas, D., Herscovitch, P. (1993). Brain metabolism in teenagers with attention deficit hyperactivity disorder. *Archives of General Psychiatry, 50*(5), 333-340.

Zametkin, A., Nordahl, T., Gross, M., King, C., Semple, W., Rumsey, J. (1990). Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *The New England Journal of Medicine, 323*, 1361 - 1366.

Zang, Y.-F., Jin, Z., Weng, X.-C., Zhang, L., Zeng, Y.-W., Yang, L. (2005). Functional MRI in attention-deficit hyperactivity disorder: Evidence for hypofrontality. *Brain and Development, 27*(8), 544-550.

Zetterstrom, T., Sharp, T., Marsden, C. A., & Ungerstedt, U. (1983). In vivo measurement of dopamine and its metabolites by intracerebral dialysis: changes after d-amphetamine. *Journal of Neurochemistry, 41*(6), 1769-1773.

Zhuang, X., Oosting, R. S., Jones, S. R., Gainetdinov, R. R., Miller, G. W., Caron, M. G. (2001). Hyperactivity and impaired response habituation in hyperdopaminergic mice. *Proceedings of the National Academy of Sciences 98*(4), 1982-1987.

Zijdenbos, A., Forghani, R., & Evans, A. C. (1998). Automatic Quantification of MS Lesions in 3D MRI Brain Data Sets: Validation of INSECT. In W. M. Wells, A. Colchester & S. Delp (Eds.), *Medical Image Computing and Computer-Assisted Interventation (MICCAI98)* (pp. 439-448). Cambridge, MA: Springer-Verlag Berlin Heidelberg.

Zijdenbos, A. P., Forghani, R., & Evans, A. C. (2002). Automatic "pipeline" analysis of 3-D MRI data for clinical trials: application to multiple sclerosis. *Medical Imaging, IEEE Transactions on, 21*(10), 1280-1291.

APPENDICES

Appendix 1. Distribution of DAT1, DRD4, and COMT genotypes across the ADHD and the control groups.

	Polymorphism	Controls	ADHD
DAT 3' UTR VNTR	10/10	60%	50%
	9/10	30%	42.86%
	9/9	10%	0%
	8/9	0%	7.14%
DAT1 Exon 9 SNP (rs6347)	AA	50%	64.29%
	AG	37.50%	35.71%
	GG	12.50%	0%
DAT1 Intron 9 SNP (rs8179029)	AA	70%	78.57%
	AG	30%	21.43%
DRD4 exon III 48-bp VNTR	2/2	0%	7.14%
	2/4	20%	28.57%
	4/4	60%	35.71%
	4/6	10%	0%
	4/7	10%	28.57%
COMT val/met	val/val	10%	14.29%
	val/met	30%	42.86%
	met/met	60%	42.86%