LONGITUDINAL AND NEUROIMAGING INVESTIGATIONS OF EXECUTIVE FUNCTIONS IN SUBTYPES OF ATTENTION DEFICIT HYPERACTIVITY DISORDER

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© Lana Dépatie, 2011
Pour mes parents, Réjane et Pierre, qui ont toujours été là pour moi...

& For Bob...
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CONTRIBUTION OF AUTHORS.

In accordance with McGill University’s requirement, an explicit statement of the contribution of individuals who have co-authored the manuscripts that appear in this dissertation is provided.

Experiment 1: Executive Eye Movements in Subtypes of ADHD.

&

Experiment 2: A Double-Blind, Placebo-Controlled, Cross-Over Study of the Effects of Methylphenidate on Executive Eye Movements in Subtypes of ADHD.

Authors: O’Driscoll GA, Dépatie L, Holahan A-LV, Savion-Lemieux T, Barr RG, Jolicoeur C & Douglas VI.

The data collection for Experiments 1 and 2 was ongoing as I began my graduate studies in Psychology. I participated in the data collection towards the end of the study. I then took over the responsibility for the study and coded and analyzed the data. I reviewed the literature and wrote the first draft of the manuscript and revised subsequent versions based on feedback. The data from these experiments have been published in a manuscript entitled “Executive Functions and methylphenidate Response in Subtypes of Attention-Deficit/Hyperactivity Disorder”. I re-wrote the manuscript into two chapters for the dissertation so that I could expand on the information that had to be excluded from the publication due to word limits. Dr. O’Driscoll was involved in every aspect of the studies, including design, data collection and analyses, the interpretation of findings and manuscript preparation. Dr. Holahan and Ms. Savion-Lemieux were involved in participant recruitment and data collection. Dr. Barr and Dr. Jolicoeur assisted with
participant recruitment. Dr. Douglas contributed to the design of the study and provided valuable comments and criticisms on the manuscript that was published and on the corresponding chapters in this dissertation.

**Experiment 3:** Longitudinal Course of Executive Functions in Subtypes of ADHD

Authors: Dépatie L, Caro J, Fulton H, Holahan A-LV, Douglas VI, O’Driscoll GA

I was responsible for this study. I was involved in the design, participant recruitment, data collection and coding, and statistical analyses. I reviewed the literature and wrote the manuscript. Ms. Caro assisted with data collection and the development of stimuli for the Time Reproduction Task. Ms. Fulton assisted with study design, data collection and data coding. Dr. Holahan contributed by recruiting participants and having collected the data for the original experiment which was the baseline for this longitudinal study. Dr. Douglas was involved in the design of the study and provided valuable comments on drafts of the manuscript included in this dissertation. Dr. O’Driscoll contributed to all aspects of the study.

**Experiment 4:** Functional Magnetic Resonance Imaging Investigation of Executive Functions in Subtypes of ADHD.

Authors: Dépatie L, Caro J, Starmans C, Holahan A-L V, Douglas VI, O’Driscoll GA

I was responsible for the design of the study, recruiting participants, programming the tasks administered in the scanner, data collection (including setting up the ISCAN
equipment to record participants’ eye movements in the scanner), data coding, statistical analysis, and writing the manuscript. Ms. Starmans assisted with coding of the eye movement data acquired in the scanner. Ms. Caro assisted with the programming of the tasks and data collection. Dr. Holahan assisted with recruitment of participants. Dr. Douglas provided conceptual support as well as valuable comments during the editing of the manuscript. Dr. O’Driscoll contributed to all aspects of the study.
The research in this dissertation makes unique contributions to our understanding of the subtypes of ADHD (ADHD-Predominantly Inattentive and ADHD-Combined) with respect to differences in executive function profiles, response to methylphenidate, the course of executive functioning in adolescence and its relationship to adaptive outcome, and the neural underpinnings of executive functioning in each subtype.

Experiment One is the first study in the literature to compare the executive functioning of the subtypes using oculomotor tests. It builds on previous neuropsychological studies comparing the subtypes by adding methodological refinements such as matched control tasks, demographically matched groups, and the exclusion of confounding comorbid conditions.

ADHD-Combined (ADHD-C) boys were impaired relative to Controls in response inhibition and motor planning but not task-switching. Compared to the ADHD-Predominantly Inattentive (ADHD-I) group, the ADHD-C group had more participants with antisaccade performance in the impaired range and made fewer predictive saccades.

Experiment Two evaluated the effect of methylphenidate in ADHD-I and ADHD-C participants using executive oculomotor tasks. To my knowledge, this was the first study to compare methylphenidate effects on neurocognitive functioning in adolescents diagnosed with the ADHD-I and ADHD-C subtypes.

Methylphenidate significantly improved inhibitory function and motor planning, with similar improvement in both subtypes. Oculomotor tests of executive function
showed significant within-subject stability across testing sessions, suggesting that impairments on these tasks reflect trait deficits.

Experiment Three evaluated the developmental course of executive functioning in adolescents with ADHD. It also assessed the relationship between measures of executive functioning, clinical symptoms and adaptive functioning in late adolescence. Our investigation adds to the small literature on the longitudinal course of executive functioning in subtypes of ADHD by examining a narrow developmental range, by matching the groups on demographic characteristics (e.g., age, SES, and IQ), and by including only individuals essentially free of comorbid disorders when initially recruited.

In late adolescence, antisaccade errors continued to distinguish participants originally diagnosed as ADHD-C from Controls. Predictive saccade rate no longer differentiated the groups. Within ADHD participants, baseline measures of executive functioning did not significantly predict clinical or adaptive outcomes. However, antisaccade error rate at follow-up was correlated with number of arrests, and number of arrests was higher in ADHD participants.

Experiment Four investigated the neural underpinnings of executive functioning in ADHD-I and ADHD-C. Our study is the first to compare neural activation in the ADHD subtypes with reference to a Control group and the first to evaluate the neural basis of antisaccade deficits in ADHD with fMRI.

Compared to Controls, both of the ADHD groups showed significantly increased antisaccade error rates in the scanner and reduced right frontal eye field (FEF) activity. The ADHD-C group also showed reduced activation of left precuneus, right superior parietal cortex, and cerebellar lobule VI. Activation in right superior parietal cortex
differentiated between the subtypes with the ADHD-C group showing hypoactivation. Antisaccade errors were significantly correlated with activation in left FEF, left precuneus and right superior parietal lobe. Parent ratings of inattention and hyperactivity/impulsivity were significantly associated with activation of left precuneus across all subjects and within ADHD subjects.

Our data suggest an important role for FEF dysfunction in ADHD, and in antisaccade performance. This region is involved in attention, working memory and saccade inhibition, all areas of reliable deficit in ADHD. Our data further suggest a role for dorsal precuneus in ADHD. This area, distinct spatially from the region of precuneus implicated in the default mode network, showed high task-related activation and a strong negative correlation with both task errors and symptom ratings.
Attention Deficit Hyperactivity Disorder (ADHD) is a commonly occurring psychiatric disorder of childhood. The criteria for diagnosis include symptoms of inattention and hyperactivity/impulsivity. The current conceptualization of the disorder divides affected individuals into subtypes, with the two most common being ADHD-Predominantly Inattentive and ADHD-Combined (inattention and hyperactivity/impulsivity). There is longstanding debate in the literature about whether the Inattentive and Combined subtypes are more correctly conceived as different forms of the same disorder or distinct diagnostic entities.

The experiments in this dissertation investigate similarities and differences between the ADHD-Inattentive and ADHD-Combined subtypes in several domains. Specifically, we used eye movement tasks to investigate the subtypes’ executive function profile in early adolescence (Experiment 1); compared the subtypes’ response to methylphenidate (Experiment 2); evaluated the longitudinal course of executive functioning (Experiment 3); and studied the neural underpinnings of executive functioning (Experiment 4).

The Inattentive and Combined subtypes had different executive function profiles in early adolescence: ADHD-Combined participants were impaired in our measure of response inhibition (antisaccades) and motor planning (predictive saccades) but not in task-switching; the ADHD-Inattentives were unimpaired on all our tasks.

Methylphenidate improved response inhibition and motor planning but did not affect task-switching. The magnitude of response to methylphenidate was similar in the two ADHD groups.
When the participants were followed up in late adolescence, clinical symptoms and executive functioning had improved significantly in both subtypes. However, both groups continued to show significant symptoms compared to Controls. The Combined participants remained impaired in response inhibition, but their motor planning deficits had remitted. In a timing reproduction task, they were impaired at short (2-10s) intervals compared to both the Inattentive group and Controls. There were no differences between the subtypes in adaptive functioning but the ADHD participants as a whole had reduced adaptive functioning compared to Controls. Antisaccade errors at follow-up were significantly related to one of the adaptive measures, number of arrests.

Our fMRI study of the antisaccade task found that both subtypes had performance impairments compared to Controls when in the scanner. Both subtypes had reduced activation in frontal-subcortical circuitry. The ADHD-C participants also had lower activation than both Controls and the ADHD-I group in dorsal parietal lobe. Frontal and parietal activation was related to antisaccade errors, and parietal activation was also related to parent ratings of ADHD symptoms.

Although it is not possible to draw definitive conclusions, our data suggest that the two subtypes may be distinct disorders. This conclusion is based on the neural activation differences in the scanner and the neurocognitive differences in the lab. Although some similarities between the subtypes were observed (methylphenidate response, impairments in adaptive functioning and frontal-subcortical involvement), these are not specific to ADHD and are arguably a tenuous basis on which to continue grouping two distinct clinical presentations into a single disorder. Nonetheless, the
conclusion is tentative and would be strengthened both by replication in a larger sample and by data suggesting distinct etiologies (e.g. liability genes) for the two subtypes.
RÉSUMÉ

Le Trouble Déficitaire de l’Attention avec Hyperactivité (TDAH) est un désordre psychiatrique de l’enfance. Les critères de diagnostic incluent des symptômes d’inattention et d’hyperactivité/impulsivité. La conceptualisation actuelle du trouble divise les individus affectés en sous-types, les deux sous-types les plus fréquents étant le TDAH-Inattentif (inattention seulement) et TDAH-Combiné (inattention et hyperactivité/impulsivité). Il existe un débat de longue date dans la littérature quant à savoir si les sous-types Inattentif et Combiné sont plus correctement conçus comme différentes formes du même désordre ou comme deux diagnostics distincts.

Les expériences dans cette thèse évaluent les similitudes et les différences entre le TDAH-Inattentif et le TDAH-Combiné dans plusieurs domaines. Plus précisément, nous avons utilisé des tâches de mouvements oculaires pour évaluer le profil de fonctionnement exécutif des sous-types en début d’adolescence (Expérience 1), comparé la réponse des sous-types au méthylphénidate (Ritalin) (Expérience 2), examiné l’évolution longitudinale du fonctionnement exécutif (Expérience 3), et étudié la base neurale du fonctionnement exécutif (Expérience 4).

Les sous-types Inattentif et Combiné ont démontré différents profils de fonctions exécutives en début d’adolescence: les participants ayant le TDAH-Combiné ont eu des déficits sur nos mesures d’inhibition (antisaccades) et de planification motrice (saccades prévisibles), mais pas sur notre mesure de «changement de tâche». Les participants du groupe TDAH-Inattentif ne démontrèrent aucun déficit à nos tâches.
Le méthylphénidate a amélioré les fonctions d’inhibition et de planification motrice, mais n’a pas affecté le «changement de tâche». L’ampleur de la réponse au méthylphénidate fut semblable pour les deux groupes de TDAH.

Quand les participants ont été suivis en fin d’adolescence, les symptômes cliniques et le fonctionnement exécutif s’étaient améliorés de façon significative chez les deux sous-types. Toutefois, les deux groupes ont continué à démontrer des symptômes cliniques significatifs comparativement aux témoins. Les participants de type Combinés continuèrent à démontrer des déficits au niveau de l’inhibition, mais leurs déficits de planification motrice n’étaient plus observés. Sur une tâche de reproduction du temps, ils ont montré un déficit pour la reproduction de courtes intervalles (2-10 secondes) comparativement aux Inattentifs et aux témoins. Il n’y a pas eu de différences entre les sous-types (Inattentif vs Combiné) en ce qui concerne le fonctionnement adaptatif, mais les participants TDAH en général démontrèrent un moins bon fonctionnement adaptatif comparativement aux témoins. Les erreurs d’antisaccade lors du suivi furent significativement reliées à une mesure du fonctionnement adaptatif, soit le nombre d’arrêstation.

Notre étude d’imagerie par résonance magnétique fonctionnelle de la tâche d’antisaccade trouva que la performance des deux sous-types dans le scanner était déficiente comparativement aux témoins. Les deux sous-types ont démontré une activation diminuée du circuit frontal-sous-cortical. Les participants du type Combiné ont aussi démontré une activation réduite du lobe pariétal supérieur comparativement aux témoins et au group Inattentif. L’activité frontale et du lobe pariétal fut associée aux
erreurs d’antisaccade. De plus, on a noté une association significative entre l’activité du lobe pariétal et les symptômes de TDAH tels que rapportés par les parents.

Même s’il n’est pas possible de tirer des conclusions définitives en ce moment, nos données suggèrent que les deux sous-types de TDAH sont des troubles distincts. Cette conclusion est basée sur les différences d’activation neurale et les différences aux profils neurocognitifs obtenues en laboratoire. Bien que certaines similitudes entre les sous-types aient été observées (la réponse au méthylphénidate, difficultés au niveau du fonctionnement adaptatif et l’implication du circuit frontal-sous-cortical), celles-ci ne sont pas spécifiques au TDAH et semblent former une base fragile afin de continuer de grouper ces deux présentations cliniques distinctes en un seul désordre. Néanmoins, nos conclusions demeurent provisoires en attendant que nos résultats soient répliqués avec de plus grands échantillons et des données qui impliqueraient différentes étiologies (ex: différents gènes) chez les deux sous-types.
Attention Deficit Hyperactivity Disorder (ADHD) is a childhood psychiatric disorder thought to be caused by genetic and environmental factors (e.g. Faraone & Biederman, 1998). It is characterized by symptoms of inattention, impulsivity and hyperactivity. Since first described at the start of the 20th century, the conceptualization of the disorder has changed frequently and the field has been rife with controversies. In recent years, researchers have debated whether inattention or hyperactivity/impulsivity or both types of symptoms are central to the diagnosis of the disorder. The diagnostic debate has been reflected in different versions of the Diagnostic and Statistical Manual of Mental Disorder (DSM) which have emphasized different primary symptoms in the conceptualization of the illness, from hyperactivity in DSM-II (American Psychiatric Association (APA), 1968), to inattention in DSM-III (APA, 1980)) and then to any 8 symptoms in DSM-III-R (APA, 1987), irrespective of symptom type. In DSM-IV, (APA, 1994), symptoms of inattention and hyperactivity/impulsivity are given equal weight; there are now three subtypes of ADHD that, along with Controls, emerge when designating individuals as high/low in inattention, hyperactivity/impulsivity, both, or neither.

The two most common subtypes of ADHD, and those central to this dissertation, are the Inattentive and the Combined subtypes. The Inattentive subtype is characterized by significant elevations in inattentive symptoms only, while the Combined subtype has significant symptoms of both inattention and hyperactivity/impulsivity. The clinical presentation of these two subtypes is quite different, leading some researchers to question whether the Inattentive and Combined subtypes should be distinct disorders instead
Emil Kraepelin established an approach for the classification of psychiatric disorders that grouped patients with symptoms of similar appearance and course into a single disorder. Other factors that are considered when determining how to group cases under a single diagnosis are commonalities in etiology, treatment response and neural substrates (e.g. Werry, 1992). In this dissertation, I provide information relevant to the question of whether the Inattentive and Combined subtypes of ADHD are similar in terms of neurocognitive profile, response to medication, course and neural substrates. For the neurocognitive assessment, I used primarily oculomotor tasks since these tasks have simple instructions, have matched control tasks to isolate the function of interest, and have been studied in healthy controls and non-human primates, thus allowing the generation of a priori hypotheses regarding the neural bases of deficits. I begin chapter one by reviewing the literature that provided the rationale for the studies. In subsequent chapters I describe the empirical work. In the first study (Chapter Two), I investigated the executive function profiles of boys with ADHD-Inattentive, ADHD-Combined and Controls in early adolescence, focusing on three executive functions: motor inhibition, task-switching and motor planning. In the second study (Chapter Three), I investigated the response of the two subtypes to methylphenidate, the most common pharmacological treatment of ADHD. In the third study (Chapter Four), I followed the participants into late adolescence and re-assessed their executive functioning to evaluate cognitive course. In the fourth study (Chapter Five), I used fMRI to investigate the neural substrates of persistent executive dysfunction in the boys diagnosed initially in early adolescence.
Finally, in the last chapter (Chapter Six) I consider issues related to the findings across studies as well as more general issues that were not possible to consider in the space limitations of a published manuscript.
Chapter One: Introduction

Chapter One:

General Introduction
Attention Deficit Hyperactivity Disorder (ADHD) involves developmentally inappropriate levels of inattention and/or hyperactivity and impulsivity (American Psychiatric Association (APA), 1994). It is a commonly occurring psychiatric disorder affecting 3 to 5% of school-aged children (APA, 1994). It is far more common in boys than girls with a male to female ratio reported as close to 9:1 (APA, 1994). Although ADHD is conceptualized as a childhood disorder, there is now compelling evidence that some individuals continue to exhibit clinical impairment in adulthood (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Woods, Lovejoy, & Ball, 2002). ADHD is associated with poorer functional outcome than is seen in typically developing individuals in a wide range of domains from academic achievement to social and occupational functioning to criminality (e.g. Faraone, Biederman, Krifcher Lehman, Spencer, Norman, Seidman, et al., 1993; Ingram, Hechtman, & Morgenstern, 1999; Satterfield & Schell, 1997; Sciberras, Roos, & Efron, 2009; Semrud-Clikeman, Biederman, Sprich-Buckminster, Krifcher Lehman, Faraone, & Norman, 1992; Weiss, Hechtman, Perlman, Hopkins, & Wener, 1979).

Family (Faraone, Biederman, & Milberger, 1994; Hechtman, 1996), twin (Levy, Hay, McStephen, Wood, & Waldman, 1997; Nadder, Silberg, Eaves, Maes, & Meyer, 1998; Sherman, McGue, & Iacono, 1997; Stevenson, 1992) and adoption (Cadoret & Stewart, 1991) studies have implicated a strong genetic component to the etiology of ADHD. Genetic influences account for the large majority of the variance in the etiology of the disorder (Levy et al, 1997; Stevenson, 1992) with heritability estimates at $\approx 76\%$ (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar, 2005). Association studies have reported a link between candidate genes coding for proteins involved in
dopamine neurotransmission and ADHD. In particular, associations have been found between ADHD and genes coding for dopamine receptors and the dopamine transporter (for review, see Gizer, Ficks, & Waldman, 2009). However, other genetic data have associated ADHD with serotonin (Gizer et al., 2009). Thus, although there is strong evidence for genetic contributions, the specific genes and their functions have not been identified. It is also unlikely that the syndrome will be accounted for by the action of a single gene (Faraone & Mick, 2010).

Environmental factors have also been hypothesized to play a role in the etiology of ADHD (Swanson, Kinsbourne, Nigg, Lanphear, Stefanatos, Volkow, et al., 2007). The influence of several maternal lifestyle factors such as smoking, alcohol, and caffeine consumption, and stress during pregnancy have been investigated (for review, see Linett, Dalsgaard, Obel, Wisbord, Henriksen, Rodriguez, et al., 2005). Nicotine exposure during gestation was found to have a large effect on risk for ADHD with one study estimating a 3-fold increased risk for developing the illness (Milberger, Biederman, Faraone, Chen, & Jones, 1996). Another environmental factor that has received substantial attention is lead exposure (for reviews see Lanphear, Hornung, Khoury, Yolton, Baghurst, Bellinger, et al., 2006; Nigg, 2006). The findings have consistently supported an association between even low levels of lead exposure and ADHD-related behaviours and diagnosis (Nigg, 2006).

Thus, like most psychiatric disorders, the etiology of ADHD seems to be multifactorial, likely involving the interaction of genes and environment.
1.1 Conceptualization of ADHD

Changes to the conceptualization of the disorder have occurred several times since the initial description (reviewed by Barkley, 1990). ADHD was initially described in the early 1900s as a childhood disorder primarily found in boys, and was called “hyperkinesis disorder of childhood” (Still, 1902). In the 1960s, the disorder was renamed “minimal brain damage” or “minimal brain dysfunction” (MBD). The disorder first appeared in the DSM-II (APA, 1968) under the label “Hyperkinetic Reaction of Childhood”, with diagnostic criteria focused on motor hyperactivity. A shift in the diagnostic construct took place in the 1970s, triggered by the pioneering work of Douglas (see Douglas, 1972) which suggested that attention dysfunction was a core feature of the disorder. As a result, the diagnostic label for the disorder in the DSM-III (APA, 1980) was changed to Attention Deficit Disorder (ADD). Along with this change came the first subtypes of the disorder, ADD with or without hyperactivity. Thus hyperactivity became a non-criterial characteristic of the disorder, while inattention was at the disorder's core. With the release of the DSM-III-R (APA, 1987), the disorder was renamed Attention Deficit Hyperactivity Disorder and the criteria changed again such that a diagnosis could be made with any 8 or more symptoms of hyperactivity, impulsivity and inattention with none of these given primacy.

1.1.2 Current Conceptualization of ADHD

The current conceptualization of ADHD includes three subtypes (APA, 1994). One subtype describes children who suffer predominantly from inattentive symptoms (ADHD-Inattentive type). These symptoms include behaviours such as: difficulty
sustaining attention on tasks, not listening when spoken to directly, difficulty organizing tasks, failing to finish schoolwork or chores, losing things such as pencils and books, and being forgetful in daily activities. To meet criteria for this subtype, children need to have 6 of the 9 inattention criteria listed in DSM-IV (APA, 1994).

Another subtype describes children with predominantly hyperactive/impulsive symptoms (ADHD-Hyperactive/Impulsive type). To meet criteria for this subtype, children must have 6 of 9 symptoms of hyperactivity/impulsivity described in the DSM-IV. Examples of symptoms include: fidgeting with hands and squirming in seat, having difficulty playing quietly, being “on the go”/appearing as if “driven by a motor”, talking excessively, blurting out answers before a question is completed and having difficulty awaiting his or her turn.

The third subtype describes children who suffer from both inattention and hyperactivity/impulsivity (ADHD-Combined type). These children exhibit 6/9 symptoms of inattention and 6/9 symptoms of hyperactivity/impulsivity.

In the case of all subtypes, to receive a diagnosis of ADHD, children must exhibit the symptoms in at least 2 settings and the symptoms must appear before the age of 7 years (APA, 1994).

The two most common subtypes are ADHD-Inattentive and ADHD-Combined. These two subtypes have different clinical presentations, with children suffering from the Inattentive subtype often appearing “spacey” and lethargic (Barkley, 1990; Diamond, 2005) while those with the Combined subtype appear restless or even frenetic (Diamond, 2005). The fact that these subtypes look different clinically has fueled a debate as to whether they should be considered part of the same disorder or as two different disorders.
(Barkley, 2001; Hinshaw, 2001; Lahey, 2001; Milich et al., 2001; Pelham, 2001). Thus, the conceptualization of this disorder continues to evolve.

1.2 Executive Functioning

Executive functions are abilities that permit an individual to initiate voluntary behaviours that are willed and actively guided (Slattery, Garvey, & Swedo, 2001). These are in contrast to behaviours that are prepotent or automatic. Executive functions include higher order cognitive functions such as planning, cognitive flexibility, inhibition, attention and working memory. The core diagnostic symptoms of ADHD suggest impairments in executive functioning. Indeed, there is now overwhelming evidence that individuals suffering from ADHD exhibit impairments in several domains of executive functioning (Barkley, Grodzinsky, & DuPaul, 1992; Boonstra et al., 2005; Douglas, 1999; Pennington & Ozonoff, 1996; Shue & Douglas, 1992; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). A recent meta-analysis reported that the most consistent impairments in ADHD are found in planning (d = .69), attention (d = .64), working memory (d = .63) and response inhibition (d = .61) (Willcutt et al, 2005).

As the neurocognitive models of ADHD have evolved, one hypothesis has focused on response inhibition as a core executive deficit of the disorder (Barkley, 1997). Response inhibition occurs when an individual must withhold an ongoing action or thought, and when the processing of distracting information must be suppressed. According to Barkley’s model, ADHD individuals have fundamental deficits in inhibition and these deficits contribute to difficulties in other executive functions (e.g., working memory) that are necessary for controlled behaviour (Barkley, 1997).
While evidence suggests that deficits in executive functioning are common in ADHD, it is not clear whether these are found equally in the different subtypes. The diagnostic symptoms of the Combined subtype, because they include impulsivity, may implicate disinhibition to a greater extent than the Inattentive subtype, where symptoms of impulsivity are not criterial. Executive functioning deficits that differentiate the Combined and Inattentive subtypes have been reported in some studies, with greater impairments in the Combined group on tasks that tap inhibition, working memory, and planning (Houghton, Douglas, West, Whiting, Wall, Langsford, et al., 1999; Klorman, Hazel-Fernandez, Shaywitz, Fletcher, Marchione, Holahan et al., 1999; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). However, other studies have reported that the Inattentive and Combined subtypes have similar neurocognitive deficits (Chhabildas, Pennington, & Willcutt, 2001; Murphy, Barkley, & Bush, 2001).

In the current dissertation, I use eye movement tests of executive functioning to evaluate the neurocognitive profile of the subtypes of ADHD. Below I provide a brief introduction to the study of eye movements in ADHD.

1.2.1 Executive Eye Movements (Saccadic Eye Movements)

Saccades are high velocity eye movements used to bring a target onto the fovea, the part of the eye with the greatest visual acuity. Reflexive saccadic eye movements are highly stereotyped in terms of movement kinetics and latency, and the neural basis of these movements have been extensively characterized in humans and in non-human primates (Leigh & Zee, 1999). Because the neural architecture supporting reflexive saccades is well known, a classic neuroscience strategy for studying executive functions
has been to add an executive component to a reflexive saccade task (e.g. Funahashi, Chafee & Goldman-Rakic, 1993; Guitton, Buchtel, & Douglas, 1985; Sawaguchi & Goldman-Rakic, 1991); this approach allows researchers to isolate the executive component of behaviour and its neural substrates from the reflexive component.

Inhibition is one function that has been extensively studied in this way using “antisaccades”, that is, saccades made away from rather than toward a peripheral target. Antisaccades take longer to generate than reflexive saccades (Hallett & Adams, 1980), with the increase in latency attributed to the additional demands of antisaccades, which are thought to include the time to inhibit the reflexive saccade toward the target, the time to calculate the new vector to an imaginary target in the opposite hemifield, and the time to generate a voluntary saccade. Percent error on the antisaccade task reflects the success/failure of inhibition, which may depend on the relative speed of inhibition compared to the speed of the reflexive response, or on the ability to hold the task goal (look away not toward) in working memory (Roberts, Hagar, & Heron, 1994).

The neural basis of antisaccade performance has been extensively studied in humans and non-human primates. A classic early study first linked performance on this task to dysfunction of the frontal lobe (Guitton et al., 1985), with elevated error rates in neurological patients with large frontal lesions. Subsequent single-unit, neuroimaging and neurological studies have reported involvement of dorsolateral prefrontal cortex (Pierrot-Deseilligny, Ploner, Muri, Gaymard, & Rivaud-Pechoux, 2002; Johnston & Everling, 2006), frontal eye fields (Everling & Munoz, 2000; O’Driscoll, Alpert, Matthisse, Levy, Rauch, & Holzman, 1995; Sweeney, Mintun, Kwee, Wiseman, Brown, Rosenberg, & Carl, 1996), supplementary motor area (O’Driscoll et al, 1995; Schlag-
Rey, Amador, Sanchez, & Schlag, 1997), ventral prefrontal cortex (Walker, Husain, Hodgson, Harrison, & Kennard, 1998) and anterior cingulate cortex (Gaymard, Rivaud, Cassarini, Dubard, Rancurel, Agid, & Pierrot-Deseilligny, 1998). Increased error rates have also been found in patients with neurodegenerative diseases of the striatum the output nuclei of the frontal cortex, (e.g., Kitagawa, Fukushima, & Tashiro, 1994; Currie, Ramsden, McArthur, & Maruff, 1991; Lasker, Zee, Hain, & Folstein, 1987).

Studies of non-human primates have shown that successful antisaccade generation depend on activity in superior colliculus (Everling, Dorris, Klein & Munoz, 1999; Munoz & Everling, 2004), a midbrain region critically involved in both saccade generation and visual attention. Preparatory (build-up) activity in the intermediate layers of this structure prior to the target appearance predicts antisaccade errors; the increase in activity that occurs when the peripheral target appears, increases the chance that a reflexive saccade will be generated toward the target (Munoz & Everling, 2004). The frontal lobe likely plays an important role in gating the preparatory activity through connections from dorsolateral prefrontal cortex (Johnston & Everling, 2006) and/or frontal eye fields (Schlag-Rey, Schlag, & Dassonville, 1992; Everling & Munoz, 2000) or indirectly via substantia nigra (e.g., Hikosaka & Wurtz, 1985).

Current models of ADHD would predict impairments on the antisaccade task given their deficits in inhibition and working memory (for review see Willcutt et al., 2005), two functions involved in antisaccade performance (Roberts et al, 1994). Further, neural hypotheses of ADHD emphasize frontal-subcortical involvement (Seidman, Valera, & Makris, 2005), and this circuitry is critical to antisaccade performance (e.g. Munoz & Everling, 2004).
The antisaccade task has been used in a few studies of ADHD (Aman, Roberts, & Pennington, 1998; Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Klein, Raschke, & Brandenbusch, 2003; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001a; Mostofsky, Lasker, Singer, Denckla, & Zee, 2001b; Munoz, Hampton, Moore, & Goldring, 1999; 2003; Nigg et al, 2002; Rothlind, Posner, & Schaugheency, 1991). Most have reported increased antisaccade errors in ADHD (Feifel et al., 2004; Klein et al., 2003; Mostofsky et al., 2001a; 2001b; Munoz et al., 1999; Munoz, Armstrong, Hampton, & Moore, 2003; Nigg et al., 2002; but see Aman et al., 1998 and Rothlind et al., 1991). Antisaccade performance in subtypes of ADHD was first investigated in this dissertation; since the publication of our findings, another study on this topic has appeared (Carr, Nigg, & Henderson, 2006).

Task-switching has been investigated in the context of the antisaccade task. Task-switching involves keeping more than one response available and selecting which to execute based on arbitrary characteristics of the cue or stimulus that indicate the desired response and which vary from trial to trial. In the “repeated” condition, the desired response on the current trial is the same as on the previous trial. In the “switch” condition, the instructed current response is different from the one performed in the previous trial. When a switch is required, response times are normally longer and the increase in latency is called the “switch cost” (see Cepeda, Cepeda, & Kramer, 2000). The switch cost is thought to reflect the requirement to inhibit the previous/primed response and to select and execute the alternative response.

Task-switching has been investigated using the antisaccade-prosaccade mixed task (e.g. Cherkasova, Manoach, Intriligator, & Barton, 2002; Hodgson, Golding,
Molyva, Rosenthal, & Kennard, 2004). In this task, the participant must switch between looking away vs. looking towards a peripheral target depending on trial by trial variation in the central fixation point (e.g., colour). Although this task has been studied in other clinical conditions including Parkinson’s (Rivaud-Pechoux, Vidailhet, Brandel, & Gaymard, 2007), schizophrenia (Barton, Cherkasova, Lindgren, Goff, Intriligator, & Manoach, 2002), anxiety (Derakshan, Smith, & Eysenck, 2009), and Asperger’s (Manoach, Lindgren, & Barton, 2004), it has not been studied in ADHD.

Motor planning is an executive function whereby individuals must prepare their response in advance and hold it online until the appropriate moment. Motor planning (also referred to as response preparation) has been studied in healthy controls using the predictive saccade task (e.g. Findlay, 1981; Gagnon, O’Driscoll, Petrides, & Pike, 2002; Smit & van Gisbergen, 1989). In this task, the timing and direction of a target’s movement are predictable. For example, a target might appear on the screen and jump between three locations in sequence (e.g., left, centre, right, centre, left, etc) at a fixed interval. After a few cycles, participants learn to predict the changes in target location and produce saccades in synchrony with target movement as opposed to reacting to it (i.e., waiting for the target to move and then generating the eye movement). This task is thought to tap motor planning because in order to release a saccade in synchrony with target movements, one must prepare the response in advance and hold it online until the target moves. Predictive saccades are identified based on latency criteria (i.e., time difference between target movement and saccade initiation), with predictive saccades having latencies < 100 ms, with the exact cut-off varying somewhat across studies.

Predictive saccades have been studied in known and putative frontal-subcortical disorders
(e.g. Bronstein & Kennard, 1985; Farber, Swerdlow, & Clementz, 1999; McDowell, Clementz, & Wixted, 1996; O’Sullivan, Shaunak, Henderson, Hawken, Crawford, & Kennard, 1997; Ventre, Zee, Papageorgiou, & Reich, 1992), however, only one study to date has investigated predictive saccades in ADHD (Feifel et al., 2004). This study found that adults with ADHD generated fewer predictive saccades than a control group. However, they also reported that ADHD participants generated on average shorter latency saccades making the findings difficult to interpret (Feifel et al., 2004).

To my knowledge, no study has used executive oculomotor tasks to investigate potential differences in the neurocognitive profile of the subtypes of ADHD. In previous eye movement studies of ADHD, investigators either included only participants with the Combined subtype (e.g., Castellanos, Marvasti, Ducharme, Walter, Israel, Krain, et al., 2000), or collapsed across subtypes (Aman et al., 1998; Feifel et al., 2004; Klein et al., 2003; Mostofsky et al., 2001a; 2001b; Munoz et al., 1999; 2003; Ross, Harris, Olincy, & Radant, 2000; Rothlind et al., 1991). Thus differences between the subtypes could not be addressed.

1.3 Neuroanatomical Substrates of ADHD

1.3.1 Frontal-Subcortical Circuitry

Similarities between the hyperkinetic reaction of childhood and frontal lobe symptoms initially led to the hypothesis of frontal involvement in this disorder (Levin, 1938). Subsequent refinement of our understanding of the role of frontal lobe in cognitive functions has strengthened that hypothesis, while development of
understanding of the connectivity of frontal lobe (Alexander & Crutcher, 1990; 
Middleton & Strick, 1997; Schmahmann, 1997) led this hypothesis to be called the 
frontal-striatal hypothesis, and with evidence of cerebellar involvement in ADHD, the 
frontal-subcortical or frontal-striatal-cerebellar hypothesis (Mostofsky, Reiss, Lockhart, 

Frontal-subcortical circuitry has been shown to be critically implicated in 
executive functions and executive eye movement tasks, including the antisaccade task. 
Electrophysiological studies of non-human primates, and neuroimaging studies in 
humans show activation of frontal and striatal regions during normal performance (e.g., 
Everling & Munoz, 2000; Funahashi, Bruce, & Goldman-Rakic, 1991; Gagnon et al, 
2002; Hikosaka, Sakamoto, & Usui, 1989; O’Driscoll et al, 1995; O’Driscoll, Wolff, 
Benkelfat, Florencio, Lal, & Evans, 2000; Sweeney et al., 1996), and lesion data in both 
populations show impairment after damage to frontal and striatal regions (Funahashi, 
Bruce, & Goldman-Rakic, 1993; Guittton et al., 1985; Keating, 1991; Pierrot-Deseilligny, 
Rivaud, Gaymard, & Agid, 1991; Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, 
& Rivau Pechoux, 2003; Rivaud, Muri, Gaymard, Vermersch, & Pierrot-Deseilligny, 
1994).

Structural imaging studies have consistently implicated abnormalities in frontal- 
subcortical circuitry in ADHD (for reviews see Castellanos, 1997; Durston, 2003; 
Seidman et al, 2005). In frontal lobe, several studies have reported decreased volumes in 
dorsolateral prefrontal cortex (DLPFC) (Castellanos, Giedd, Marsh, Hamburger, Vaituzis, 
Dickstein, et al., 1996; Castellanos, Giedd, Berquin, Walter, Sharp, Tran, et al., 2001; 
Castellanos, Lee, Sharp, Jeffries, Greenstein, Clasen, et al., 2002; Durston, Hulshoff Pol,
Schnack, Buitelaar, Steenhuis, Minderaa, et al., 2004; Filipek, Semrud-Clikeman, Steingrad, Kennedy, & Biederman, 1997; Hill, Campbell, Hart, Yeo, Vigil, & Brooks, 2003; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Kates, Frederikse, Mostofsky, Folley, Cooper, Mazur-Hopkins, et al., 2002; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). Recently, decreased volume in premotor cortex has also been reported (Mostofsky et al., 2002; Ranta, Crocetti, Clauss, Kraut, Mostofsky, & Kaufmann, 2009; Shaw, Lerch, Greenstein, Sharp, Clasen, Evans, et al., 2006). Premotor cortex, in frontal lobe, is the location of frontal eye fields (FEFs) (Paus, 1996), the executive portion of the oculomotor circuit. FEFs have been implicated in oculomotor inhibition (e.g., Hanes & Schall, 1996; Schall, 2004; Sumner, Edden, Bompas, Evans, & Singh, 2010) and antisaccade performance (O’Driscoll et al., 1995; Everling & Munoz, 2000).

The striatum is hypothesized to be involved in the etiology of ADHD (Lou, 1996). In animal models, striatal lesions have been reported to result in motor hyperactivity (e.g., Isaacs, Brundin, Kelly, Gage, & Bjorklund, 1984; Mason & Fibiger, 1979) as well as deficits in inhibitory function (e.g., Kodsi & Swerdlow, 1997) and working memory (e.g., Levy et al, 1997), all of which are also observed in ADHD. Volumetric reductions in striatum is one of the most robust findings in ADHD (Castellanos, Giedd, Eckburg, Marsh, Vaituzis, Kaysen, et al., 1994; Castellanos et al., 1996; 2001; 2002; Castellanos, Sharp, Gottesman, Greenstein, Giedd, & Rapoport, 2003; Filipek et al, 1997; Hynd, Hern, Novey, Eliopulos, Marshall, Gonzalez, & Voeller, 1993; Mataro, Garcia-Sanchez, Junque, Estevez-Gonzalez, & Pujol, 1997; Semrud-Clikeman, Filipek, Biederman, Steingard, Kennedy, Renshaw, & Bekken, 1994).
In cerebellum, volumetric reductions in ADHD have also been reported. These include cerebellar reductions in the hemisphere (Mackie, Shaw, Lenroot, Pierson, Greenstein, Nugent et al, 2007) and the vermis (Berquin, Giedd, Jacobsen, Hamburger, Krain, Rapoport, & Castellanos, 1998; Bussing, Grudnik, Mason, Wasiak, & Leonard, 2002; Castellanos et al., 1996; 2001; Hill et al., 2003; Mostofsky et al., 1998). The cerebellum is thought to be primarily involved in motor control although there is now increasing evidence implicating cerebellum in cognitive functions (Desmond & Fiez, 1998; Schmahmann & Sherman, 1998). Further, neuroimaging studies have shown prefrontal-cerebellar connections (Middleton & Strick, 2001) providing additional support for the role of cerebellum in cognitive functions. Thus it is increasingly hypothesized that cerebellar regions play a role in executive function deficits in ADHD (Durston, 2003).

Neuroimaging studies of response inhibition have also implicated frontal-subcortical networks in ADHD. Decreased frontal activation has been reported in ADHD during inhibition tasks from the Stroop (Bush, Frazier, Rauch, Seidman, Whalen, Jenike, et al., 1999; Zang, Jin, Weng, Zhang, Zeng, Yang, et al., 2005), to the stop-signal task (Pliszka, Glahn, Semrun-Clikeman, Franklin, Perez III, Xiong, et al., 2006; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, et al., 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Rubia, Halari, Smith, Mohammed, Scott, Giampietro, et al., 2008) and go/no-go task (Booth, Burman, Meyer, Lei, Trommer, Davenport, et al., 2005; Durston, Tottenham, Thomas, Davidson, Eigsti, Yang, et al., 2003; Durston, Davidson, Mulder, Spicer, Galvan, Tottenham, et al., 2007; Suskauer, Simmonds, Fotedar, Blankner, Pekar, Denckla, & Mostofsky, 2008; Tamm, Menon, Ringel, & Reiss, 2004).
Similarly, striatal hypoactivation during inhibition tasks has been reported consistently (Booth et al, 2005; Durston et al., 2003; Rubia et al., 1999; Rubia, Taylor, Smith, Oksannen, Overmeyer, & Newman, 2001; Teicher, Anderson, Polcari, Glod, Maas, & Renshaw, 2000; Vaidya, Austin, Kirkorian, Ridlehuber, Desmond, Glover, & Gabrieli, 1998; Zang et al., 2005) and a few studies have reported decreased activation in cerebellum (Durston et al., 2007; Suskauer et al., 2008; Zang et al., 2005).

Given the differential involvement of motor symptoms in the two subtypes and the centrality of striatum to motor functions, one might hypothesize greater involvement of frontal-striatal circuitry in the Combined subtype. To date, there has been only one study investigating the neural substrates of subtypes of ADHD using fMRI (Solanto, Schulz, Fan, Tang, & Newcorn, 2009). This study compared activation in ADHD-Is and ADHD-Cs on the go/nogo task, a measure of inhibition. They found that ADHD-Cs had lower activations than ADHD-Is in middle frontal gyrus and inferior parietal lobe. However, this study did not include a control group; thus differences between the subtypes that were found could not be interpreted in relation to a normal standard.

1.3.2 Parietal Lobe

In recent years, there has been increasing interest in the role of neural circuits other than frontal-subcortical circuit in the pathology of ADHD (Cherkasova & Hechtman, 2009; Stefanatos & Wasserstein, 2001). Given that parietal regions are involved in visual attention processes and orienting (Posner, Walker, Friedrich, & Rafal, 1984; Lewin, Friedman, Wu, Miller, Thompson, Klein, et al., 1996) parietal dysfunction has been hypothesized to play a role in ADHD. Deficits on parietal tasks have been
reported in ADHD, including on tests of attention shifting (e.g., Koschack, Kunert, Derichs, Weniger, & Irle, 2003; Tamm, Menon, & Reiss, 2006) and spatial relations (Aman et al., 1998).

Neuroimaging studies have yielded evidence of parietal abnormalities in ADHD. Decreased total parietal volume (Castellanos et al., 2002; Filipek et al., 1997; Wang, Jiang, Cao, & Wang, 2007), decreased grey (Carmona, Vilarroya, Bielsa, Tremols, Soliva, Rovira, et al., 2005; Hynd et al, 1990; McAlonan, Cheung, Cheung, Chua, Murphy, Suckling, et al., 2007) and white matter volume (McAlonan et al., 2007) and decreased cortical thickness (Makris, Biederman, Valera, Bush, Kaiser, Kennedy, et al., 2007; Shaw, Eckstrand, Sharp, Blumenthal, Lerch, Greenstein, et al., 2007) of parietal areas have all been reported. Further, decreased parietal activation in ADHD has been found in functional imaging studies of response inhibition (Rubia et al., 2005; 2008), interference control (Vaidya, Bunge, Dudukovic, Zalecki, Elliott, & Gabrieli, 2005) and task-switching (Smith, Taylor, Brammer, Toone, Rubia, 2006). However, increased parietal activation during inhibition has also been reported (Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Epstein, Casey, Tonev, Davidson, Reiss, Garrett, et al., 2007). The inconsistencies in the direction of findings may be related to the multiple roles of parietal lobe. For example, recent research has suggested ventromedial parietal cortex involvement in “default-mode” or resting-state activity (Broyd, Demanuele, Deben, Helps, James, & Sonuga-Barke, 2009; Castellanos, Margulies, Kelly, Uddin, Ghaffari, Kirsch, et al., 2008). Default mode regions are thought to be involved in internally focused thought. Thus activity in these regions is suppressed during performance of externally focused goal-directed tasks. Increased activation in the medial
parietal cortex (posterior cingulate/precuneus) during task performance is thought to be a neural correlate of mind-wandering (Gilbert, Dumontheil, Simons, Firth, & Burgess, 2007), and has been reported to be elevated in ADHD (Fassbender, Zhang, Buzy, Cortes, Mizuiri, Beckett, & Schweitzer, 2009; Liddle, Hollis, Batty, Groom, Totman, Liotti, Scerif, & Liddle, 2010).

1.4 Neurochemical substrates of ADHD

It has long been hypothesized that ADHD is associated with neurochemical imbalances (Wender, 1971). The research on the neurochemical substrates of ADHD has yielded evidence implicating different neurotransmitters (Gonon, 2008; Pliszka, McCracken, & Maas, 1996; Zametkin & Rapoport, 1987), with no single neurotransmitter system likely to account for all of the impairments observed (Faraone & Biederman, 1998). Current neurochemical hypotheses focus primarily on the catecholamines (i.e., dopamine and norepinephrine) (Levy, 2009), with the dopamine hypothesis of ADHD receiving the most attention (e.g., Gonon, 2008).

In its simplest form, the dopamine hypothesis of ADHD suggests that the disorder is associated with excess clearance of dopamine from the synapse resulting in a hypodopaminergic state. Evidence supporting this hypothesis includes the following: 1) striatal dopamine transporter density is increased in ADHD (Dougherty, Bonab, Spencer, Rauch, Madras, & Fischman, 1999; Dresel, Krause, Krause, LaFourgere, Brinkbaumer, Kung, et al., 2000; Krause, Dresel, Krause, Kung, & Tatsch, 2000; Spencer, Biederman, Madras, Faraone, Dougherty, Bonab, & Fischman, 2005; Volkow, Wang, Fowler, Logan, Gerasimov, Maynard, et al., 2001) which is consistent with reduced synaptic dopamine
levels; 2) in animal models, destruction of dopamine neurons can produce significant
motor hyperactivity (e.g., Isacson et al., 1984; Koob, Stinus, & Le Moal, 1981; Mason &
Fibiger, 1979; Miller, Heffner, Kotake, & Seiden, 1981); and 3) stimulant medications,
an effective treatment of ADHD, decrease dopamine transporter availability and increase
extracellular dopamine levels (e.g. Dresel et al., 2000; Krause et al., 2000; Seeman &
Madras, 1998; Volkow et al., 2001).

1.5 Pharmacological Treatment of ADHD

The stimulant methylphenidate (Ritalin) is commonly prescribed in the treatment
of ADHD (Conners, 2002). It has been shown to improve attention as measured by
questionnaires and cognitive tasks (e.g., Greenhill, Swanson, Vitiello, Davies, Clevenger,
Wu, et al., 2001; Kempton, Vance, Maruff, Luk, Costin, & Pantelis, 1999; Losier,
McGrath, & Klein, 1996) and to reduce motor hyperactivity as measured by
questionnaire and truncal actometer (e.g., Greenhill, Swanson, Vitiello, Davies,
Clevenger, Wu et al, 2001; Porrino, Rapoport, Behar, Ismond, & Bunney, 1983).
Methylphenidate improves cognitive functioning in ADHD and in healthy controls,
particularly in tests of response inhibition, attention and working memory (Pietrzak,
Mollica, Maruff, & Snyder, 2006). Methylphenidate’s therapeutic action is thought to be
associated with its dopamine agonist effect (e.g., Castellanos, 1997).

Pharmacological manipulations of dopamine impact oculomotor measures of
disinhibition (Allman, Benkelfat, Durand, Sibon, Dagher, Leyton, et al., 2010; Reilly,
Lencer, Bishop, Keedy, & Sweeney, 2008). For example, nicotine and d-amphetamine
which increase synaptic dopamine have been reported to decrease antisaccade errors in
Controls (Allman et al, 2010; Dépatie, O’Driscoll, Holahan, Atkinson, Thavundayil, Ng Ying Kin, & Lal, 2002; Larrison, Briand, & Sereno, 2004; Powell, Dawkins, & Davis, 2002; Rycroft, Hutton, & Rusted, 2006). Methylphenidate’s effects on antisaccade performance in Controls have not been studied. However, methylphenidate effects on antisaccades have been reported in ADHD (e.g. Aman et al., 1998; Klein, Fischer, Fischer, & Hartnegg, 2002; Mostofsky et al., 2001a; Munoz et al., 1999). Results have been conflicting with differences likely attributable to methodological confounds including for example naturalistic assignment to medication, fixed drug/placebo order and lack of placebo control. No study involved a double-blind, placebo-controlled comparison. In terms of subtypes of ADHD, only one study has investigated methylphenidate’s effects on executive functions in the different subtypes of ADHD (Barkley, DuPaul, & McMurray, 1991) and no study has investigated methylphenidate effects on eye movements in subtypes of ADHD.

1.6 Course of ADHD

The issue of whether ADHD persists into adulthood continues to be debated (Barkley, 1997; Faraone, 2000; Faraone, Biederman, Spencer, Wilens, Seidman, Mick, & Doyle, 2000; Hill & Schoener, 1996; Shaffer, 1994). Some have argued that ADHD is a disorder of childhood, since symptoms of ADHD decline significantly during adolescence and persistence rates for meeting the full clinical criteria fall to 15% by age 25 years (for review see Faraone, Biederman, & Mick, 2006). On the other hand, ADHD is found in adulthood and some researchers have reported persistence in the majority of participants followed longitudinally (e.g., Barkley, Fischer, Smallish, & Fletcher, 2002;
An issue in longitudinal research is how persistence is defined (Barkley et al., 2002; Biederman, Mick, & Faraone, 2000; Faraone et al., 2006). Some studies look for syndromatic persistence, i.e. maintenance of full diagnostic status, and other for symptomatic persistence, i.e. maintenance of partial diagnostic status with functional impairments (Keck, McElroy, Strakowski, West, Sax, Hawkins, et al., 1998). When cases meeting DSM-IV criteria for ADHD in partial remission are included, persistence rates are reported to be between 40 and 60% (Faraone et al., 2006).

There is clear evidence for the waning of ADHD symptoms with development (e.g., Faraone et al., 2006). If the improvements in the clinical presentation of the disorder reflect maturation of frontal-subcortical circuitry, then one might expect deficits in executive functioning also to decrease with age. Cross-sectional studies of adult ADHD have reported deficits in executive functioning (for review see Boonstra et al., 2005; Woods et al., 2002) indicating that maturational improvements have not meant the resolution of cognitive symptoms. However, participants in these cross-sectional studies of adults may represent the severe end of the diagnostic spectrum given that many people diagnosed in childhood achieve full to partial remission. Few longitudinal studies to date have investigated the course of executive functioning in late adolescence or early adulthood in ADHD (Biederman, Petty, Fried, Boyle, Spencer, Seidman, et al., 2007; Biederman, Petty, Doyle, Spencer, Henderson, Marion, et al., 2008; Fischer, Barkley, Smallish, & Fletcher, 2005; Hinshaw, Carte, Fan, Jassy, & Owens, 2007; Hopkins, Perlman, Hechtman, & Weiss, 1979). Only one of these studies took subtypes into account (Hinshaw et al., 2007) and that study focused exclusively on girls, who represent
a small minority of individuals diagnosed with ADHD.

1.7 Present Dissertation

My primary goal in conducting the research described in the subsequent chapters was to clarify whether the Inattentive and Combined subtypes should be considered as two distinct disorders or subtypes of the same disorder, based on their similarities and differences in a number of domains. I was particularly interested in the following questions: 1) do the subtypes have similar or distinct executive functioning profiles?; 2) does methylphenidate affect executive functioning of both subtypes similarly?; 3) do the subtypes exhibit similar or distinct longitudinal course in their executive functioning?; and 4) do the subtypes share similar or distinct underlying neural substrates? Although a definitive conclusion would require a high degree of consistency in the answers to these questions, as well as replication, the goal here was to gather evidence that would inform the correct conceptualization of the disorder.
Chapter Two: Executive Functions in Subtypes of ADHD

Executive Eye Movements In Subtypes Of ADHD

Experiment 1


2.1 ABSTRACT:

**Background:** Children with Attention-deficit/hyperactivity disorder (ADHD) have deficits in executive functions, deficits that are thought to tap frontal-striatal circuitry. Oculomotor tasks are a well-established means of studying executive functions and frontal-striatal functioning in both nonhuman primates and humans. There is on-going controversy as to whether the different subtypes of ADHD constitute a single disorder or whether the different clinical presentations reflect important differences in pathophysiology (Barkley, 2001; Hinshaw, 2001; Lahey, 2001; Milich, Balentine, & Lynam, 2001; Pelham, 2001). We assessed executive functions in the two most common subtypes of ADHD using established oculomotor tests. Performance differences between the subtypes would suggest differential involvement of frontal-striatal circuitry.

**Methods:** Participants were 32 boys, aged 11.5–13.9 years, divided into three groups, ADHD-Combined (n = 10), ADHD-Inattentive (n = 12), and Controls (n = 10). Executive functions assessed were response inhibition (tapped with antisaccades), task-switching (antisaccade-prosaccade mixed) and motor planning (predictive saccades).

**Results:** The ADHD-Combined boys were impaired relative to Controls in response inhibition (p < .007) and motor planning (p < .003) but not task-switching (p > .92). Compared to the ADHD-Inattentive group, the ADHD-Combined group had more participants with antisaccade performance in the impaired range (p < .04) and made fewer predictive saccades (p < .03).

**Conclusions:** ADHD-Combined but not ADHD-Inattentive boys showed impairments on response inhibition and motor planning. These deficits are consistent with involvement of frontal-striatal circuitry. Their absence in the Inattentive group suggests that the
Combined subtype involves distinct or additional neural structures that are spared in the Inattentive subtype.
2.2 INTRODUCTION:

Attention-deficit hyperactivity disorder (ADHD) has been divided into subtypes, with the most commonly occurring being ADHD-Combined (ADHD-C; inattention and hyperactivity/impulsivity) and ADHD-Inattentive (ADHD-I; inattention only) (American Psychiatric Association, 1994). Symptoms of ADHD have been attributed to deficits in frontal–striatal pathways, which underlie executive functions.

Executive functions are capacities that allow one to generate voluntary behaviours that are controlled and actively guided (Slattery, Garvey, & Swedo, 2001). The inattention and hyperactivity/impulsivity observed in ADHD suggest deficits in the voluntary control of behaviour. It is not clear, however, whether impairments exist across executive functions or whether specific functions are implicated. For example, Barkley (1997) proposed a model of ADHD in which disinhibition is the core deficit, whereas others have proposed more generalized deficits in self-regulation (Douglas, 1999).

It is also not clear to what extent deficits occur across subtypes. The few studies of subtype differences in executive functions are divided as to whether the ADHD-C group specifically is impaired (e.g., Barkley, 1997; Houghton, Douglas, West, Whiting, Wall, Langsford, et al., 1999; Klorman, Hazel-Fernandez, Shaywitz, Fletcher, Marchione, Holahan, et al., 1999; Lockwood, Marcotte, & Stern, 2001; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002) or whether both subtypes show deficits (Chhabildas, Pennington, & Willcutt, 2001; Murphy, Barkley, & Bush, 2001; Scheres, Oosterlaan, Geurts, Morein-Zamir, Meiran, Schut, et al., 2004). A number of methodological shortcomings found across these studies, including lack of matched control tasks,
inclusion of comorbid disorders and lack of matching on age or intelligence quotient (IQ) between groups, cloud the interpretation of the results.

Eye movement tasks are a well-established means to investigate executive functions in nonhuman primates and humans. These tasks have several advantages over neuropsychological tasks. First, eye movements depend on structures implicated in attention and in motor control (Corbetta, Akbudak, Conturo, Snyder, Ollinger, Drury, et al., 1998; Gitelman, Nobre, Parrish, LaBar, Kim, Meyer, & Mesulam, 1999; Schall, 2004), both criterial areas of dysfunction in ADHD. Second, the instructions are simple, so deficits cannot be attributed to failure of comprehension. Third, control tasks exist that are matched on all variables except the executive function of interest. Fourth, the neural substrates have been well established in both nonhuman primates and humans (e.g., Everling & Munoz, 2000; Funahashi, Bruce, & Goldman-Rakic, 1991; Gagnon, O’Driscoll, Petrides, & Pike, 2002; Hikosaka, 1989; O’Driscoll, Alpert, Matthysse, Levy, Rauch, & Holzman, 1995; 2000; Sweeney, Mintun, Kwee, Wiseman, Brown, Rosenberg, & Carl, 1996). Finally, the tasks depend on frontal-striatal circuits (e.g., Funahashi, Bruce, & Goldman-Rakic, 1993; Guitton, Buchtel, & Douglas, 1985; Keating, 1991; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, & Rivaud-Pechoux, 2003; Rivaud, Muri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994), the same circuits implicated in imaging studies of ADHD (e.g., Castellanos, Giedd, Marsh, Hamburger, Vaituzis, Dickstein, et al., 1996).

In the present study, our goal was to use oculomotor tasks to evaluate the executive functions of response inhibition, task-switching and motor planning in subtypes of ADHD. The antisaccade task (Aman, Roberts, & Pennington, 1998; Feifel, Farber,
Clementz, Perry, & Anllo-Vento, 2004; Klein, Raschke, & Brandenbusch, 2003; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001a; Mostofsky, Lasker, Singer, Denckla, & Zee, 2001b; Munoz, Hampton, Moore, & Goldring, 1999; Munoz, Armstrong, Hampton, & Moore, 2003; Rothlind, Posner, & Schaugency, 1991) and a memory-guided saccade task that involves delaying a saccade (Castellanos, Marvasti, Ducharme, Walter, Israel, Krain, et al., 2000; Mostofsky et al., 2001b; Ross & Radant, 1994; Ross, Harris, Olincy, & Radant, 2000) have been used previously to investigate inhibitory function in several studies of ADHD. Most reported significant deficits (Castellanos et al., 2000; Feifel et al., 2004; Klein et al., 2003; Mostofsky et al., 2001a, 2001b; Munoz et al., 1999, 2003; Ross & Radant, 1994; Ross, Harris, Olincy, & Radant, 2000), but none of these studies compared subtypes.

Task-switching or response flexibility has been argued to play a role in ADHD deficits in some neuropsychological tasks (Pennington & Ozonoff 1996; Seidman, Biederman, Faraone, Milberger, Norman, Seiverd, et al., 1995); however, this function has not been investigated in ADHD with eye movements nor has it been compared across subtypes.

Motor planning or response preparation has been examined in one study of the predictive saccade task (Feifel et al., 2004); however, conclusions regarding the integrity of this function were difficult to draw because ADHD adults were found to have a reduced number of predictive saccades but shorter latencies. Nonetheless, skeletomotor studies have suggested that ADHD children have difficulty with preplanning motor acts and controlling their temporal onset (e.g., Rubia, Taylor, & Taylor, 1999; Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003).
The present study is the first to use oculomotor tests of executive function to evaluate subtype differences. It constitutes an advance over previous neuropsychological research on subtypes by providing well-designed control tasks for the measures of executive function (thus isolating the functions of interest), and by evaluating groups that are essentially free of comorbid disorders and are similar in age, socioeconomic status, and IQ.

We hypothesized that the ADHD-C group would have greater baseline deficits in executive functions because their abnormalities in motor control (e.g., excessive movement, disinhibition) suggest greater involvement of frontal-striatal circuitry.

2.3 METHODS AND MATERIALS:

2.3.1 Participants

Controls (n = 10), ADHD-I (n = 12) and ADHD-C (n = 10) participants were enrolled in the study. Inclusion criteria for all participants were an estimated full-scale IQ above 85 (Wechsler, 1991) and visual acuity (corrected) of at least 20/40. All participants were between 11.5 and 13.9 years old. We chose this window because previous developmental studies (Fischer, Biscaldi, & Gezeck, 1997; Klein & Foerster, 2001; Malone & Iacono, 2002; Munoz, Broughton, Goldring, & Armstrong, 1998; Munoz et al., 2003; Ross & Radant, 1994) and our own piloting showed that normally developing boys below the age of 11 years had significant difficulty with oculomotor inhibition. We set the upper age limit at 14 years because we wanted ADHD-C subjects who met full DSM-IV criteria, and longitudinal studies of ADHD suggest that hyperactivity declines during adolescence (Gittelman, Mannuzza, Shenker, & Bonagura,
ADHD patients were recruited from the Montreal Children’s Hospital, Montréal, Québec, the Douglas Hospital, Verdun, Québec and by referrals from family physicians and pediatricians. Because far more boys are referred for ADHD than girls (APA, 1994) and our referral sources see almost exclusively boys, only boys were included. Control boys were recruited by advertisement in local newspapers and by word-of-mouth.

To meet diagnostic inclusion criteria, ADHD boys had to meet criteria for the disorder in at least two settings and by two independent raters. Criteria were assessed using several measures: the Parent Behavioural Checklist and the Teacher Behavioural Checklist which included the abbreviated Connors’ Parent and Teacher Rating Scales - Revised (Goyette, Conners, & Ulrich, 1978) and items from the Child Symptom Inventory-4 Rating Scale (CSI-4) (Gadow & Sprafkin, 1994; 1998); the Diagnostic Interview Schedule for Children-Revised (DISC-IV) (Shaffer, Schwab-Stone, Fisher, & Cohen, 1993); previous diagnostic assessments by a psychologist or psychiatrist, and; blinded ratings of their behaviour in the laboratory. On the checklists, boys in the ADHD-C group had to obtain a score above the 1.5 criterion on both the Inattention and Hyperactivity/Impulsivity dimensions of the CSI-4 (Gadow & Sprafkin, 1994; 1998). Boys in the ADHD-I group had to have a score above the 1.5 criterion on the Inattention dimension but not the Hyperactivity/Impulsivity dimension and boys in the Control group had to have a score below the 1.5 criterion on both dimensions (Gadow & Sprafkin, 1994; 1998).
The three groups did not differ in terms of demographic characteristics. However, as expected, the three groups did differ in terms of clinical symptoms of ADHD (Table 2.1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Subjects (n = 10)</th>
<th>ADHD-I (n = 12)</th>
<th>ADHD-C (n = 10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.66 ± .58</td>
<td>12.74 ± .60</td>
<td>12.38 ± .57</td>
<td>0.29</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>110 ± 10.9</td>
<td>108.54 ± 10.7</td>
<td>108.15 ± 8.7</td>
<td>0.92</td>
</tr>
<tr>
<td>Father's SES¹</td>
<td>3.0 ± 2.3</td>
<td>4.0 ± 1.5</td>
<td>3.2 ± 1.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Reading Performance Woodcock (%)</td>
<td>63.89 ± 8.47</td>
<td>63.48 ± 13.46</td>
<td>54.03 ± 21.92</td>
<td>0.59</td>
</tr>
<tr>
<td>Currently Prescribed MPH (n)</td>
<td>10</td>
<td>10</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>DSM-IV Symptoms² Inattention</td>
<td>.29 ± .25</td>
<td>2.03 ± .34</td>
<td>2.18 ± .30</td>
<td>0.001</td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>.08 ± .17</td>
<td>.85 ± .41</td>
<td>1.73 ± .56</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n. Data were analyzed by one-way analysis of variance. ADHD-C, Attention Deficit Hyperactivity Disorder-Combined type; ADHD-I, ADHD-Inattentive; IQ, intelligence quotient; MPH, methylphenidate.

¹SES, socioeconomic status; father's occupation ranked on an ordinal scale from 1 (major professional) to 9 (unemployed), from a modified version of the Index of Social Status (Hollingshead and Redlich, 1958).

²Parent ratings of their child's symptoms on the Inattention and Hyperactivity-Impulsivity scales of the Child Symptom Inventory-4 Rating Scale (Gadow & Sprafkin, 1994, 1998). A score of 1.5 and above is considered clinically significant.

ADHD boys were excluded from participating if they had comorbid disorders as assessed using the CSI-4 (Gadow & Sprafkin, 1994; 1998) and the DISC-IV (Shaffer et al., 1993), with the exception that ADHD boys with Oppositional Defiant Disorder (ODD) were not excluded because ODD is highly comorbid with ADHD (Anderson, Williams, McGee, & Silva, 1987; Bird, Gould, & Staghezza, 1993). In addition, one ADHD-I boy and one ADHD-C boy met the minimum criteria for Generalized Anxiety Disorder (GAD); in both cases, ADHD predated GAD, ADHD scores were greater than GAD scores, and GAD was considered secondary to academic difficulties resulting
from ADHD. Therefore, these boys were not excluded. Control boys were required to have no psychopathology as assessed using the abbreviated Connors’ Parent Rating Scale - Revised (Goyette et al., 1978), the CSI-4 (Gadow and Sprafkin, 1994; 1998) and the DISC-IV (Shaffer et al., 1993).

Subjects with a reading disorder (RD) were excluded from the study. This was done because reading disorder is associated with abnormalities in oculomotor control (Biscaldi, Fischer, & Hartnegg, 2000; Fischer & Weber, 1990) that could obscure the interpretation of the oculomotor results. Reading level was assessed in native English speakers with the Woodcock Reading Mastery Tests (English) (Woodcock, 1987). Boys had to score above the 20\textsuperscript{th} percentile based on the average of the Word Identification and Passage Comprehension subtests of this test. For French-speaking boys (n= 10), no standardized reading test of Québec French was available; thus, boys were excluded if any reading difficulty was suggested in psychiatric or educational assessments or reported by the parents.

The study was approved by the Department of Psychology Ethics Review Board at McGill University, Montréal, Québec, the Montréal Children’s Hospital Institutional Review Board, Montréal, Québec, and the Douglas Hospital Research Ethics Board, Verdun, Québec. After a detailed description of the study, a parent gave written informed consent and the child gave written assent to participate in the study. Subjects were compensated for their time and inconvenience.
2.3.2 Procedures

The participants’ performance on a battery of executive eye movement tasks was compared in order to assess whether different subtypes of ADHD were impaired in executive functioning and whether the two subtypes differed from each other. Testing occurred between 10:00 am and 1:00 pm. ADHD boys who were regularly taking medication (all boys who were taking medication were prescribed methylphenidate) for the treatment of the disorder were asked not to take their medication for a minimum of 24 hours before testing. Due to the short half-life of methylphenidate, this was considered to be a sufficient time to ensure washout (Canadian Pharmaceutical Association, 1999).

2.3.3 Apparatus

For all tasks, the stimulus was a square (.5° x .5°) presented against a black background. For the blocked antisaccade and blocked prosaccade tasks, the square was red for half of the participants and green for the other half of the participants with colour counterbalanced across subjects. Oculomotor data were recorded in a darkened room with subjects seated 57 cm from the computer monitor. The tasks were administered using a 100 mega hertz IBM clone computer (monitor refresh rate = 120.79 Hz). An infrared pupil tracker (250 Hz) mounted on a headband (Eyelink, SR Research Ltd., Mississauga, ON, Canada) was used to record eye movements. All eye movements were recorded from the subjects’ dominant eye. The spatial resolution of the system used is 0.25° of visual angle. A three-point calibration was performed across 24° of visual angle. Calibration was repeated until the fixation error on validation was less than 0.5°. The system makes an automatic drift correction prior to each trial. The tests were
administered by two experimenters, one operating the eye movement system, the other explaining the tasks and encouraging on-task behaviour (e.g., telling the participant how many trials remained, repeating instructions after three consecutive errors, illuminating the room for breaks as necessary, etc.). These measures were taken to ensure that any deficits in performance were sufficiently robust that they would be detected even in an optimal testing situation.

2.3.4 Tasks

Response Inhibition (Antisaccade Task):

The target was presented at the center of the screen for a variable interval (1000, 1200 or 1400 ms). It then stepped from the center of the screen to either left or right (± 11 degrees). The direction of movement was random with the restriction that the stimulus could not appear on the same side on more than 3 consecutive trials. Participants were instructed not to look at the peripheral stimulus when it appeared but rather to direct their gaze to the mirror position on the opposite side of the computer screen. Forty-eight trials were presented, preceded by 9 trials of practice with feedback. This task taps inhibitory functions because participants have to withheld the natural tendency to look toward the peripheral target before generating the antisaccade (Figure 2.1).
**Figure 2.1. Antisaccade Task**

Schematic of the sequence of events in the antisaccade task. The stimulus (square) is not to scale. The yellow arrow indicates the direction of a correct antisaccade on this trial.

**Task-Switching (Antisaccade-Prosaccade Mixed Tasks):**

On the antisaccade-prosaccade mixed task, participants performed either a (pro)saccade (i.e. toward the peripheral target) or an antisaccade (away from the target) depending on the colour of the central fixation point. Half of the subjects were instructed to perform antisaccades whenever the fixation point was red and half whenever the fixation point was green (Figure 2.2). Forty-eight trials were presented in the antisaccade-prosaccade mixed task after 15 practice trials with feedback.

Task-switching tasks like this tap “the control processes that reconfigure mental resources for a change of task” (Monsell, 2003, p. 134), with the critical variable being switch cost—“the amount by which performance degrades when the system has to
perform a different task on the current trial than it did on the previous trial” (Altmann, 2004, p. 616). This task also taps response inhibition because on half of the trials (antisaccade trials), the subjects have to withhold the tendency to look toward the peripheral target.

In both the antisaccade and antisaccade-prosaccade mixed tasks, the subjects were required to perform at least three antisaccades correctly in the practice trials. If this was not done, the number of practice trials was extended until the third correct antisaccade was accomplished (practice was extended for one ADHD-C subject on the antisaccade task and for four subjects on the mixed task (three ADHD-I and one ADHD-C participants).
Figure 2.2. Antisaccade-Prosaccade Mixed Task

Schematic of the sequence of events in the antisaccade-prosaccade task. The stimuli (red and green squares) are not to scale. The yellow arrow indicates the direction of a correct antisaccade on the first trial (red square) and the direction of a correct prosaccade on the second trial (green square).

Motor Planning (“Totally-Predictable Task” and “Direction-Predictable Task”):

In the Totally-Predictable Task (TPT), the target stepped in a repeating sequence from the center to 11 degrees to the right, to the center, to 11 degrees to the left, and back again. The target remained at each location for 600 ms. Thus both the timing and the direction of the target movement were predictable (Figure 2.3). When exposed to this
type of stimulus, healthy Controls rapidly begin to move their eyes in synchrony with the target (e.g. Gagnon et al., 2002). To do this, they must prepare the saccades in advance of the target movement.

**Figure 2.3. Totally-Predictable Saccade Task**

Schematic of the sequence of events in the Totally-Predictable Task (TPT). The stimulus (red square) is not to scale. The yellow arrow indicates the direction of eye movements as the target steps in predictable fashion.

In the Direction-Predictable Task (DPT), the target stepped in a repeating sequence from the center to 11 degrees to the right, to the center, to 11 degrees to the left and back again. However, the timing of the target movement was randomized between 500 and 2000 ms (Figure 2.4). Thus, in this task the direction and amplitude of each target movement was known in advance while the moment the target would move was not. This task taps motor planning less than the TPT because subjects don’t know when they will be required to move their eyes, and thus generally wait for the target to move rather than preparing to move in advance (Gagnon et al., 2002).
In previous psychophysical work, we have shown that the percentage of predictive saccades is highest when the direction and timing of target movement is known, is intermediate when only direction is known and is absent when neither direction nor timing is known (Gagnon et al., 2002).

**Figure 2.4. Direction-Predictable Saccade Task**

Schematic of the sequence of events in the Direction-Predictive saccade task (i.e., while the direction of target movement was predictable, the timing was not). The stimulus (red square) is not to scale. The yellow arrow indicates the direction of eye movements as the target steps.

**Control Task (Prosaccade Task):**

Target movement in this task was identical to that in the antisaccade task; neither the direction nor timing of the target movement from center was predictable. Only the instructions differed between this task and the antisaccade task, as in this task participants were instructed to direct their gaze toward the peripheral target as soon as it appeared (Figure 2.5). Forty-eight trials were presented after 9 trials of practice with feedback.
This task is similar to the prosaccade task used in previous neuroimaging studies and psychophysical studies (McDowell & Clementz, 2001; O’Driscoll et al., 1995, Sereno & Holzman, 1995).

**Figure 2.5. Prosaccade Task**

Schematic of the sequence of events in the prosaccade task. The stimulus (red square) is not to scale. The yellow arrow indicates the direction of a correct prosaccade on this trial.

The order of task administration was randomized with the restriction that the subjects never performed the mixed task first. The order of presentation of the prosaccade and the antisaccade tasks was counterbalanced.
2.3.5 Analysis

Eye Movement Analysis

All eye movements were parsed quantitatively using a semi-automated custom analysis software package (SR Research, Mississauga, ON). The data were also visually inspected to ensure that artifacts were excluded and that automated data selection captured the response portion of the trace.

Within each trial, the first saccade greater than 3° with a minimum velocity of 22°/s and acceleration of 4000°/s² was identified. Trials were excluded from the analyses if the subject: 1) blinked in the 100 ms before the peripheral stimulus appeared or during the saccade, 2) was not fixating the central target (>2.5° off the fixation point) at the time of peripheral target presentation, 3) did not respond (saccade amplitude < 3 degrees), 4) generated an anticipatory response (latency less than 70 ms with the exception of the analyses of the predictive saccade task where latencies <70 ms were included and classified as predictive saccades) or 5) generated a saccade in the wrong direction (for antisaccade and antisaccade-prosaccade mixed tasks, direction errors were analyzed separately).

For each subject, values > 3 SD from the subject’s own mean were excluded as outliers. Less than 2.5% of the data were excluded for this reason.

Statistical Analyses

Because of the high inter-subject variability in ADHD and the potential for outliers to drive results in samples of this size, we approached the analyses in two ways.
In the first approach, we used winsorization to replace subject values greater than 3 SD from the mean of all subjects with the next highest value. This approach maintains the rank order of the subject on the variable but prevents extreme values from affecting the mean (Howell, 1987). In the second approach, we retained the outliers. Less than 1% of all values were outliers. We then compared the results of the two approaches to see to what extent outlier values were accounting for effects. The two approaches yielded essentially identical results, indicating that the results were not accounted for by subject outliers. Therefore, the results we report here are based on the original data.

Dependent variables were analyzed with mixed Analysis of Variance (ANOVAs), with direction as the within-subjects factor and Group as the between-subjects factor. When the direction term did not interact with Group, it was dropped from the analysis and data were pooled across direction. Significant effects in the ANOVAs were followed up with contrasts.

Response Inhibition and Task-Switching (Antisaccade, Antisaccade-Prosaccade Mixed Task)

The dependent variables were percent error (i.e. for the antisaccade trials, the proportion of trials on which the subject looked toward the peripheral stimulus) and saccade latency. Saccade peak velocity and amplitude were not analyzed since subjects were not given specific instructions or feedback about the required amplitude of response.

In the antisaccade task, the data were analyzed with one-way ANOVAs with Group as the between-subjects variable.
For the antisaccade-prosaccade mixed task, the data were analyzed using mixed ANOVAs with Group as the between-subjects variable and Task (antisaccade or prosaccade) and Switch (task on the current trial same/different from the task on the previous trial) as the within-subjects variables.

Motor Planning ( Totally-Predictable and Direction-Predictable Tasks )

For each target step, semi-automated software (SR Research, Mississauga, Ontario, Canada) selected a 600ms block of time centered on the moment at which the target changed position. Within this selection, the first saccade with amplitude >3 degrees in the direction of the target was selected. (If the initial saccade was in the wrong direction, no saccade was entered for that target step. In practice, direction errors were extremely rare.)

The percentage of predictive saccades ( latency <70ms ) (Smit & van Gisbergen, 1989) was analyzed using a mixed ANOVA with Task (TPT vs. DPT) and Direction as the within-subjects variables and Group as the between-subjects variable. Two-tailed t-tests were used to test for differences post hoc if the overall F of the ANOVA was significant. Saccade characteristics ( i.e., latency, amplitude and peak velocity) were analyzed with the addition of the within-subjects term Saccade Type (predictive vs. reflexive). Saccade Type was included as a term in the analysis because predictive and reflexive (or prosaccades) saccades have well-documented differences in saccade characteristics ( e.g. Gagnon et al., 2002).
Control Task (Prosaccade Task)

Dependent variables in the analysis were saccade latency, amplitude and peak velocity. Analyses were mixed ANOVAs with direction as the within-subjects factor and Group as the between-subjects factor.

Developmental Trends

It has recently been suggested that executive function deficits in ADHD may reflect a developmental delay (Durston, Tottenham, Thomas, Davidson, Eigsti, Yang, et al., 2003; Munoz et al., 2003). According to this hypothesis, executive functions come on-line later in ADHD individuals than in healthy control participants. In order to investigate this question, we evaluated the correlation between age and performance (using Pearson’s r) on variables in which ADHD and Control boys differed, with the hypothesis that ADHD boys would show weaker developmental trends than Controls. The magnitude of the relationship between age and performance in each group was compared across groups with Fisher’s z transformation (Rosenthal & Rosnow, 1984).

The alpha level for the analyses was set at 0.05. Data are reported as the means ± standard deviations.

2.4 RESULTS:

2.4.1 Response Inhibition (Antisaccade Task)

There was a significant main effect of Group on antisaccade percent error (F(2,29) = 4.30, p = .023). ADHD-C boys made more antisaccade errors than Control boys (t (29)
ADHD-I boys did not differ from Control boys \( (t(29) = -1.66, p = .107) \) or from ADHD-C boys \( (t(29) = -1.40, p = .173) \) (Figure 2.6). We compared the proportion of subjects with impaired motor inhibition based on the antisaccade task (percent error $>2$ SD above Control mean, meaning that participants with impaired performance had an error rate $>25\%$) across groups. No Control subjects, $16.7\%$ of ADHD-I subjects, and $60\%$ of ADHD-C subjects \( (\chi^2 = 9.98, p = .007) \) were impaired. Inhibitory deficits characterized more ADHD-C than ADHD-I subjects \( (Z = -2.06, p = .04) \).

There was no main effect of Group on antisaccade latency \( (F(1,25) = .341, p = .714) \).

**Figure 2.6. Group Differences in Antisaccade Errors.**

ADHD-I: Attention Deficit Hyperactivity Disorder Inattentive; ADHD-C: ADHD-Combined
Horizontal lines indicate group mean.

*Boys with ADHD-C made significantly more antisaccade errors than Control boys. Mean error rate in ADHD-I boys did not differ significantly from either of the other groups, but the proportion of participants with impaired performance (25%) was lower in the ADHD-I group than*
in the ADHD-C group. Two ADHD-C participants are represented at 34% error rate with one triangle.

2.4.2 Task-Switching (Antisaccade-Prosaccade Mixed Task)

There was a significant main effect of Switch \( (F(1,29) = 6.331, p = .018) \) on percent error, reflecting the fact that participants made more errors when they were required to switch response from the previous trial (15.99% ± 10.03%) than when the required response was the same as on the previous trial (11.43% ± 8.15%). However, there was no Group x Switch interaction \( (F(2,29) = .08, p = .926) \); thus, the groups were equally affected by the requirement to switch response (Figure 2.7).

There was a significant Group x Task interaction \( (F(2,29) = 4.57, p = .019) \), reflecting the fact that ADHD-C boys had a larger difference in error rate between the saccade and antisaccade tasks than both Control boys \( (t(29) = -2.78, p = .008) \) and ADHD-I boys \( (t(29) = -2.57, p = .02) \), who did not differ from each other \( (t(29) = -.448, p = .657) \)(Figure 2.8). This reflected, in the ADHD-C group, a decreased ability to inhibit the prepotent response on the antisaccade task and an increased tendency to make the prepotent response on the prosaccade task.

**Figure 2.7.** *Errors on the Antisaccade-Prosaccade Mixed Task as a Function of the Requirement to Switch Response from the Previous Trial.*
ADHD-I: Attention Deficit Hyperactivity Disorder Inattentive type; ADHD-C: ADHD-Combined Type.

Percent error was significantly higher on trials when subjects were required to change response from the previous trial (mean ± SE) (regardless of whether the required response was a saccade or antisaccade) than when the required response was the same; however, there was no Group x Switch interaction (p = .926), indicating that the three groups were equally affected by the requirement to change response.

Figure 2.8. Errors on the Antisaccade-Prosaccade Mixed Task as a Function of Group and Task.
ADHD-I: Attention Deficit Hyperactivity Disorder Inattentive type;
ADHD-C: ADHD-Combined Type.
*Boys with ADHD-C made more antisaccade errors than the other two groups and made fewer prosaccade errors than the other two groups, so the difference between the tasks was significantly larger in the ADHD-C group than in both the other two groups (Group x Task, \( p = .019 \)).

In the latency analysis, antisaccades took longer to generate (252.73 ± 38.99 ms) than prosaccades (187.50 ± 22.24 ms) \( (F(1,29) = 96.06, p = .001) \). Group did not affect latencies as a main effect or in interaction with other variables (all \( p’s > .19 \)).

The absence of Group x Switch interactions on both error and latency data indicate that the ADHD groups were not impaired in the switching component of the task.

2.4.3 Motor Planning (“Totally-Predictable” and “Direction-Predictable” Tasks)

As expected, there was a main effect of Task on percent predictive saccades, with subjects generating more predictive saccades when both timing and direction of the target movement were predictable (TPT) than when only target direction was predictable (DPT)
(F (1,29) = 57.8, p = .001). There was a Group x Task interaction (F (2,29) = 4.2, p = .025), indicating that the difference in percent predictive saccades between the DPT and TPT tasks was smaller in the ADHD-C group (13.1% ± 12.8%) than in Control participants (38.8% ± 20.4%, t (18) = 3.37, p = .003) and ADHD-I participants (33.9% ± 26.6%, t (16.4, corrected for unequal variances) = 2.39, p = .029). The ADHD-C boys differed from the other two groups in percent predictive saccades in the TPT (all p’s = .03; see Figure 2.9) but not in the DPT (Control subjects, 8.9% ± 6.2%; ADHD-I, 11.9% ± 7.8%; ADHD-C, 12.4% ± 7.0%; all p’s = .25).

Predictive saccades had significantly shorter latencies, smaller amplitudes, and lower peak velocities than reflexive saccades. Group did not affect saccade characteristics and did not interact with other variables (all p’s = .59). Thus, whereas the ADHD-C group did differ from the other two groups in proportion of predictive saccades, the characteristics of the predictive and reflexive saccades they generated did not differ from the other groups.
Figure 2.9. Percent Predictive Saccade in the Direction-Predictable and Totally-Predictable Tasks.

ADHD-I: Attention Deficit Hyperactivity Disorder Inattentive type; ADHD-C: ADHD-Combined Type.
DPT: Direction-Predictable Task, TPT: Totally-Predictable Task.
Horizontal lines indicate group mean.
There was a significant Group x Task interaction (p = .025) with ADHD-C boys showing a smaller difference between the two conditions than the other groups. Boys with ADHD-C did not differ from the other groups on the DPT but made significantly fewer predictive saccades than the other two groups on the TPT.

2.4.4 Saccade Control Task

There were no main effects of Group on any of the dependent measures (Table 2.2). Thus, all the groups were similar in the characteristics of their prosaccades.
### Table 2.2. Performance on the Saccade Control Task.

<table>
<thead>
<tr>
<th></th>
<th>Control Subjects</th>
<th>ADHD-I</th>
<th>ADHD-C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency (msec)</td>
<td>189.06 ± 29.35</td>
<td>179.05 ± 17.83</td>
<td>188.11 ± 21.51</td>
<td>.53</td>
</tr>
<tr>
<td>Amplitude (°)</td>
<td>11.07 ± 1.44</td>
<td>10.69 ± 0.76</td>
<td>10.61 ± 0.90</td>
<td>.58</td>
</tr>
<tr>
<td>Peak Velocity (°/sec)</td>
<td>419.68 ± 89.94</td>
<td>393.15 ± 66.75</td>
<td>381.23 ± 75.82</td>
<td>.53</td>
</tr>
</tbody>
</table>

ADHD-I: Attention Deficit Hyperactivity Disorder Inattentive type; ADHD-C: ADHD-Combined Type.

Data are presented as mean ± SD

#### 2.4.5 Developmental Trends:

Antisaccade errors were significantly correlated with age in Controls ($r = -.83$, $n = 10$, $p = .003$), but not in ADHD-I ($r = -.20$, $n = 12$, $p = .53$) or ADHD-C boys ($r = .028$, $n = 10$, $p = .94$) (Figure 2.10). For the antisaccade and age correlation, the slope for the Controls was significantly steeper than the slope of both the ADHD-I ($z = -1.95$, $p = .026$) and the ADHD-C ($z = -2.26$, $p = .012$) groups.

Percentage of predictive saccades was significantly correlated with age in Controls ($r = .81$, $n = 10$, $p = .005$). The correlation did not attain significance in ADHD-I boys ($r = .39$, $n = 12$, $p = .21$) and was completely absent in ADHD-C boys ($r = .08$, $n = 10$, $p = .81$) (Figure 2.11). The slope of the correlation in Controls was significantly steeper than the slope in the ADHD-C group ($z = 2.28$, $p = .011$). The difference in slope between the ADHD groups did not reach significance ($z = 1.43$, $p = .076$).
Figure 2.10. *Percent Antisaccade Errors as a Function of Age.*

ADHD-I: Attention Deficit Hyperactivity Disorder Inattentive type; ADHD-C: ADHD-Combined Type.

Pearson’s correlations show significant negative correlations between antisaccade error rates and age in Controls (p = 0.003) but not in ADHD-Is (p = 0.53) or ADHD-Cs (p = 0.94).

Figure 2.11. *Percent Predictive Saccades as a Function of Age.*

ADHD-I: Attention Deficit Hyperactivity Disorder Inattentive type; ADHD-C: ADHD-Combined Type.

Pearson’s correlations show significant positive correlations between percent predictive saccades and age in Controls (p = 0.005) but not in ADHD-Is (p = 0.21) or ADHD-Cs (p = 0.81).

2.5 DISCUSSION:

Our main findings were that 1) ADHD-I and ADHD-C subtypes differed in measures of executive function, with ADHD-C but not ADHD-I showing deficits in response inhibition and motor planning; 2) neither subtype was impaired in task-
switching; and 3) improvements in response inhibition and motor planning between the ages of 11 and 14 years were observed in Control participants but not in ADHD-C participants. Below, we discuss the implications of these findings for understanding subtypes of ADHD.

The ADHD-C participants made significantly more antisaccade errors than Control participants, but the ADHD-I participants did not. Although the difference in mean error rate between the ADHD-C and ADHD-I groups did not reach significance, the proportion of subjects with inhibitory deficits did: only 16.7% of ADHD-I participants had error rates >2 SD above the Control mean, compared with 60% of ADHD-C participants ($p < .04$). Furthermore, in the mixed task, the ADHD-C group had a significantly larger difference between antisaccade and prosaccade percent error than both the ADHD-I and Control groups, indicating an increased tendency to make the prepotent response, rather than to inhibit it, in both tasks. This finding is consistent with the findings of other studies in which different inhibition tasks (Stop Task, Continuous Performance Test commission errors) were used to compare ADHD subtypes (e.g., Chhabildas et al., 2001; Hinshaw, Carte, Sami, Treuting, & Zupan, 2002; Nigg et al., 2002).

Neither ADHD group was impaired in task-switching, consistent with some previous reports (Nigg et al., 2002; Pennington & Ozonoff, 1996; Scheres et al., 2004). Although task-switching deficits have been reported (Cepeda, Cepeda, & Kramer, 2000), design issues might account for the different results. Cepeda and colleagues presented the task set information at the same time as the stimulus. Thus, impulsive subjects could respond before reading the instructions, allowing inhibitory deficits to influence
performance. In the current study, the task set was cued in advance; with this approach, the switch cost isolates task-switching deficits from other factors (Monsell, 2003).

Boys with the ADHD-C subtype had robust deficits in motor planning: 70% of Control participants and 75% of ADHD-I boys made more than 30% predictive saccades in the TPT, compared with 10% of ADHD-C boys. The TPT makes greater demands than the DPT on motor planning and timing, functions that are subserved in part by the frontal eye fields (FEFs) and cerebellum (O’Driscoll, Wolff, Benkelfat, Florencio, Lal, & Evans, 2000; Gagnon et al., 2002). Lesions to these regions impair predictive saccades (Isotalo, Pyykko, Juhola, & Aslto, 1995; Rivaud, et al., 1994) while having little effect on visually guided saccades. Deficits on the TPT might reflect involvement of these regions in ADHD-C.

The FEF is of interest in ADHD for several reasons. First, neuroimaging and electrophysiological studies have shown that this area is involved in spatial attention (Corbetta, Kincade, & Shulman, 2002; Moore & Fallah, 2004) and selective attention (Thompson & Schall, 2000), functions thought to be affected in ADHD (Brodeur & Pond, 2001; Douglas, 1999; Nigg, Swanson, & Hinshaw, 1997). Second, the precentral gyrus, where FEF is located (Paus, 1996), has the highest density of dopamine receptors in the frontal lobe (Brown, Crane, & Goldman, 1979). If ADHD is a disorder of dopamine function, this region of frontal cortex is likely to be affected. Finally, the FEF is part of the premotor cortex, an important interface of cognition and motor control. Many symptoms of ADHD-C seem to reflect difficulty exerting cognitive control over motor output, and thus might involve regions where these functions interface.
Cerebellar abnormalities could also underlie predictive saccade deficits. Cerebellum plays a role in timing (Isotalo et al., 1995; Ivry, 1993; Ivry, Keele, & Diener, 1988; Penhune, Zatorre, & Evans, 1998), and predictive saccades involve the synchronization of eye movements with target movements. We have shown that the TPT is associated with cerebellar activation, whereas the DPT is not (Gagnon et al., 2002), presumably reflecting the greater demands on timing functions in the TPT. Frontal and cerebellar regions are reciprocally connected (Kelly & Strick, 2003), and such connections might be crucial for synchronizing motor responses with rhythmic stimuli (O’Driscoll et al., 2000).

Cerebellar dysfunction has been proposed in ADHD-C on the basis of deficits in balance, rhythm reproduction, and coordination (e.g., Barkley, Murphy, & Bush, 2001; Raberger & Wimmer, 2003; Smith, Taylor, Rogers, Newman, & Rubia, 2002). Neuroimaging studies have reported a reduction in the volumes of cerebellar structures in ADHD-C, even after controlling for total brain volume (Berquin, Giedd, Jacobsen, Hamburger, Krain, Rapoport, & Castellanos, 1998; Castellanos et al., 2001; Castellanos, Lee, Sharp, Jeffries, Greenstein, Clasen, et al., 2002; Mostofsky, Reiss, Lockhart, & Denckla, 1998). The predictive saccade deficits we observed here are consistent with cerebellar dysfunction, and suggest that cerebellar abnormalities may be more implicated in the Combined subtype.

Performance on visually guided saccades did not differ between groups. The difference between the findings here and those of Munoz et al., (2003), who reported longer latencies and lower peak velocities in ADHD, likely reflect differences in the treatment of outlying values (excluded here and included by Munoz et al., 2003). It has
previously been shown, in an analysis of reaction time (RT) distributions, that ADHD children have larger tails in their RT distributions, but when these extreme values are excluded, RTs do not differ from those of age-matched control subjects (Leth-Steensen, King Elbaz, & Douglas, 2000). However, the differences in findings in peak velocity may reflect power differences between studies because our data showed nonsignificant group differences in the same direction (see Table 2.2).

Previous antisaccade research has indicated that percent error is negatively related to age (Fischer et al., 1997; Klein & Foerster, 2001; Malone & Iacono, 2002; Munoz et al., 2003). We replicated this finding in the Control group (r = .83) but not in the ADHD groups (ADHD-I, r= -.20; ADHD-C, r = -.02); the magnitude of the correlations was smaller in both ADHD groups than in Control subjects (all p’s < .03). Whether the absence of improvement with age reflects a “maturational lag” (El Sayed, Larsson, Persson, Santosh, & Rydelius, 2003) or an arrest is not clear because there have been few longitudinal studies of executive functions in ADHD and a consensus has not yet emerged as to whether executive function deficits in childhood persist into adulthood (e.g., Fischer & Weber, 1990; Seidman, Biederman, Faraone, Weber, Ouellette, 1997; Seidman, Biederman, Weber, Hatch, & Faraone, 1998).

The two subtypes of ADHD studied in the current investigation differed in their executive function profile with the ADHD-C boys, but not ADHD-I boys, impaired in executive motor control. These differences in executive function likely correspond to differences in the pathophysiology of the subtypes. Our behavioural data suggest frontal-striatal circuitry involvement in the symptoms of the Combined type. It is possible that symptoms of the Inattentive subtype tap different cortical and subcortical regions. To
speculate, right parietal dysfunction has been associated with deficits in arousal and orienting (Aman et al., 1998; Arnsten, 2009; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005), and could account for a profile of attention deficits in the absence of inhibitory deficits (Chambers, Payne, Stokes, & Mattingley, 2004a; Chambers, Stokes, & Mattingley, 2004b; Chambers, Bellgrove, Stokes, Henderson, Garavan, Robertson, et al., 2006). Alternatively, attention deficits may be subserved by the same regions in both subtypes but the executive functioning deficits specific to ADHD-C may reflect the additional involvement of other structures. This interpretation has recently been supported in an imaging study of inhibitory control in subtypes of ADHD (Solanto, Schulz, Fan, Tang, & Newcorn, 2009). There were no differences in inhibitory performance of ADHD-Is and ADHD-Cs on a go/no-go task. However, there were differences in areas activated by the subtypes.

Interpretation of the results in the present study is constrained by limitations in the design. The primary limitation is that of sample size. Although the rigor of the inclusion criteria and the homogeneity of the sample increased our power to detect differences and to ascribe them to ADHD rather than to confounding factors, additional between-group differences might have been found with larger samples.

There is currently debate as to whether ADHD-C and ADHD-I constitute subtypes of the same disorder or are two different disorders (Barkley, 2001; Hinshaw, 2001; Lahey 2001; Milich et al., 2001; Pelham, 2001). Differences in cognitive profiles would be one piece of evidence that they may be different disorders. Cognitive differences between ADHD-I and ADHD-C children have been found previously in some studies (Frank & Ben-Nun, 1988; Klorman et al., 1999; Milich et al., 2001; Nigg et al.,
2002; Trommer, Hoeppner, Lorber, & Armstrong, 1988) but not in others (see Milich et al., 2001 for review). Previous study designs, however, have generally included comorbid disorders, or used groups that differed in age or IQ, or did not use matched control tasks to isolate the cognitive function of interest, all factors that cloud the interpretation of differences. The findings from the present study suggest that when these factors are controlled, the executive function profiles of ADHD-C and ADHD-I differ.
2.6 REFERENCES:


Chapter Two: Executive Functions in Subtypes of ADHD


Gitelman, D.R., Nobre, A.C., Parrish, T.B., LaBar, K.S., Kim, Y.H., Meyer, J.R., &


Chapter Two: Executive Functions in Subtypes of ADHD


Klein, C.H., Raschke, A., & Brandenbusch, A. (2003). Development of pro- and antisaccades in children with attention-deficit hyperactivity disorder (ADHD) and


Chapter Two: Executive Functions in Subtypes of ADHD


In Chapter Two, I described an investigation of oculomotor measures of executive functioning in subtypes of Attention Deficit Hyperactivity Disorder (ADHD) and reported that boys with ADHD-Combined subtype were impaired on response inhibition and motor planning, while ADHD-Inattentive boys were not. In Chapter Three, a double-blind, placebo-controlled, cross-over trial of the effect of methylphenidate -- the most commonly prescribed pharmacological treatment of ADHD -- on oculomotor tests of executive function was conducted. The primary goal of the study was to characterize the effect of methylphenidate on executive functioning in subtypes of ADHD. Subsidiary goals included evaluating the stability of performance on oculomotor tests of executive function over time. This is one of the first studies investigating subtype response to methylphenidate on executive functioning tasks.
Chapter Three:

A Double-Blind, Placebo-Controlled, Cross-Over Study of the Effects of Methylphenidate on Executive Eye Movements in Subtypes of ADHD

Experiment 2
3.1 ABSTRACT:

**Background:** Attention Deficit Hyperactivity Disorder (ADHD) has been divided into subtypes, with the two most common being ADHD-Predominantly Inattentive (ADHD-I) and ADHD-Combined (ADHD-C). These subtypes appear different in clinical presentation and in executive functioning. However, methylphenidate is the primary pharmacological treatment for both. Here we investigated the effects of methylphenidate on oculomotor tests of executive functioning in boys diagnosed with ADHD-I or ADHD-C. We also evaluated the stability of performance on the executive functioning tasks. Since methylphenidate is used to target clinical symptoms in both subtypes, we hypothesized that methylphenidate-induced improvements in executive functioning would be observed in both ADHD-I and ADHD-C boys.

**Methods:** Boys (11.5 – 13.9 years) with ADHD-I (n = 12) and ADHD-C (n = 9) were administered a single dose of 0.5 mg/kg of methylphenidate in a double-blind, placebo-controlled, crossover design. They then performed a battery of executive eye movement tasks assessing response inhibition (antisaccade task), task-switching (antisaccade-prosaccade mixed task) and motor planning (predictive saccades).

**Results:** Methylphenidate significantly reduced antisaccade errors (p = .006) and increased percent predictive saccades (p = .007) but did not affect the participants’ ability to switch response from one trial to another (p = .50). There were no Group x Drug interactions on any measures (all p’s > .14). The average time between baseline (Experiment 1) and placebo sessions was 49 days (± 26.1 days). Intraclass r's between performance at baseline and performance on placebo indicated good to excellent test–
retest reliability for antisaccade percent errors ($r = .79, p = .001$), and for percent predictive saccades ($r = .62, p = .001$).

**Conclusions:** Methylphenidate significantly improved inhibitory function and motor planning in ADHD, with similar improvement in both subtypes. These findings support the clinical practice of using MPH as a first-line treatment in both subtypes (Conners, 2002).
3.2 INTRODUCTION:

Current diagnostic criteria divide Attention Deficit/Hyperactivity Disorder into subtypes, with the two most commonly occurring subtypes being Predominantly Inattentive (ADHD-I) and Combined (ADHD-C) (American Psychiatric Association, APA 1994). ADHD-I is associated with clinically significant symptoms of inattention, including, for example, making careless mistakes in schoolwork, not listening when spoken to directly, and failing to finish school work and chores (APA, 1994). The Combined subtype is characterized by clinically significant symptoms of inattention along with symptoms of hyperactivity/impulsivity including, for example, fidgeting with hands, squirming in seat and difficulty playing quietly (APA, 1994). The two subtypes thus have different presentations, with the Inattentive subtype often appearing sluggish (i.e., appears confused or seems to be in a fog, daydreaming, underactive and lacks energy) (Carlson & Mann, 2002; Lahey, Pelham, Schaughency, Atkins, Murphy, Hynd, et al., 1988; McBurnett, Pfiffner, & Frick, 2001) while the Combined subtype often appears as if “driven by a motor” (Milich, Balentine, & Lynam, 2001)). Because of these differences, there is debate as to whether the two subtypes are actually part of the same disorder or whether they are more correctly conceptualized as two distinct disorders (Barkley, 2001; Hinshaw, 2001; Lahey, 2001; Milich et al., 2001; Pelham, 2001).

One criterion used to evaluate the distinctness of the subtypes is the response to pharmacotherapy (Cantwell & Baker, 1988; Cantwell, 1996; Milich et al., 2001). Psychostimulant drugs, in particular methylphenidate (MPH), are the first-line pharmacological treatment for children with ADHD (Conners, 2002) with both subtypes having significant reductions of clinical symptoms on MPH (Barbaresi, Katusic,
Colligan, Weaver, Leibson, & Jacobsen, 2006; Barkley, DuPaul, & McMurray, 1991; Gorman, Klorman, Thatcher, & Borgstedt, 2006; Stein, Sarampote, Waldman, Robb, Conlon, Pearl, et al., 2003). Whether the two groups have similar improvements in executive function on MPH is less clear. Only one study to date has compared the subtypes in terms of the effect of MPH on executive functions (Barkley, DuPaul, & McMurray, 1991). Participants received a low (5 mg bid), moderate (10 mg bid) or high (15 mg bid) dose of MPH in a triple-blind, placebo-controlled, crossover design in which each drug condition was administered for one week. Participants were administered the Continuous Performance Task (CPT), Wisconsin Selective Reminding Test (memory and verbal learning task) and the Kagan Matching Familiar Figures Test (impulsivity) one week after having been administered each methylphenidate/placebo dose. MPH reduced CPT omission errors with both the moderate and high doses improving performance over placebo. There were no effects of MPH on other measures of cognitive functioning and no Group x Drug interactions. Thus, MPH seemed to have similar effects in both subtypes (Barkley, DuPaul, & McMurray, 1991). The absence of an effect on the measure of impulsivity was surprising, given MPH’s effects on clinical symptoms of impulsivity, and may have been related to the choice of laboratory test.

Recently oculomotor tasks have been reported to be sensitive and stable measures of executive functions that may be ideal for pharmacological research (Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008). Eye movements have been helpful in understanding the pathophysiology and treatment effects in psychiatric and neurological disorders (reviewed in Reilly, et al., 2008). Eye movements provide reliable and quantifiable pre-and post-treatment measurements to quantify drug effects. Further, the instructions for
eye movement tasks are easy for participants to understand, an advantage in the investigation of psychiatric and neurologic disorders in whom cognitive function may be compromised.

Oculomotor measures of executive functions are sensitive to naturally occurring and experimental manipulations of dopamine (DA) activity. Clinical populations with putative reductions in DA activity, such as Parkinson’s, ADHD and schizophrenia, have been reported to show deficits on oculomotor measures of executive function (Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001; Park & Holzman, 1992), including measures of inhibition (Amador, Hood, Schiess, Izor, & Sereno, 2006; Calkins, Iacono, & Curtis, 2003; Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Fukushima, Fukushima, Chiba, Tanaka, Yamashita, & Kato, 1988; Munoz, Hampton, Moore, & Goldring, 1999).

Performance on oculomotor measures of executive function has been reported to improve with increases in DA. For example, oculomotor inhibition improves with nicotine, an indirect DA agonist (Dépatie, O’Driscoll, Holahan, Atkinson, Thavundayil, Ng Ying Kin, & Lal, 2002; Larrison, Briand, & Sereno, 2004; Powell, Dawkins, & Davis, 2002; Rycroft, Hutton, & Rusted, 2006), d-amphetamine, an agonist that increases DA release from the presynaptic nerve terminal (Allman, Benkelfat, Durand, Sibon, Dagher, Leyton, et al., 2010; Wonodi, Cassady, Adami, Avila, & Thaker, 2006) and levodopa, a DA precursor (Hood, Amador, Cain, Briand, Al-Refai, Schiess, & Sereno, 2007). Studies of the effect of MPH on oculomotor inhibition in ADHD have yielded conflicting results (Aman, Roberts, & Pennington, 1998; Klein, Fischer, Fischer, & Hartnegg, 2002; Mostofsky, et al., 2001; Munoz et al., 1999), and thus far no study has evaluated the effect of subtype.
In the current study, I evaluate the effect of MPH in ADHD-I and ADHD-C boys using oculomotor measures of executive function. To my knowledge, this is the first study to compare MPH response on neurocognitive measures in adolescents diagnosed with these ADHD subtypes. Because MPH is clinically effective in both subtypes (e.g., Barkley et al., 1991), we hypothesized that both groups would show improvement in executive functions.

3.3 METHODS AND MATERIALS:

3.3.1 Participants

ADHD-I and ADHD-C boys who had previously participated in Experiment 1 were invited to take part in a double-blind, placebo-controlled, crossover study of a challenge dose (0.5mg/kg) of MPH on executive functioning. All but one ADHD-C participant agreed to participate. The inclusion criteria are described in detail in Chapter Two and are reviewed more briefly below.

Participants were boys aged 11.5 to 13.9 years, with an estimated full-scale IQ score above 85 (Wechsler, 1991). They had normal or corrected-to-normal vision. They had been diagnosed with ADHD-C or ADHD-I by a psychologist or psychiatrist prior to entering the study. Criterial symptoms of ADHD were assessed using several measures, including 1) the Diagnostic Interview Schedule for Children-Revised (DISC-IV); 2) blind ratings of the participants’ behaviour in the lab during the testing sessions; and 3) the Parent Behavioural Checklist and the Teacher Behavioural Checklist. The latter checklists included the abbreviated Conners’ Parent and Teacher Rating Scales - Revised
(Goyette, Conners, & Ulrich, 1978) and items from the Child Symptom Inventory-4 Rating Scale (CSI-4) (Gadow and Sprafkin, 1994; 1998). The CSI-4 included ratings of DSM-IV symptoms of inattention and hyperactivity/impulsivity. In order to be included in the Inattentive group, boys had to meet the 1.5 clinical cutoff on the Inattention symptoms scale but not on the Hyperactivity/Impulsivity scale. For inclusion in the Combined group, participants’ had to meet the 1.5 clinical cutoff on both the inattention and the hyperactivity/impulsivity scales of the checklist (Gadow and Sprafkin, 1994; 1998). The groups did not differ in terms of demographic characteristics (Table 3.1).

**Table 3.1. Demographics and Diagnostic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ADHD-I (n = 12)</th>
<th>ADHD-C (n = 9)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.74 ± .60</td>
<td>12.45 ± .54</td>
<td>0.25</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>108.54 ± 10.7</td>
<td>108.90 ± 8.57</td>
<td>0.94</td>
</tr>
<tr>
<td>Father's SES¹</td>
<td>4.0 ± 1.5</td>
<td>3.4 ± 1.65</td>
<td>0.67</td>
</tr>
<tr>
<td>Reading Performance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woodcock (%)</td>
<td>63.48 ± 13.46</td>
<td>53.42 ± 23.12</td>
<td>0.65</td>
</tr>
<tr>
<td>Currently Prescribed MPH (n)</td>
<td>10</td>
<td>9</td>
<td>0.17</td>
</tr>
<tr>
<td>DSM-IV Symptoms²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>2.03 ± .34</td>
<td>2.23 ± .27</td>
<td>0.14</td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>.85 ± .41</td>
<td>1.82 ± .64</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n. Data were analyzed by independent samples t-tests. ADHD-C, Attention Deficit Hyperactivity Disorder-Combined type; ADHD-I, ADHD- Inattentive; IQ, intelligence quotient; MPH, methylphenidate.

¹SES, socioeconomic status; father's occupation ranked on an ordinal scale from 1 (major professional) to 9 (unemployed), from a modified version of the Index of Social Status (Hollingshead and Redlich, 1958).

²Parent ratings of their child’s symptoms on the Inattention and Hyperactivity-Impulsivity scales of the Child Symptom Inventory-4 Rating Scale (Gadow & Sprafkin, 1994, 1998). A score of 1.5 and above is considered clinically significant.

Comorbid disorders were exclusion criteria with the exception of Oppositional Defiant Disorder (ODD) since exclusion on this basis could compromise the representativeness of the sample (Anderson, Williams, McGee, & Silva, 1987; Bird,
Gould, & Staghezza, 1993). Two boys met criteria for Generalized Anxiety Disorder (GAD) but were included because ADHD had been diagnosed prior to GAD, GAD was less severe than the ADHD, and was thought to be secondary to academic difficulties arising from the ADHD. Participants with a reading disability were excluded (see Chapter 2 for a description of reading assessment) because increased antisaccade errors have been found among children and adolescents with reading disability (e.g., Biscaldi, Fischer, & Hartnegg, 2000).

Ethics approval for the study was obtained from the Department of Psychology Ethics Review Board (McGill University, Montréal, Québec), the Montréal Children’s Hospital Institutional Review Board, Montréal, Québec, and the Douglas Hospital Research Ethics Board, Verdun, Québec. A parent provided written informed consent and the boys provided written assent. All boys received compensation for their time and inconvenience.

3.3.2 Procedures

In each of two testing sessions, participants completed a battery of executive eye movement tasks identical to the battery administered in Experiment 1. In one of the sessions, a capsule containing 0.5 mg/kg of Methylphenidate HCl (Ciba Pharmaceuticals, Canada Ltd.) to a maximum of 30 mg was administered. This dose has been reported to optimize performance (Douglas, Barr, Amin, O’Neill, & Britton, 1988) while resulting in few side effects. In the other session, an identical looking capsule which contained a placebo (100 mg of lactose) was administered. The order of drug administration was randomized and counterbalanced between subjects. Testing occurred between 10:00 am
and 1:00 pm. The pill was administered at 9:00 am to allow one hour for the medication to be absorbed (Solanto & Conners, 1982; Coffey, Greenblatt, & Shader, 1983). ADHD boys who were regularly taking stimulant medication were asked not to take their medication for a minimum of 24 hours before testing. A minimum interval of 3 weeks was imposed between Experiment 1 and the start of Experiment 2 to reduce practice effects; the average interval (35.19 days ± 11.83 days) did not differ between the groups (t(15) = 0.07, p = 0.94). The average time between methylphenidate and placebo sessions was 39.56 days (SD: 19.29 days) and did not differ between the groups (t(15) = 1.03, p = .32).

### 3.3.3 Apparatus

The testing equipment and tasks were identical to those used in Experiment 1. Briefly, eye movement data were collected with participants seated 57 cm from the computer monitor in a darkened room. An infrared pupil tracker (250 Hz) mounted on a headband (Eyelink: SR Research, Mississauga, Ontario, Canada) illuminated the participants’ dominant eye. This system offers a spatial resolution of .25° of visual angle. Before each task, a calibration was performed across 24° and a drift correction was performed before each trial. Then a .5° x .5° red square against a dark background appeared on the monitor.

### 3.3.4 Tasks

The tasks assessed response inhibition (antisaccade task), task-switching (antisaccade-prosaccade mixed task) and motor planning (totally-predictable saccade
task) along with matched control tasks. The order of task administration for each subject was the same as the order in which they performed the tasks in Experiment 1.

**Antisaccade and Prosaccade Tasks**

A square appeared in the centre of the computer screen for 1000, 1200 or 1400 ms. It then stepped 11° to the left or right of the screen and remained on the screen 600 ms. The direction of target appearance was pseudo-random in that it could not appear on the same side on more than 3 consecutive trials. For the prosaccade control task, they were instructed to direct their gaze toward the peripheral target as soon as it appeared. For the antisaccade task, participants were instructed not to look at the peripheral target but rather to look to the mirror position on the opposite side of the screen. Participants performed a total of 57 trials, with 9 practice trials followed by 48 test trials.

**Antisaccade-Prosaccade Mixed Task**

On the antisaccade-prosaccade mixed task, participants performed an antisaccade or a prosaccade depending on the colour of the central target. Half of the participants were instructed to antisaccade when the central target was red and the other half when the target was green. A block of 15 practice trials preceded the 48 test trials.

**Totally-Predictable and Direction-Predictable Tasks**

For the totally-predictable task (predictive saccades), the target moved in a rhythmic and predictable fashion by jumping every 600 ms from the centre to 11° right, back to centre, 11° left, back to centre, etc. This type of movement rapidly elicits predictive saccades from healthy individuals (Gagnon, O’Driscoll, Petrides, & Pike,
In the direction-predictable task, which served as a control task for the totally-predictable task, the target moved in a similar fashion (i.e., centre, right, centre, left, centre, etc.) with the exception that the timing of the target movement varied randomly between 500 and 2000 ms. Thus, while the direction of the target movement was known in advance, the timing was not. This task elicits significantly fewer predictive saccades, despite the fact that target direction is known in advance (Gagnon et al., 2002). For both tasks, participants were instructed to move their eyes at the same time the target moved.

### 3.3.5 Analysis

Analyses were conducted as in Experiment 1, except that the ANOVAs had the additional within-subjects term Medication (MPH, placebo) and the Group term had only two levels (ADHD-I, ADHD-C). Order of drug administration was included in initial analyses but was not significant as a main effect nor in interactions and so was dropped. Below, significant Medication and Group main effects and interactions are reported. For the antisaccade-prosaccade mixed task, data were not available for one ADHD-C subject for two of the conditions (antisaccade latency for repeated trials on placebo and antisaccade latency for switched trials on MPH), so a group mean substitution was performed for these conditions.

**Test-Retest Reliability:**

We evaluated the test-retest reliability of variables that significantly differentiated the ADHD groups from Controls. To do this, we calculated the intra-class correlation of performance in Experiment 1 and on placebo in Experiment 2.
The alpha level for the analyses was set at 0.05. Data are reported as the mean ± standard deviations.

3.4 RESULTS:

3.4.1 Antisaccade and Prosaccade tasks (Response Inhibition and Control Tasks)

Methylphenidate decreased antisaccade percent error ($F(1,19) = 9.66$, $p = .006$) (Fig 3.1). There was no Group x Medication interaction ($F(1,19) = 1.04$, $p = .20$; $d = .57$; antisaccade percent error: ADHD-I Placebo, 15.9% ± 8.5; ADHD-I MPH, 10.9% ± 8.68%; ADHD-C Placebo, 29.7% ± 23.8%; ADHD-C MPH, 19.8% ± 17.4%). MPH decreased antisaccade latency ($F(1,19) = 5.85$, $p = .026$), with the effect significant in both ADHD-I (-7.86 ± 20.93 ms) and ADHD-C (-25.92 ± 42.19 ms) boys. There was no Group x Medication interaction on antisaccade latency ($F(1,19) = 1.67$, $p = .21$, $d = .57$).
Figure 3.1. Effects of Methylphenidate on Antisaccade Errors.

ADHD-I: Attention Deficit Hyperactivity Disorder Predominantly Inattentive type;  
ADHD-C: ADHD-Combined  
MPH: methylphenidate  
Data are presented as means ± standard errors  
MPH decreased antisaccade errors (p = .006). The magnitude of improvement was similar in both ADHD groups (p = .20).

Prosaccade latency was significantly reduced by MPH (Medication: F(1,19) = 7.58, p = .013: ADHD-I: -5.48 ± 8.28 ms, ADHD-C: -15.55 ± 24.88 ms). There was no Group x Medication interaction (F(1,19) = 14.74, p = .203). Medication did not affect prosaccade amplitude or peak velocity, and there were no Group x Medication interactions on these variables (all p’s = .14).

3.4.2 Antisaccade-Prosaccade Mixed Task (Task-Switching)

There was a main effect of Medication (F(1,19) = 7.497, p = .013) (Figure 3.2) on errors in the antisaccade-prosaccade mixed task. There were no Medication x Switch
(F(1,19) = .474, p = .50) or Group x Medication x Switch (F(1,19) = 2.56, p = .126) interactions. Error rates were reduced by MPH equally on switch trials and repeated trials and this occurred for both antisaccades and prosaccades. On placebo, the difference between the prosaccade and antisaccade error rates was larger in the ADHD-C group than in the ADHD-I group; the difference between the groups was reduced by MPH (Group x Medication x Task interaction: (F(1,19) = 3.66, p = .07, d = .88) (Figure 3.3).

**Figure 3.2. Effects of Methylphenidate on Errors as a Function of Switching in the Antisaccade-Prosaccade Mixed Task.**

ADHD-I: Attention Deficit Hyperactivity Disorder Predominantly Inattentive type; ADHD-C: ADHD-Combined

MPH: methylphenidate; Repeated: trials where the response was identical to the preceding trial; Switched: trials where the response was different from that of the previous trial.

Data are presented as means ± standard error.

MPH decreased errors (p = .013) on the Antisaccade-Prosaccade Mixed task. The magnitude of improvement was similar for both switched and repeated trials (Medication x Switch: (F(1,19) = .474, p = .50)) and this was observed in both ADHD groups (Group x Medication x Switch: (F(1,19) = 2.56, p = .126)).
Figure 3.3. Effects of Methylphenidate on Errors in the Antisaccade-Prosaccade Mixed Task.

|               | ADHD-I: Attention Deficit Hyperactivity Disorder Predominantly Inattentive type; ADHD-C: ADHD-Combined type; AS: antisaccades; PRO: prosaccades; MPH: methylphenidate. Data are presented as means ± standard error. There was a Group x Medication x Task interaction (p = .07) on Antisaccade-Prosaccade Mixed task errors. On placebo, the difference between antisaccade and prosaccade errors was larger in the ADHD-Cs than ADHD-Is. MPH reduced this difference between the groups. The latency analysis for the mixed task did not yield a significant effect of Medication. There was a trend for a Medication x Task interaction (F(1,19) = 4.19, p = .055) with significantly reduced latencies in the prosaccade trials (-17.03 ± 21.71 ms, (t (20) = 3.39, p = .003)) but not the antisaccade trials (-1.01 ± 23.91 ms). This effect did not interact with Group (Group x Medication x Task: F(1,19) = .06, p = .81).

3.4.3 “Totally-Predictable” and “Direction-Predictable” Tasks (Motor Planning)

As was observed in Experiment 1, the ADHD-C group had a smaller difference in percent predictive saccades between the TPT and DPT conditions than the ADHD-I
group (Group x Task Interaction: \( F(1,18) = 5.2, p = .035 \); ADHD-C: 19.4% ± 14.4%; ADHD-I: 39.3% ± 21.6%). Methylphenidate increased the proportion of predictive saccades (\( F(1,18) = 9.3, p = .007 \)), and the effect was significantly greater in the TPT than in the DPT (Medication x Task: \( F(1,18) = 12.9, p = .002 \); paired \( t(19) = 3.7, p = .001 \)). The effect was similar in both groups (Group x Task x Medication: \( p > .8, d = .09 \)) (Figure 3.4).

**Figure 3.4. Effect of Methylphenidate on Predictive Saccades.**

ADHD-I: Attention Deficit Hyperactivity Disorder Predominantly Inattentive type;
ADHD-C: ADHD-Combined
TPT: totally-predictable task; DPT: direction-predictable task; MPH: methylphenidate.
Data are presented as means ± standard error.
MPH increased the percentage of predictive saccades (\( p = .007 \)). This effect was more pronounced in the TPT than the DPT (\( p = .002 \)).

In the analyses of saccade amplitude, methylphenidate increased saccade amplitude (\( F(1,16) = 11.2, p = .004 \)), with a trend for a greater effect on predictive
saccades (.72° ± 1.3°) than reflexive saccades (.27° ± .62°) (Medication x Saccade Type: (F(1,16) = 3.7, p = .074)). There was also a significant Group x Task interaction (F(1,16) = 6.4, p = .02), indicating that ADHD-I boys made slightly larger amplitude saccades in the TPT than in the DPT, whereas the pattern was reversed in ADHD-C; however, the difference in amplitude between the two tasks was nonsignificant in both groups (p’s > .1).

3.4.4 Test–Retest Reliability

We used the intraclass correlation coefficient to evaluate test–retest reliability (Experiment 1 to placebo phase of Experiment 2) for the variables that differentiated ADHD from Control participants in Experiment 1. Correlation coefficients did not differ between subtypes (Fisher’s Z test, all p’s > .2) and therefore analyses were conducted across subtypes. Test–retest reliability for antisaccade percent errors (r = .79, p = .001) was excellent and for percent predictive saccades on the TPT (r = .62, p = .001) was good (Cicchetti, 1994).

3.5 DISCUSSION:

The effect of methylphenidate on response inhibition and motor planning was of similar magnitude in the two ADHD subtypes, consistent with the notion that both groups respond to this first-line treatment. Specifically, methylphenidate: 1) decreased error rates and latency of eye movements on the antisaccade task; 2) decreased error rates on the antisaccade-prosaccade mixed task regardless of whether the required response was switched or repeated; 3) increased both the proportion of predictive saccades and the
amplitude of predictive saccades in the totally-predictable task; and 4) decreased prosaccade latency whether the participant was performing solely prosaccades or performing them in the context of a mixed prosaccade-antisaccade task.

There were no significant interactions between group membership (i.e., ADHD-I, ADHD-C) and medication on any of our dependent measures, suggesting that the effect of MPH was similar in both subtypes. Thus, notwithstanding the differences in the baseline executive function profile in the two subtypes (see Experiment 1), MPH was equally effective in improving executive functions in the two groups. These findings are consistent with the small body of clinical literature on MPH response as a function of subtype (e.g., Barkley et al., 1991; Stein, et al., 2003).

MPH significantly improved antisaccade performance by decreasing both error rates and latency in the two groups. These findings are consistent with the positive effects of MPH on other inhibitory tasks, including the Stop Task (Scheres, Oosterlaan, Swanson, Morein-Zamir, Meiran, Schut, et al., 2003; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; Tannock, Schachar & Logan, 1995) where it decreases stop signal reaction time. It has also been reported to decrease errors of commission on the Continuous Performance Test (CPT) (Conklin, Reddick, Ashford, Ogg, Howard, Brannon Morris, et al., 2010; Fernandez-Jaen, Fernandez-Mayoralas, Pardos, Calleja-Perez, & Munos-Jareno, 2009; Losier, McGrath, & Klein, 1996), although this finding has not been consistently found (Aman, Marks, Turbott, Wilsher, & Merry, 1991; Barkley, McMurray, Eldebrook, & Robbins, 1989; Barkley et al., 1991; Klorman, Brumaghim, Fitzpatrick, & Borgstedt, 1991; Solanto, Wender, & Bartell, 1997). Differences in the CPT protocols used could account for the inconsistencies. Specifically, the extent to
which the CPT taps inhibition varies; it is generally higher in studies that create a strong response bias by having frequent targets. In CPT protocols where targets are infrequent, demands on sustained attention are higher, and those on inhibition are reduced (see Riccio, Waldrup, Reynolds, & Lowe, 2001 for review).

The effect of MPH on antisaccade performance in ADHD has been investigated in four previous studies (Aman, Roberts, & Pennington, 1998; Klein et al., 2002; Mostofsky et al., 2001; Munoz et al., 1999). Two of these studies reported decreased antisaccade errors on MPH (Klein et al., 2002; Munoz et al., 1999) while two found no effect (Aman, Roberts, & Pennington, 1998; Mostofsky et al., 2001). However, none of these studies involved a double-blind placebo controlled crossover design and none compared subtypes. Two compared a group of participants receiving MPH to a separate group receiving no medication and used naturalistic group membership rather than random assignment (Munoz et al., 1999; Mostofsky et al., 2001). Another administered MPH always before placebo, thus confounding practice effects with placebo effects (Aman et al., 1998). The use of a double-blind, placebo-controlled, crossover design in the present study eliminates these confounds, making it possible to attribute the reduction of antisaccade errors unambiguously to the medication.

MPH did not reduce the cost of task-switching, although it did reduce errors on both the tasks being performed. Two previous studies have examined MPH effects on task-switching (Cepeda, Cepeda, & Kramer, 2000; Kramer, Cepeda, & Cepeda, 2001). In both of these, MPH reduced task errors as it did here. Both studies examined switch-cost, i.e., how errors increase as a function of the demand to change tasks vs. continuing with the same task. MPH decreased the switch cost in both studies, whereas in the current
study it did not. Differences in task demands may account for the different results. In our study, the participants were required to switch responses while attending to the same aspects of the target; in studies that found MPH to reduce switch cost, the participant was required to switch attention to a different aspect of the stimulus (e.g., from form to number) to determine the response. It is possible that the neural substrates of attentional switching are different from those of pure response switching, and that the former is more amenable to MPH intervention.

MPH increased the proportion of predictive saccades in both subtypes. To my knowledge, this is the first study investigating the effects of MPH on oculomotor tasks of motor planning. Motor timing abnormalities have previously been reported in ADHD (e.g. Rubia, Noorloos, Smith, Gunning, & Sergeant, 2003); it has been proposed that dopaminergic pathways are involved in this function among healthy adults (Meck, 1996). The positive effects of MPH on motor timing are thought to involve its dopamine agonist effects (Volkow, Wang, Fowler, Logan, Angrist, Hitzemann, et al., 1997). Further, MPH increases metabolism in frontal and cerebellar areas (Volkow et al., 1997) which have been implicated in both motor timing (Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, et al., 1998; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, et al., 2000; Rubia, Taylor, Smith, Oksanen, Overmeyer, & Newman, 2001) and predictive saccade performance (O’Driscoll, Wolff, Benkelfat, Florencio, Lal, & Evans, 2000). It is likely that reciprocal connections between frontal and cerebellar areas (Kelly & Strick, 2003) coordinate the timing, motor preparation and response execution role of these areas (Diener, Dichgans, Guschlbauer, Racher, & Langenback, 1989). The methylphenidate-induced increase in predictive saccades observed in the current study has recently been
replicated by our lab; this effect seems to depend on the predictability of target timing (Allman, Ettinger, Joober, Pintsov, Ng Ying Kin, & O’Driscoll, in preparation). Specifically, MPH resulted in increased predictive saccades on tasks where both the timing and direction, or only the timing of target movement was predictable. However, it was not found when only the direction of target movement was predictable (Allman et al., in preparation). Thus, it appears that the effects of MPH are associated with improvements in the processing of timing information for motor preparation.

The interpretation of the results in the current study is constrained by some aspects of the methodology. First, our sample is small. However, this limitation is to some degree offset by other aspects of the design: the fact that all participants were essentially free of comorbid disorders would be expected to decrease noise in the data and increase the signal related to ADHD. In addition, use of a repeated-measures design reduced noise associated with individual differences, further increasing power. A second potential limitation of the study is the fact that we used a single dose of MPH and did not evaluate dose-response separately in the two subtypes. As a result, we cannot rule out the possibility that there is a differential effect of subtype on medication response at higher or lower doses (Barkley et al., 1991). Nevertheless, the dose administered in the current study is consistent with doses used in clinical studies (e.g. Barbaresi, Katusic, Colligan, Weaver, Leibson, & Jacobsen, 2006) and thus is relevant to the effects of MPH on cognition in clinical practice.

We previously reported differences in the neurocognitive profiles of ADHD-C and ADHD-I subtypes using oculomotor measures of executive function. In the current study, MPH significantly improved measures of inhibition and motor planning and did so
equally in the ADHD-C and ADHD-I boys. Thus, despite the differences in cognitive profiles between subtypes, this medication improved cognition in both.
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CHAPTER FOUR: PREFACE

In Chapter Two, we observed that ADHD-Combined (ADHD-C) boys were impaired on response inhibition and motor planning, but were unimpaired on task-switching. ADHD-Inattentive (ADHD-I) boys were unimpaired on all of our tests of executive motor control. Cross-sectional analyses of age-related changes on the tasks differed across groups, with Control boys showing a strong developmental trend (older boys out-performing younger boys), while the ADHD-C boys showed no improvement across the 11.5-13.9 year age range. Although the age/performance data were cross-sectional, they suggested that deficits in executive functions in ADHD-C boys could reflect a maturational delay in frontal-striatal development.

In the current chapter, I report data from a long-term prospective follow-up of the 32 boys who had participated in the original investigation of executive functions in subtypes of ADHD. The primary goal of the study was to determine whether deficits observed in ADHD-C boys in early adolescence would persist or remit in late adolescence. The executive functioning assessment was identical to that conducted in early adolescence. Along with that battery, I added a time reproduction task that has been reported to be sensitive to deficits in ADHD-I (Bauermeister, Barkley, Martinez, Cumba, Ramirez, Reina, et al., 2005; Mullins, Bellgrove, Gill, & Robertson, 2005) because I had found no deficits in the ADHD-I group in the initial battery. I also included two measures of real-life functioning, i.e. number of grades repeated and number of arrests, which have been used in other outcome studies of individuals with ADHD (Barkley, 2002; Barkley, Fischer, Edelbrock, & Smallish, 1990; Barkley, Fischer,
Smallish, & Fletcher, 2006; Bernfort, Nordfeldt, & Persson, 2008; Biederman, Petty, Ball, Fried, Doyle, & Cohen, 2009; Klein & Mannuzza, 1991; Lambert, 1988; Mannuzza, Klein, Bessler, Malloy, & Hynes, 1997; Mannuzza, Klein, & Moulton III, 2008; Moffitt & Silva, 1988; Satterfield, Hoppe, & Schell, 1982; Satterfield & Schell, 1997; Sobanski, Bruggemann, Alm, Kern, Deschner, Schubert, et al., 2007) and without ADHD (Babinski, Hartsough, & Lambert, 1999; Erickson, Lamberti, Weisman, Crilly, Nihalani, Stefanovics, et al., 2009; Jimerson, 1999; Jimerson, Anderson, & Whipple, 2002; McCoy & Reynolds, 1999). This was done to evaluate whether executive functioning in early adolescence predicted aspects of the presentation in late adolescence including adaptive functioning.
Chapter Four: Developmental Course of Executive Functioning

Chapter Four:

Longitudinal Course of Executive Functions in Subtypes of ADHD

Experiment 3
4.1 ABSTRACT:

**Background:** Symptoms of hyperactivity in ADHD have been widely reported to decline during adolescence. However, less is known of the developmental course of executive functions in ADHD. We conducted a 5-year follow-up study of executive functioning in ADHD participants and Controls who had originally been studied in early adolescence. We hypothesized that like hyperactivity, executive functioning deficits would decrease with age although not to the point of eliminating between-group differences. We conducted exploratory analyses to evaluate whether executive dysfunction in adolescence related to clinical or adaptive functioning measures.

**Methods:** Participants were males, aged 15.3–21.4 years, who had been diagnosed in childhood with the Inattentive (ADHD-I) \((n = 12)\) or Combined subtype (ADHD-C) \((n = 10)\) and Controls \((n = 10)\). The follow-up battery included antisaccades to measure inhibition, predictive saccades to measure motor planning, and a time reproduction task. Adaptive functioning measures were number of grades repeated & arrests.

**Results:** Although the ADHD-C and ADHD-I groups improved in terms of clinical symptoms and executive functioning across the 5 year follow-up, antisaccade errors continued to distinguish boys originally diagnosed as ADHD-C from Controls \((p<.006)\). Predictive saccade rate no longer differentiated the groups \((p = .22)\). Time reproduction at short intervals (2-10 sec) distinguished ADHD-C participants from the other groups \((p = .007)\). Baseline measures of executive functioning were significantly associated with the same measures at follow-up. Within ADHD participants, baseline measures of executive functioning did not significantly predict clinical or adaptive outcomes.
However, antisaccade error rate at follow-up was correlated with number of arrests, and number of arrests was higher in ADHD participants.

Conclusions: Although both groups continued to differ significantly from Controls in symptom measures, only the ADHD-C group differed in neurocognitive performance. Antisaccade deficits were persistent across time and related to clinical and adaptive functioning. For the Combined subtype, these results are consistent with the conceptualization of disinhibition as a core deficit.
4.2 INTRODUCTION:

Deficits in executive functioning are widely reported among children with Attention Deficit Hyperactivity Disorder (ADHD) (Barkley, Grodzinsky, & DuPaul, 1992; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Douglas, 1999; Pennington & Ozonoff, 1996; Shue & Douglas, 1992; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). In one model of ADHD, disinhibition has been proposed to be the central deficit in the disorder, leading to multiple additional executive function impairments (Barkley, 1997; 2000). If disinhibition is a “core” feature of the disorder, we would expect to observe relative stability in measures of disinhibition over time and continued deficits through developmental stages.

There is now compelling evidence to suggest that the severity of ADHD symptomatology declines through adolescence to adulthood (Barkley, Fischer, Edelbrock, & Smallish, 1990; Faraone, Biederman, & Mick, 2006; Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Hart, Lahey, Loeber, Applegate, & Frick, 1995; Mannuzza, Klein, Bonagura, Malloy, Giampino, & Addalli, 1991). Only 20-30% of initially hyperactive participants remain hyperactive at the end of adolescence (Gittelman et al., 1985; Mannuzza et al., 1991). However, symptoms of inattention tend to remain stable in early to mid-adolescence (Hart et al., 1995) and show a modest decline by early adulthood (Biederman, Mick, & Faraone, 2000).

Maturation of frontal-subcortical circuitry could be responsible for the reduction in the criterial symptoms of ADHD in late adolescence. Dysfunction of frontal-striatal circuitry has been hypothesized to underlie both the symptoms of inattention and hyperactivity/impulsivity, and the executive function deficits in ADHD (e.g. Arnsten,
2006; Brennan & Arnsten, 2008; Max, Fox, Lancaster, Kochunov, Mathews, Manes, et al., 2002). Thus, the reported declines in hyperactivity during adolescence, to the extent that they tap neural maturation, may be paralleled by gains in executive functioning. If ADHD is a maturational delay in this process, ADHD children may ultimately attain normotypic performance but at a later age than Controls (El-Sayed, Larsson, Persson, Santosh, & Rydelius, 2003; Kinsbourne, 1973; Russell, Oades, Tannock, Killeen, Auerbach, Johansen, et al., 2006).

Cross-sectional studies of cognitive outcomes in adult ADHD are limited in their ability to shed light on the developmental trajectory of ADHD. Specifically, when these studies use individuals who were diagnosed in adulthood (Barkley, Murphy, & Kwasnik, 1996; Epstein, Conners, Starenios, & Erhardt, 1998; Epstein, Johnson, Varia, & Conners, 2001; Marx, Hubner, Herpertz, Berger, Reuter, Kircher, et al., 2010; Rapport, Van Voorhis, Tzelepis, & Friedman, 2001; Walker, Shores, Trollor, Lee, & Sachdev, 2000), the relationship to outcome in people diagnosed as children is unclear, because only a minority of children affected with ADHD in childhood remain affected in adulthood (Barkley, Fischer, Smallish, & Fletcher, 2002; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1993; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998). In the available longitudinal studies of ADHD, executive function measures have generally not been taken in childhood (e.g., Hoy, Weiss, Minde, & Cohen, 1978; Weiss, Minde, Douglas, & Nemeth, 1971), and the cognitive measures that were included (e.g., IQ) (Biederman, Faraone, Milberger, Curtis, Chen, Marrs, et al., 1996; Weiss et al., 1971) provide only limited information on the developmental trajectory of executive functions (e.g., Biederman et al., 1996; Drechsler, Brandeis, Foldenyi, Imhof, & Steinhausen, 2005).
Executive functions have been assessed longitudinally in five prospective studies of ADHD that followed participants to mid-adolescence or early adulthood (Biederman, Petty, Fried, Boyle, Spencer, Seidman, et al., 2007; Biederman, Petty, Doyle, Spencer, Henderson, Marion, et al., 2008; Fischer, Barkley, Smallish, & Fletcher, 2005; Hinshaw, Carte, Fan, Jassy, & Owens, 2007; Hopkins, Perlman, Hechtman, & Weiss, 1979). Overall, executive function deficits improved during the varying follow-up periods (from 5 to 8 years) (Biederman et al., 2007; 2008; Fischer et al., 2005; Hinshaw et al., 2007) but ADHD participants generally remained impaired relative to controls on some measures.

Here we review the five longitudinal studies of executive functions in ADHD (Biederman et al., 2007; 2008; Hopkins et al., 1979; Fischer et al., 2005; Hinshaw et al., 2007), with our focus on measures of inhibition. In an early study of individuals “with hyperactivity,” (antedating DSM-II), Stroop impairments were not observed initially in early to mid-adolescence (Cohen, Weiss, & Minde, 1972) but were observed 5 years later (Hopkins et al., 1979). In studies using the Continuous Performance Task (CPT), one found increased commission errors in adolescence (Fischer, Barkley, Edelbrock, & Smallish, 1990) and these persisted in adulthood in the subset of participants who continued to meet criteria for ADHD (Fischer et al., 2005). A later study of girls (ages 6-12) with ADHD-Combined found increased CPT commission errors in childhood (Hinshaw, Carte, Sami, Treuting, & Zupan, 2002) but not in early adolescence (mean age: 14) (Hinshaw et al., 2007). In another study of ADHD girls assessed initially between 6-18 years of age (mean age: 11.3 years) and followed up 5 years later (Biederman et al., 2008), CPT deficits were not found after age 16, while Stroop deficits persisted. Finally, one study did not compare the groups on any individual measure, but
classified participants at baseline (ages 9-22) as having executive function impairments if they had deficits on any two measures in an 8-item battery (Biederman, 2007). Thirty percent of ADHD vs. 12% of Controls were classified as impaired at baseline. Although executive functioning showed significant temporal stability across 7 years, Controls were not assessed at follow-up so between-group comparisons at that point could not be made.

Several factors constrain the interpretation of findings from previous longitudinal investigations. First, in studies with a young age range at intake (e.g. 6-12 years), persistence in deficits in executive functioning could be attributable to those who are still preadolescent at follow-up (Hinshaw et al., 2007). Second, two of the major studies focused exclusively on girls (Biederman et al., 2008; Hinshaw et al., 2007) while the majority of patients diagnosed with ADHD are male (American Psychiatric Association (APA), 1994) and the course of the disorder may differ between sexes (Hinshaw et al., 2007). Third, the ADHD and Control groups were generally not matched on demographic variables, a factor which makes it difficult to determine whether the persistence of deficits is related to the higher functioning in a demographically better Control group or to true persistence of cognitive features of the illness (Biederman et al., 2007; 2008; Fischer et al., 2005). Finally, the previous longitudinal investigations of executive functioning in males with ADHD have either focused solely on ADHD-Combined subtype or have collapsed across subtypes, potentially reducing the magnitude of executive function deficits if course differs across the subtypes.

We conducted a longitudinal investigation of antisaccade and predictive saccade performance, both of which distinguish ADHD-C boys from Controls (see Experiment 1). The developmental trajectory of performance on the antisaccade task, an eye
movement task that taps inhibitory function, has been investigated in typically developing populations using cross-sectional samples (Fischer, Biscaldi, & Gezeck, 1997; Fukushima, Hatta, & Fukushima, 2000; Klein & Foerster, 2001). Performance on this task improves sharply between the ages of 11 and 14 years (Munoz, Armstrong, Hampton, & Moore, 2003), continues to improve through adolescence, and reaches peak around early to mid twenties (Fischer et al., 1997; Klein & Foerster, 2001; Malone & Iacono, 2002; Munoz, Broughton, Goldring, & Armstrong, 1998; Munoz et al., 2003). In ADHD, evidence of a developmental delay on this task was reported in a cross-sectional study of performance across age groups (Munoz et al., 2003). To our knowledge, there has not been a longitudinal study of developmental effects on antisaccade performance in ADHD. In addition, we are not aware of longitudinal studies of predictive saccades, although deficits in ADHD-Combined in childhood have been reported (Experiment 1).

The goals of the study were to use oculomotor measures to assess the longitudinal course of executive functioning in ADHD and to determine whether measures of executive functioning relate to clinical, cognitive and adaptive functioning measures at follow-up. This study adds to the small literature on the developmental course of executive functions in ADHD by considering the subtypes of ADHD separately, by examining a narrow developmental range so that all participants were studied first in early adolescence and then in mid-to-late adolescence, by matching the groups on age, socioeconomic status, and IQ, and by including only individuals essentially free of comorbid disorders at baseline. To investigate potential links between laboratory measures of executive function and real-world functioning, measures of adaptive functioning were collected. ADHD children generally perform more poorly in school
(Faraone, Biederman, Krifcher Lehman, Spencer, Norman, et al., 1993; Mannuzza et al., 1993; Semrud-Clikeman, Biederman, Sprich-Buckminster, Krifcher Lehman, Faraone, & Norman, 1992; Weiss, Hechtman, Perlman, Hopkins, & Wener, 1979) and are at higher risk of criminality than unaffected individuals (Bernfort, Nordfeldt, & Persson, 2008; Loney, Whaley-Klahn, & Conboy, 1983; Mannuzza, Klein, Konig, & Giampino, 1989; Satterfield, Hoppe, & Schell, 1982; Satterfield & Schell, 1997). Therefore, measures in the domains of academic performance and criminality were added.

We hypothesized that ADHD-C participants would improve in executive functioning with age consistent with the maturation of neural circuitry supporting these functions. However we also hypothesized that as with hyperactivity, performance on measures of executive functioning would continue to differentiate ADHD-C participants from Controls. Finally, consistent with the notion of disinhibition as a core deficit, we hypothesized that early inhibitory function would predict later inhibitory function and would correlate with clinical and adaptive measures in late adolescence.

4.3 METHODS AND MATERIALS:

4.3.1 Participants

In late adolescence (henceforth “follow-up”), the Control (n=10) and ADHD (n=22) participants who had originally been tested on executive eye movement tasks between ages 11.5 to 13.9 years (Experiment 1, henceforth “baseline”) were re-contacted and invited to participate in a follow-up study in which they would perform a battery of tasks similar to that in Experiment 1 and their parents would complete similar clinical
scales. Participation rate in the follow-up was 90% for the ADHD-C group, 75% for the ADHD-I group, and 100% for the Control group and did not differ across groups (p = .21). Two ADHD-I and one ADHD-C participants declined to be tested at follow-up.

One ADHD-I participant could not be located. The groups at follow-up did not differ in their demographic characteristics but continued to differ in ADHD diagnostic symptoms (Table 4.1). The average time to follow-up was 5.5 years (± 1.8 years) and did not differ between groups (F(2,27) = 1.30, p = 0.29).

### Table 4.1 Demographics and Diagnostic Characteristics at Follow-Up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control Subjects</th>
<th>ADHD-I</th>
<th>ADHD-C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (at follow-up/at baseline)</td>
<td>(10/10)</td>
<td>(9/12)</td>
<td>(9/10)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>18.7 ± 2.34</td>
<td>17.31 ± 0.9</td>
<td>17.9 ± 1.6</td>
<td>0.24</td>
</tr>
<tr>
<td>Age Range (y)</td>
<td>15.33-21.42</td>
<td>16.0-18.75</td>
<td>15.58-20.08</td>
<td></td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>112.0 ± 12.18</td>
<td>110.11 ± 11.95</td>
<td>109.06 ± 8.76</td>
<td>0.82</td>
</tr>
<tr>
<td>Father's SES¹</td>
<td>2.63 ± 1.85</td>
<td>4.38 ± 1.41</td>
<td>3.44 ± 1.74</td>
<td>0.14</td>
</tr>
<tr>
<td>Currently Prescribed MPH (n)</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>DSM-IV Symptoms²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>.23 ± .27</td>
<td>1.32 ± .76</td>
<td>1.83 ± .59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>.08 ± .17</td>
<td>.85 ± .41</td>
<td>1.73 ± .56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Meet Criteria for ADHD-I</td>
<td>0</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Meet Criteria for ADHD-C</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n. Data were analyzed by one-way analysis of variance. ADHD-C, Attention Deficit Hyperactivity Disorder-Combined type; ADHD-I, ADHD-Inattentive; IQ, intelligence quotient; MPH, methylphenidate.

¹SES, socioeconomic status; father’s occupation ranked on an ordinal scale from 1 (major professional) to 9 (unemployed), from a modified version of the Index of Social Status (Hollingshead and Redlich, 1958).

²Parent ratings of their child’s symptoms on the Inattention and Hyperactivity-Impulsivity scales of the Child Symptom Inventory-4 Rating Scale (Gadow & Sprafkin, 1994, 1998). A score of 1.5 or above is considered clinically significant.

At the time of the initial study, ADHD participants had been rigorously diagnosed with either ADHD-Combined type (n=10) or Predominantly Inattentive type (n=12) by at least 2 independent raters (i.e., psychiatrist, parents, teachers), and showed symptoms in
at least two settings (see Experiment 1).

To assess ADHD symptoms and comorbid disorders at follow-up, parents completed 1) the abbreviated Conner’s Rating Scale (i.e., CPRS-R (Goyette, Conners, & Ulrich, 1978) if the participant was <18 years or the Conner’s Adult ADHD Rating Scale – Observer form (CAARS-O) (Conners, Erhardt, & Sparrow, 1999) if the participant was >18 years old) and 2) items from the Child Symptom Inventory – 4 Rating Scale (CSI-4) (Gadow & Sprafkin, 1994; 1998).

To assess the presence of DSM-IV Axis I disorders at follow-up, participants were interviewed with the Structured Clinical Interview for DSM-IV disorders (SCID-IV) (First, Spitzer, Gibbon, & Williams, 1996). No participant met criteria for current or past mood or psychotic disorders. The two ADHD participants who had met criteria for Generalized Anxiety Disorder (GAD) at baseline no longer met criteria as assessed by the SCID. However, one ADHD-C and a different ADHD-I participant did meet criteria for GAD on the parent ratings of the CSI-4 at follow-up. Two Controls, four ADHD-I and three ADHD-C participants met criteria for current or past substance abuse and/or dependence. All participants meeting criteria for drug abuse/dependence did so due to cannabis consumption. One ADHD-C participant had been diagnosed with Asperger’s syndrome in the follow-up period.

During the SCID-IV interview, adaptive functioning measures were collected. The participants’ and their parents’ verbal reports were used to determine the number of grades repeated and the number of times participants had been arrested. This method has been used in previous studies (e.g., Barkley et al., 1990; Hechtman, Weiss, Perlman, & Amsel, 1984) and yielded good agreement between the caregivers’ and participants’
reports (Barkley et al., 1990).

The study was approved by the Research Ethics Board of the Montréal Neurological Institute, Montréal, Québec, Canada and the Research Ethics Board of the Institut Universitaire de Gériatrie de Montréal, Québec, Canada. For participants < 18 years old, a parent gave written informed consent and the participant provided written assent. Participants >18 years old gave written informed consent. Participants were compensated for the time and inconvenience.

4.3.2 Tasks

Executive Function Tasks

Participants performed the same eye movement tests as administered in Experiment 1 (for a detailed description of the tasks, see Experiment 1). Analyses focus on tasks that differentiated Controls from ADHD-C participants at baseline, i.e. the Antisaccade task (inhibition) and the Predictive Saccade Task (motor planning).

Antisaccade Task

The target stepped from the center of the computer screen to 11° left or right every 1000, 1200 or 1400 ms. Direction of target movement from center was pseudo-random. Participants were instructed that when the target stepped into the periphery they were to not look at the peripheral target but rather to direct their gaze to the opposite side on the computer screen. Fifty-seven trials were presented (9 practice trials followed by 48 test trials).
Predictive Saccade Task

The target moved back and forth across the screen in 11° steps (centre, right, centre, left, centre, etc.) with a step every 600 ms. Thus, both the timing and direction of the target movement were predictable. Participants were asked to move their eyes in synchrony with the target movement (i.e., “keep your eyes on the square, don’t go ahead, don’t fall behind”).

Prosaccade Task:

The prosaccade task was identical to the antisaccade task except that participants were instructed to look at the peripheral target when it stepped from the centre into the periphery.

Time Reproduction Task:

Because none of our tasks in Experiment 1 differentiated ADHD-I participants from Controls, we added a task that had been reported in the literature to do this, a Time Reproduction task (Bauermeister, Barkley, Martinez, Cumba, Ramirez, Reina et al., 2005; Mullins, Bellgrove, Gill, & Armstrong, 2005).

The task was an adapted version of the computerized task developed by Mullins and colleagues (2005). At the beginning of each trial, written instructions were presented for two seconds (i.e., “A shape will appear. Try to remember how long the shape stays on the screen”). A geometric shape then appeared for a variable duration (2, 4, 6, 8, 10, 12, 24, 36, 48 or 60 seconds). Its disappearance was followed by a second set of instructions (i.e., “click to see the shape again. Click again when it should disappear”).
The participants then pressed a mouse button once for the shape to reappear and pressed again to make the shape disappear when the duration of the shape’s presentation would have elapsed. The color and shape of figures presented and the display periods were randomized.

The first five trials of the time reproduction task were practice trials to ensure that the participants understood the task. Following the practice trials, all participants completed a total of 30 trials. The task took approximately 20 minutes to complete.

### 4.3.3 Apparatus

**Eye Movements:**

Oculomotor tasks were administered using a Dell DHM computer. Oculomotor data were recorded from the participant’s dominant eye using an infrared pupil tracker (250 Hz) mounted on a headband (Eyelink II, SR Research Ltd., Osgoode, ON, Canada). Calibration was performed across 24° with a drift correction prior to each trial. Testing conditions were the same as in Experiment 1, with participants tested in a darkened room and seated 57cm from a computer monitor. Breaks were provided between tasks.

**Time Reproduction Task:**

The time reproduction task was administered using an IBM computer (Corporation, Intel-Pentium 4, CPU 3.06 GHz, 504 of RAM). The geometric shapes (sphere, cube, cylinder, diamond, dodecahedron and cone) were presented in different colours (red, green, blue, yellow, magenta and cyan) against a black background on a Sony 19” LCD computer monitor.
4.3.4 Procedures

Participants came to the laboratory where they performed the eye movement tests and where clinical scales were filled out and a semi-structured psychiatric interview conducted (SCID-IV). As at baseline, oculomotor testing was conducted between 10 am and 1 pm including breaks. Participants who were taking stimulant medication (n = 6) were asked not to take it for 24 hours before testing. For each participant, order of task administration was the same at follow-up as at baseline (at which time randomization and counterbalancing was done).

4.3.5 Analysis

Clinical Symptoms

Parent ratings of ADHD symptoms were analyzed using a three-way mixed ANOVA with Group (Controls, ADHD-I, ADHD-C) as the between-subjects factor and Session (baseline, follow-up) and Symptom type (inattention, hyperactivity/impulsivity) as within-subjects factors.

Eye Movements

Saccades were identified using the criteria described in Experiment 1. Dependent variables for the Antisaccade Task were percent errors and antisaccade latency. For the Predictive Saccade Task, the dependent variable was percent predictive saccade (latency < 70 ms). For the Prosaccade task, dependent variables were latency, amplitude and peak velocity.

Eye movement data were analyzed with two-way mixed ANOVAs: Group was
the between-subjects variable and Session (baseline, follow-up) was the within-subjects variable. Direction was initially included in the model but was dropped as it was not significant as a main effect nor in interaction with other variables. Significant group results as main effects or in interaction are reported. Significant ANOVA effects were followed up with contrasts.

Stability of executive functioning over time was evaluated using the intraclass correlation (ICC) between baseline and follow-up measures across all participants. Because a large ICC could be driven by a tendency of Control participants to be close to ceiling on all measures and ADHD-C participants not to be, analyses were also conducted separately for each group.

*Time Reproduction Task:*

Dependent measures were accuracy coefficient, absolute discrepancy and intra-individual variability (Mullins et al., 2005). The accuracy coefficient is the participant’s produced interval divided by the target interval so that overestimations yield scores >1.00, and underestimations yield scores <1.00. Absolute discrepancy is the unsigned difference between the time interval presented and the interval the participant produced so that over and underestimations are not differentiated. Intraindividual variability was the individual’s standard deviations (SD) for the accuracy coefficient and for the absolute discrepancy score. These variables were calculated separately for short (2-10 seconds), medium (12-24 seconds), and long (36-60 seconds) stimulus durations (following Mullins et al., 2005). Analyses were two-way mixed ANOVAs with Group as the between-subjects factor and Time Interval (short, medium and long) as the within-
Adaptive Functioning Measures

We conducted exploratory analyses to evaluate whether laboratory measures of executive function were related to real-life adaptive functioning. Dependent measures were number of grades repeated and number of arrests, two established measures of functional outcome in ADHD (Barkley, 2002; Barkley et al., 1990; 2006; Bernfort et al., 2008; Biederman et al., 2009; Klein & Mannuzza, 1991; Lambert, 1988; Mannuzza et al., 1997, 2008; Moffitt & Silva, 1988; Satterfield et al., 1982; Satterfield & Schell, 1997; Sobanski et al., 2007) and Controls (Babinski et al., 1999; Erickson et al., 2009; Jimerson, 1999; Jimerson et al., 2002; Kurlychek, Brame, & Bushway, 2006; McCoy & Reynolds, 1999). Because measures acquired at baseline could be considered predictors of later adaptive functioning while measures acquired at follow-up could be correlates (or even consequences) of adaptive functioning, two stepwise regressions were run, first using only measures acquired at baseline and then measures acquired only in late adolescence. Potential predictors were demographic variables (IQ, SES, age), clinical variables (ADHD subtype, parental ratings of ADHD symptoms, as well as ratings of depression, anxiety, conduct disorder and oppositional defiant disorder from the CSI-4), and measures of executive functioning (i.e., antisaccade errors and percent predictive saccades).

The alpha level was set at 0.05. Data are reported as the means ± standard deviations. Analyses were done using SPSS 18.0 (SPSS for Windows, Rel. 18.0. 2009).
4.4 RESULTS:

4.4.1 Clinical Symptoms

Between baseline and follow-up (5.5 years ± 1.8 years), parent ratings of symptom severity declined (Session: F(1,23) = 9.8, p = .005). The expected main effect of Group and the Group x Symptom Type interaction reflected differences between the ADHD subtypes and Controls. These were qualified by a significant Group x Symptom Type x Session interaction (F(2,23) = 5.20, p = 0.014) (Figure 4.1). This interaction reflected the fact that between early and late adolescence, the ADHD-I group had a larger drop in inattention symptoms than Controls (t_{corrected for unequal variance} = 2.5, p = 0.03; ADHD-C vs. Controls, p = .2) while the ADHD-C group had a larger drop in hyperactivity/impulsivity ratings than Controls (t_{corrected for unequal variance} = 2.73, p = 0.02; ADHD-I vs. Controls, p = .34). The ADHD groups did not differ from each other.

Figure 4.1. Parent Ratings of ADHD Symptoms at Baseline and Follow-Up.

ADHD-I, Attention Deficit Hyperactivity Disorder Inattentive type; ADHD-C, ADHD-Combined type.
Bars represent the parent ratings of DSM-IV ADHD symptoms on the CSI-IV. Parent ratings of inattention (white bars) and hyperactivity (gray bars) are shown for baseline (i.e., early adolescence,) and follow-up (i.e., late adolescence, shaded bars). The decrease in Inattention between baseline and follow-up differed between ADHD-Is and Controls but not between ADHD groups. The decrease in Hyperactivity/Impulsivity differed between ADHD-C and Controls but not between ADHD groups.

4.4.2 Eye Movements

4.4.2.a. Antisaccade Task (Inhibition)

Antisaccade errors showed significant effects of Session (F(1,25) = 26.94, p<0.001) and Group (F(2,25) = 6.21, p = 0.006). All three groups made significantly fewer errors at follow-up than at baseline. Nonetheless, ADHD-C participants made more errors than Controls both at baseline (t(29) = 2.93, p = 0.007) and at follow-up (t(25) = -2.27, p = 0.032) (Figure 4.2). The Group x Session interaction was not significant (F(2,25) = 2.65, p = .09). At follow-up, 33.3% percent of ADHD-Cs, 11.1% of ADHD-Is and none of the Control participants had error rates > 2 SD above the Control mean (cut-off value >13%). More ADHD-C participants had antisaccade deficits than Controls (Mann-Whitney test, Z=-1.94, p=.053). Thus, the boys diagnosed as ADHD-C in childhood continued to show impairments in an oculomotor test of inhibition in late adolescence. The other groups did not differ.
ADHD-I, Attention Deficit Hyperactivity Disorder Inattentive Type; ADHD-C, ADHD-Combined type.

There were significant main effects of Group (p = 0.006) and Session p<0.001 and no Group x Session (p < 0.001) interaction. The Group effect was driven by higher antisaccade error rates in the ADHD-C group compared to Controls at both baseline and follow-up.

For antisaccade latency, Group had no effect (p’s >.22).

4.4.2.b. Saccade Control Task

For all prosaccade parameters, Group was not significant as a main effect nor in interaction with other variables (p’s > 0.56).

4.4.2.c. Predictive Saccade Task

For proportion of predictive saccades, there was no main effect of Group (F(2,25) = 1.63, p = 0.22) (Figure 4.3) and no Group x Session interaction (F(2,25) = 2.01, p =
Thus, the impairment in generating predictive saccades observed in the ADHD-C group in early adolescence was no longer evident in late adolescence.

**Figure 4.3. Percent Predictive Saccades by Group and Session.**

ADHD-I, Attention Deficit Hyperactivity Disorder Inattentive type; ADHD-C, ADHD-Combined type.

Differences in predictive saccades that had been observed in early adolescence were no longer evident in late adolescence. The Group x Session interaction was not significant (p > .16).

4.4.3. *Stability of Measures over Time*

Early adolescent measures of symptom severity were significantly associated with late adolescent measures: parent ratings of inattention and of hyperactivity/impulsivity on the CSI-4 at baseline were significantly correlated with their ratings five years later (inattention: ICC = .72, n = 26 p < .001; hyperactivity/impulsivity: ICC = .68, n=26 p < .001).
Performance on both the antisaccade task and the predictive saccade task showed stability across the five year follow-up with the intraclass correlation coefficient for antisaccade percent error 0.49 (p = .045), antisaccade latency 0.55 (p = .021) and percent predictive saccades 0.79 (p < .001).

4.4.4. Time Reproduction Task:

For accuracy coefficient, there was a significant Group x Time Interval interaction (F(4,50) = 4.02, p = .007) (Fig. 4.4). Groups differed at the short time interval (F(2,25) = 7.23, p = .003) but not the medium or long intervals (p’s > .2). ADHD-C participants perceived the short intervals to be longer than did the other two groups (p’s < .03) who did not differ (Controls: .94 ± .10; ADHD-I: .87 ± .10; ADHD-C: 1.05 ± .11) (Fig. 4.5). This effect was significant even without the two highest values in the figure. Fifty percent of Controls, 78% of ADHD-Is but only 11% of ADHD-Cs perceived the short durations to be <95% of the actual duration (ADHD-C vs. Control: Z=-2.15, p=.032; ADHD-C vs. ADHD-I: Z=-2.77, p=.006, ADHD-I vs. Control, ns). Thus short intervals seemed significantly longer to the ADHD-C group than to the other two groups.

For absolute discrepancy scores, there was no main effect of Group and no Group x Time Interval interaction (p’s > .5).
There was a significant Group x Time Interval interaction on accuracy coefficient scores \((p = 0.007)\) with ADHD-Cs overestimating short durations compared to the other two groups.

ADHD-Is, ADHD-Inattentive type; ADHD-Cs, ADHD-Combined type. Group means are represented by horizontal lines. ADHD-Cs perceived the short time intervals to be longer than did Controls \((t(25) = -2.38, p = .025)\) and ADHD-Is \((t(25) = -3.77, p = .001)\). This effect was not driven by the individuals who showed the largest overestimation but by the absence of ADHD-C.
individuals who underestimated the duration. The ADHD-C group had fewer participants underestimating short durations than the other groups (see results).

For the standard deviation of accuracy coefficient scores and the standard deviation of absolute discrepancy scores, there were no effects of Group and no Group by Time Interval interactions (p’s >.2).

4.4.5. Adaptive Functioning:

4.4.5.a. Grades repeated: Across all participants, 7/28 had repeated at least one grade. All of the people repeating grades had been diagnosed with ADHD, with no difference between the subtypes (ADHD-I: 4/9; ADHD-C: 3/9); taking the subtypes together, significantly more ADHD boys repeated a grade than Controls (Z=-2.24, p=.025).

We also evaluated number of grades repeated. Again there was no difference between subtypes (ADHD-I: .89 ± 1.17 ADHD-C: .56 ± .88) but the ADHD groups taken together had repeated more grades than Controls (Mann-Whitney: z = -2.21, p = .027) (mean for group: 0.72 ± 1.02; range 0 to 3; Controls 0).

In the stepwise regression analyses to predict number of grades repeated, we included only ADHD participants since no Control had repeated a grade. Surprisingly, no measure acquired in early or late adolescence -- diagnostic group, parent ratings of symptom severity, IQ, SES, performance on laboratory measures, self reported drug abuse -- was significantly associated with the number of grades repeated.
4.4.5.b Arrests: Twenty-eight percent (5/18) of the ADHD sample had been arrested during the follow-up period compared to 0/10 Controls, a difference that approached significance in this small sample (Mann-Whitney: z = -1.81, p = .071). The subtypes did not differ in number of people arrested (ADHD-I: 2/9; ADHD-C: 3/9) nor in number of arrests (ADHD-I: 1.33 ± 3.32; ADHD-C: 2.0 ± 3.16) (p’s> .6). Taken together, the ADHD group tended to have a higher number of arrests than Controls (mean # of arrests for ADHD participants: 1.6 ± 3.16, range 0 to 10).

For the stepwise regression to predict number of arrests, only ADHD participants were included because no Control had been arrested. No measure taken in early adolescence (ADHD subtype, clinical ratings, executive function measures, IQ, socioeconomic status) was significantly associated with subsequent arrests. Among follow-up measures, the number of antisaccade errors was related to number of arrests (F = 5.27, r = 0.51, p = .036). Parental ratings of hyperactivity/impulsivity, inattention, self reported drug use, and other laboratory performance measures were not associated with number of arrests.

4.5 DISCUSSION:

Participants diagnosed with ADHD-C in childhood continued to be impaired on the antisaccade task in late adolescence, but not on the predictive saccade task. They were also impaired on the time reproduction task for short time intervals. Antisaccade performance in late adolescence was significantly related both to antisaccade performance in early adolescence and to one measure of adaptive functioning in late adolescence, number of arrests. Participants diagnosed with ADHD-I in childhood,
although still significantly different from Controls in terms of parent-rated clinical symptoms, were not different from Controls on any of our measures of executive function.

Our longitudinal findings of continued antisaccade impairments in ADHD-C in late adolescence are consistent with reported impairments in adult ADHD in cross-sectional studies (Carr, Nigg, & Henderson, 2006; Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Munoz et al., 2003; Nigg, Butler, Huang-Pollock, & Henderson, 2002). A key difference between cross-sectional studies of ADHD adults and longitudinal studies of individuals diagnosed in childhood is that in the normal course of the disorder, a substantial proportion of childhood cases no longer meet criteria as adults (Barkley et al., 1990; 2002; Gittelman et al., 1985). Thus, the severity of any cognitive deficits in a group identified as children might be mitigated by the recovery of a proportion of the group. In our data, 66% of those diagnosed with ADHD-C in early adolescence no longer met full criteria for the Combined subtype in late adolescence. This is consistent with reported rates of decline in the literature (Gittelman et al., 1985). Even with the developmental decline in hyperactivity and impulsivity, laboratory measures of disinhibition continued to identify this group. Thus, disinhibition relative to Controls seems to persist both across developmental stages and across variations in symptom severity in individuals once diagnosed with ADHD-C.

On the time reproduction task, participants diagnosed at baseline with ADHD-C perceived the duration of the shortest time intervals (2-10s) to be longer than did the other two groups. Previous investigations have found ADHD-C children to be impaired relative to Controls on time reproduction tasks (Barkley, Koplowitz, Anderson, &
McMurray, 1997; Bauermeister et al., 2005; Brown, 1990; Kerns, McInerney, & Wilde, 2001; Marx et al., 2010; McInerney & Kerns, 2003; Mullins et al., 2005; Smith, Taylor, Rogers, Newman, & Rubia, 2002; Zakay, 1990) and have reported overestimation of short time intervals (McInerney & Kerns, 2003; Plummer & Humphrey, 2009). However, unlike the few other studies that considered subtypes separately (Bauermeister et al., 2005; Mullins et al., 2005), we did not find the ADHD-I group to be impaired. This discrepancy may reflect differences in the age of the cohorts among studies, as previous reports have included young children. Time reproduction difficulties in ADHD-I may remit with age, as was observed with motor planning deficits in ADHD-C. It is also possible that because only one third of the ADHD-I group continued to meet diagnostic criteria for ADHD in late adolescence, the lack of effect is due to symptom remission in this group.

Frontal-striatal circuitry is thought to be involved in the perception of intervals in the second range (Buhusi & Meck, 2005) while cerebellum is primarily implicated in the perception of intervals in the millisecond range (Ivry & Spencer, 2004). Targets of 2 seconds or more have been associated with activation of prefrontal cortex (Jones, Rosenkrans, Rothwell, & Jahanshahi, 2004; Lewis & Miall, 2003) while imaging studies of tasks using subsecond intervals report cerebellar activation (Gagnon, O’Driscoll, Petrides, & Pike, 2002; Lewis & Miall, 2003; O’Driscoll, Wolff, Benkelfat, Florencio, Lal, & Evans, 2000). In neurological studies, frontal lesions are associated with deficits in the suprasecond range but not in the millisecond range (Mangels, Ivry, & Shimizu, 1998). Thus, given the ADHD-C participants’ deficits on the time reproduction task (i.e., second range) but not on the predictive saccade task (i.e., millisecond range), the
impairment observed in the ADHD-C participants in late adolescence suggests frontal-striatal involvement.

In early adolescence, the ADHD-C participants had shown deficits on the predictive saccade task but performance had normalized at follow-up. The only previous study of predictive saccades in adults with ADHD, a cross-sectional study (Feifel et al., 2004), also found no difference in proportion of predictive saccades. Based on these data, it could be argued that ADHD may be associated with early dysfunctions of cerebellar structures which remit by late adolescence. This explanation is partly supported by cross-sectional and longitudinal volumetric studies in ADHD, which have reported decreased cerebellar volume in ADHD children (Berquin, Giedd, Jacobsen, Hamberger, Krain, Rapoport, et al., 1998; Castellanos, Giedd, Berquin, Walter, Sharp, Tran, et al., 2001; Castellanos, Lee, Sharp, Jeiffries, Greenstein, Clasen, et al., 2002; Hill, Campbell, Hart, Yeo, Vigil, & Brooks, 2003; Mostofsky, Reiss, Lockhart, & Denckla, 1998) but volumetric normalization of cerebellar areas by age 16.5 years (Mackie, Shaw, Lenroot, Pierson, Greenstein, Nugent, et al., 2007). Thus the remission of the predictive saccade deficits may reflect a recovery of cerebellar structure/function with maturation.

The frontal cortex is an important component of attentional and executive function networks (Jones et al., 2004; Liston, McEwen, & Casey, 2009; MacDonald, Cohen, Stenger, & Carter, 2000; Posner & Petersen, 1990; Seidman, Yurgelun-Todd, Kremen, Woods, Goldstein, Faraone, et al., 1994) and has been implicated in ADHD in a large body of literature (Bush, Valera, & Seidman, 2005; Spalletta, Pasini, Pau, Guido, Menghini, & Caltagirone, 2001). Deficits on various inhibition tasks in ADHD have been attributed to dysfunction of frontal-striatal circuitry in imaging studies (e.g., Booth,
Burman, Meyer, Lei, Trommer, Davenport, et al., 2005; Durston, Davidson, Mulder, Spicer, Galvan, Tottenham, et al., 2007; Pliszka, Glaahn, Semrun-Clikeman, Franklin, Perez III, Xiong, & Liotti, 2006; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Rubia, Halari, Smith, Mohammed, Scott, Giampietro, et al., 2008). That both antisaccade deficits and suprasecond time reproduction deficits were found in participants originally diagnosed with ADHD-C suggest continued frontal-striatal dysfunction in this group. It is possible to parcellate the frontal cortex and relate antisaccade errors to dysfunction of specific regions, including frontal eye fields, supplementary eye fields and dorsolateral prefrontal cortex (e.g., Desouza, Menon, & Everling, 2003; Doricchi, Perani, Incoccia, Grassi, Cappa, Bettinardi, et al., 1997; Everling & Fischer, 1998; Everling & Munoz, 2000; Funahashi, Bruce, & Goldman-Rakic, 1993; Gaymard, Francois, Ploner, Condy, & Rivaud-Pechoux, 2003; Guittton et al, 1985; Munoz & Everling, 2004; Pierrot-Deseilligny et al, 1991; Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, & Rivaud-Pechoux, 2003; Rivaud et al, 1994; Schlag-Rey, Amador, Sanchez, & Schlag, 1997; Sweeney, Mintun, Kwee, Wiseman, Brown, Rosenberg, et al., 1996; Wegener, Johnston, & Everling, 2008) implicating these areas in the pathophysiology of ADHD-C.

In our measures of adaptive functioning, ADHD participants were more likely to have repeated grades and to have been arrested than Control participants. This finding replicates larger investigations that have reported more negative outcomes in ADHD (i.e., academic failure, lower educational attainment and legal troubles) (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007; Barkley et al., 1990; 2006; Barkley, Fischer, Smallish, & Fletcher, 2004; Biederman et al., 2009; Faraone et al., 1993; Fischer et al., 1990; Fischer, Barkley, Fletcher, & Smallish, 1993; Hinshaw, 1992; Mannuzza et al.,
2008; Satterfield et al., 1982; Satterfield & Schell, 1997; Semrud-Clikeman et al., 1992; Weiss & Hechtman, 1986). Our results suggest an important relationship between laboratory measures and real world measures, with antisaccade errors in late adolescence the only measure in our study to be significantly associated with number of arrests.

The findings of this study must be considered in the context of its limitations. The sample sizes in the current study are small, reducing our power to detect small effects. One important non-significant effect of interest, predictive saccades in late adolescence, had an effect size in the medium range (d = .36); a sample of 125 participants would be required for this effect to achieve significance. The magnitude of this non-significant effect is overshadowed by the much larger, persistent between-group difference in antisaccade performance (d = 1.05), and the relevance of these deficits to adaptive functioning. In terms of predicting adaptive functioning, two baseline measures showed a trend level correlation with number of arrests, that is, parental ratings of inattention (r = - .46, n=18, p=.058) and percent predictive saccades (r = -.41, n=18, p=.096). As these effect sizes would be significant with a modest increase in sample size, the absence of significant predictors in part reflects the lower power associated with our sample size, rather than an intrinsic inability of earlier measures to predict later behaviour.

Several other limitations deserve consideration. First, because the follow-up was conducted by the same researchers who conducted the baseline assessment, they were not blind to diagnostic group. Nonetheless, the measures of executive function and time reproduction were computerized in both administration and scoring, thus minimizing the potential for biases to affect the results. Second, all participants were male and all but
two were Caucasian (one ADHD-C participant and one Control). Thus our results may not generalize to females or to non-Caucasian ethnic groups with ADHD. Third, ADHD is often associated with comorbid disorders (e.g., Anderson, Williams, McGee, & Silva, 1987; Biederman, Newcom, & Sprich, 1991; Bird, Ganino, Rubio-Stipec, Gould, Ribera, Sesman, et al., 1988) but the ADHD participants here had been selected in early adolescence to be free of comorbid disorders other than ODD. Therefore, the outcomes observed here may differ from outcomes in samples with a higher degree of comorbidity. The advantage of this approach is that the data elucidate the longitudinal course of executive functioning in ADHD without the confound of such frequently comorbid conditions as conduct disorder, anxiety and depression (Biederman et al., 1991; Spencer, 2006) which themselves compromise executive function (e.g., Micco, Henin, Biederman, Rosenbaum, Petty, Rindlaub, et al., 2009; Sergeant, Geurts, & Oossterlaan, 2002). Finally, maturation of the frontal lobe is not thought to be completed until the mid-20s or later (Gogtay, Giedd, Lusk, Hayashi, Greenstein, Vaituzis, et al., 2004; Huttenlocher, 1990; Sowell, Thompson, & Toga, 2004), and antisaccade performance similarly improves to the mid twenties (Fischer et al., 1997; Munoz et al., 1998). In the current study, the substantial age-related improvement in antisaccade performance across all groups is consistent with the notion of an improvement with maturation of neural circuitry. However, it has been hypothesized that ADHD is associated with delayed maturation (El-Sayed et al., 2003; Kinsbourne, 1973; Russell et al., 2006). At their current ages, our participants have presumably not reached their asymptote of performance and thus it is possible that ADHD-C could ultimately achieve normotypic performance, although presumably at a later age than Controls.
Conclusions:

Our 5-year follow-up study found that the ADHD participants had poorer adaptive functioning than Controls, but that only the ADHD-C group was impaired in our laboratory measure of inhibition. Across the ADHD groups, laboratory-assessed disinhibition was significantly associated with number of arrests. The stability of inhibitory performance across age span and symptom variation, the association with adaptive functioning, and the impairment in ADHD-C at both time periods, is consistent with the conceptualization of disinhibition as a core deficit in ADHD-Combined subtype.
4.6 REFERENCES


Chapter Four: Developmental Course of Executive Functioning


Chapter Four: Developmental Course of Executive Functioning


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CHAPTER FIVE: PREFACE

In Chapter Four, I described a longitudinal follow-up study of oculomotor measures of executive functioning in subtypes of Attention Deficit Hyperactivity Disorder (ADHD). I reported that deficits in oculomotor response inhibition observed in early adolescence in boys with ADHD-Combined persisted in late adolescence, while their deficits in motor planning remitted. In Chapter Five, I conducted an fMRI investigation of these oculomotor tests of executive function. The primary goal of the study was to determine whether deficits in inhibition reflected differences from Controls in functioning of frontal-subcortical circuitry and whether differences between the ADHD-Combined group and Controls would be observed only in the task in which the group was impaired, or also in the task in which their performance had normalized. Additional goals included investigating whether the two ADHD subtypes had common or distinct neural substrates. Common neural substrates would provide support for the current conceptualization of ADHD whereas different neural substrates would suggest the subtypes might be better characterized as distinct disorders.
Chapter Five: fMRI Investigation of Executive Functioning

Chapter Five:

Functional Magnetic Resonance Imaging Investigation of Executive Function in Subtypes of ADHD

Experiment 4
5.1 ABSTRACT:

**Background:** Attention Deficit Hyperactivity Disorder (ADHD) is associated with deficits in oculomotor inhibition. Here we used functional magnetic resonance imaging (fMRI) to investigate the neural substrates of antisaccade performance in the ADHD-Combined and ADHD-Inattentive subtypes. We hypothesized that the ADHD-Combined group would show reduced activation of frontal-subcortical circuitry and that task-related activation would be correlated with antisaccade performance.

**Methods:** Control (n = 10), ADHD-Inattentive (n = 8) and ADHD-Combined (n = 9) adolescent males performed the antisaccade (response inhibition) and predictive saccade (motor planning) tasks along with matched control tasks during fMRI. Eye movements were monitored in the scanner. Brain areas more active in antisaccades and predictive saccades were identified in the three groups. Activations in the three groups were compared using FMRISTAT. In addition, correlations were used to investigate the relationship between activation and performance and between activation and parent ratings of ADHD symptoms.

**Results:** Compared to Controls, both ADHD groups showed significantly increased antisaccade errors rates. During antisaccades, Controls activated frontal eye fields (FEFs), left supplementary eye fields, left precuneus, right superior parietal cortex, right putamen, and cerebellar lobules VI and IX. Both ADHD groups showed reduced activation of frontal-subcortical circuitry, including right FEFs, putamen and cerebellar lobule VI. The ADHD-Combined group also showed reduced activation in dorsal parietal cortex compared to Controls and to the ADHD-Inattentive group. Antisaccade
errors and parent ratings of ADHD symptoms were significantly correlated with activation in precuneus.

**Conclusions:** Oculomotor disinhibition and reduced activation in frontal-subcortical circuitry were found in both subtypes. Activations in both frontal and parietal regions of the dorsal attentional network were associated with task performance in the scanner, while dorsal parietal activation was related to subtype and to clinical measures of symptom severity.
INTRODUCTION:

Attention Deficit Hyperactivity Disorder (ADHD) is characterized by developmentally inappropriate symptoms of inattention, motor hyperactivity and impulsivity (American Psychiatric Association, 1994). Executive functions are abilities that allow the generation of willed, controlled and actively guided behaviours (Slattery, Garvey, & Swedo, 2001). Impairments in executive functioning are reflected in a predominance of behaviours that are reflexive, prepotent or automatic.

The clinical presentation of ADHD certainly suggests deficits in the voluntary control of attention and motor behaviour. Indeed, deficits in executive functions in ADHD have been shown in neuropsychological tests tapping response inhibition, motor planning, set shifting, attention and working memory (Barkley, Grodzinsky, & DuPaul, 1992; Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Douglas, 1999; Pennington & Ozonoff, 1996; Shue & Douglas, 1992; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Deficits in inhibitory function have been proposed to be at the core of difficulties experienced in ADHD and possibly to underlie deficits in other executive functions (Barkley, 1997).

The antisaccade task has been used extensively to investigate inhibitory function in humans and in non-human primates (e.g., Everling & Munoz, 2000; Funahashi, Bruce, & Goldman-Rakic, 1991; Gagnon, O’Driscoll, Petrides, & Pike, 2002; Hikosaka, 1989; O’Driscoll, Alpert, Matthisse, Levy, Rauch, & Holzman, 1995; O’Driscoll, Wolff, Benkelfat, Florencio, Lal, & Evans, 2000; Sweeney, Mintun, Kwee, Wiseman, Brown, Rosenberg, & Carl, 1996). An advantage of this task is that it has a natural comparison task that allows some isolation of the executive function of interest, and that its neural
correlates have been well-described. Electrophysiological studies of non-human primates and neuroimaging studies of humans show that normal antisaccade performance relies on frontal-subcortical circuitry (e.g. Everling & Munoz, 2000; Funahashi et al, 1991; Gagnon et al, 2002; Hikosaka, 1989; O’Driscoll et al, 1995, 2000; Sweeney et al, 1996), and lesion data in both populations show impairment after damage to frontal and striatal regions (e.g. Funahashi, Bruce, & Goldman-Rakic, 1993; Guitton, Buchtel, & Douglas, 1985; Keating, 1991; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Pierrot-Deseilligny, Muri, Ploner, Gaymard, Demeret, & Rivaud-Pechoux, 2003; Rivaud, Muri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994). The areas tapped by the antisaccade task are also involved in attention and motor control (Corbetta, Akbudak, Conturo, Snyder, Ollinger, Drury, et al, 1998; Gitelman, Nobre, Parrish, LaBar, Kim, Meyer, & Mesulam, 1999; Schall, 2004), two key areas of dysfunction in ADHD.

Antisaccade deficits have been reported in ADHD. Increased antisaccade errors (Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Klein, Raschke, & Brandenbusch, 2003; Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001a; Mostofsky, Lasker, Singer, Denckla, & Zee, 2001b; Munoz, Hampton, Moore, & Goldring, 1999; Munoz, Armstrong, Hampton, & Moore, 2003), and increased antisaccade latency (Klein et al, 2003; Munoz et al, 1999, 2003) have been found. In addition, individuals with ADHD have been reported to have difficulty withholding saccades during a delay in a memory-guided saccade task (Ross, Harris, Olincy, & Radant, 2000). These findings are consistent with impulsivity in ADHD, and with involvement of frontal-subcortical dysfunction in ADHD.
Functional neuroimaging investigations have linked disinhibition in ADHD to abnormal activation of frontal-subcortical circuitry (Durston, 2003; Durston, Tottenham, Thomas, Davidson, Eigsti, Yang, et al, 2003; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, & Bullmore, 1999; Rubia, Taylor, Smith, Oksannen, Overmeyer, & Newman, 2001; Vaidya, Austin, Kirkorian, Ridlehuber, Desmond, Glover, & Gabrieli, 1998). These studies have generally used variations of the stop-signal task, the go/no-go task, the Continuous Performance Task (CPT) and the Stroop task. Findings have included decreased activation in frontal areas (Booth, Burman, Meyer, Lei, Trommer, Davenport, et al, 2005; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Durston, Davidson, Mulder, Spicer, Galvan, Tottenham, et al, 2007; Epstein, Casey, Tonev, Davidson, Reiss, Garrett, et al, 2007; Pliszka, Glahn, Semrun-Clikeman, Franklin, Perez III, et al, 2006; Rubia et al, 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Rubia, Halari, Smith, Mohammed, Scott, Giampietro, et al, 2008; Smith, Taylor, Brammer, Toone, Rubia, 2006; Suskauer, Simmonds, Foteder, Blankner, Pekar, Denckla, & Mostofsky, 2008; Zang, Jin, Weng, Zhang, Zeng, Yang, et al, 2005), dorsal anterior cingulate (Bush, Frazier, Rauch, Seidman, Whalen, Jenike, et al, 1999; Durston et al, 2007; Pliszka et al, 2006; Tamm, Menon, Ringel, & Reiss, 2004; Zang et al, 2005), striatum (Booth et al, 2005; Durston et al, 2003; Epstein et al, 2007; Rubia et al, 1999; Vaidya et al, 1998) and cerebellum (Durston et al., 2007; Suskauer et al., 2008; Zang et al., 2005). However, this general summary masks many inconsistencies: for example, of five studies of the go/no-go task, three reported increased ventral prefrontal activation in ADHD (Durston et al, 2003; Schultz et al, 2004; Vaidya et al, 1998), one reported a significant decrease in this area (Booth et al, 2005) and one found no difference (Tamm...
et al, 2004). Similarly, inconsistent findings have been reported with regard to activation in the striatum and anterior cingulate cortex (Booth et al, 2005; Durston et al, 2003; Schulz, Fan, Tang, Newcorn, Buchsbaum, Cheung, & Halperin, 2004; Tamm et al, 2004; Vaidya et al, 1998).

Contributing to inconsistencies may be the heterogeneous nature of ADHD. Several functional neuroimaging investigations have averaged across participants with ADHD-C and ADHD-I (Booth et al, 2005; Durston et al, 2003; Schulz et al, 2004; Vaidya et al, 1998) although these subtypes are clinically distinct and may not be part of the same disorder (e.g., Diamond, 2005; Milich, Balentine, & Lynam, 2001). Sample homogeneity can be increased by including only the Combined subtype (Rubia et al, 2005; Tamm et al, 2004; Vaidya, Bunge, Dudukovic, Zalecki, Elliott, & Gabrieli, 2005) or by looking at the subtypes as separate groups. The latter approach has the advantage of elucidating the similarities and differences in the pathophysiology of the two groups.

To date, only one study has used functional Magnetic Resonance Imaging (fMRI) to investigate the neural substrates of executive functioning in subtypes of ADHD (Solanto, Schulz, Fan, Yang, & Newcorn, 2009). In that study, children with ADHD-I and ADHD-C subtypes performed a go/no-go task while in the scanner. The two groups did not differ in task performance. The only difference between the groups in an *a priori* area was in the middle frontal gyrus bilaterally, where the ADHD-C group had lower activation than the ADHD-I’s (Solanto et al, 2009). They also had lower activation in inferior parietal lobe, which the authors attributed to the Inattentives overactivating this region. However, as there was no Control group, it is impossible to know whether
differences between the groups constituted overactivation (inefficiency) in one group vs. hypoactivation in the other.

In the present study, we investigated the neural substrates of disinhibition in subtypes of ADHD. As our behavioural study had found executive function deficits in participants originally diagnosed as ADHD-C, we hypothesized that any task-related differences in activation from Controls would be greater in this subtype. We hypothesized differences in activation would be found in the frontal-subcortical circuitry that support oculomotor inhibition, and further that the decreased activation in these structures would relate to performance and possibly to symptoms.

5.3 METHODS AND MATERIALS:

5.3.1 Participants

Participants who had taken part in Experiment 3 (i.e., behavioural follow-up) were invited to take part in an fMRI study assessing brain areas implicated in executive functions in ADHD. All but one participant (who was ineligible due to dental braces) took part in the fMRI study (Table 5.1). Time between the behavioural follow-up (Experiment 3) and fMRI (Experiment 4) sessions did not differ across groups (average 199.15 days ± 150.26 days) (F(2,26)=.92, p=.41).
Table 5.1  Demographics and Diagnostic Characteristics at Follow-Up

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control Participants</th>
<th>ADHD-I</th>
<th>ADHD-C</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (at follow-up/at baseline)</td>
<td>(10/10)</td>
<td>(8/12)</td>
<td>(9/10)</td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>19.2 ± 1.97</td>
<td>17.71 ± 0.89</td>
<td>18.47 ± 1.39</td>
<td>0.14</td>
</tr>
<tr>
<td>Full-Scale IQ</td>
<td>112 ± 12.18</td>
<td>111 ± 12.46</td>
<td>109.06 ± 8.76</td>
<td>0.83</td>
</tr>
<tr>
<td>Father’s SES1</td>
<td>2.63 ± 1.85</td>
<td>4.57 ± 1.40</td>
<td>3.44 ± 1.74</td>
<td>0.11</td>
</tr>
<tr>
<td>Currently Prescribed MPH (n)</td>
<td>2</td>
<td>3</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>DSM-IV Symptoms2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td>.23 ± .27</td>
<td>1.11 ± .46</td>
<td>1.83 ± .59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyperactivity/Impulsivity</td>
<td>.08 ± .17</td>
<td>.45 ± .51</td>
<td>1.73 ± .56</td>
<td>0.001</td>
</tr>
<tr>
<td>Syndromatic Persistence3</td>
<td>2</td>
<td>7</td>
<td></td>
<td>0.053</td>
</tr>
<tr>
<td>Symptomatic Persistence4</td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or n. Data were analyzed by one-way analysis of variance.

ADHD-C, Attention Deficit Hyperactivity Disorder-Combined type; ADHD-I, ADHD-Inattentive;
IQ, intelligence quotient; MPH, methylphenidate.

1SES, socioeconomic status; father’s occupation ranked on an ordinal scale from 1 (major professional) to 9 (unemployed), from a modified version of the Index of Social Status (Hollingshead and Redlich, 1958).

2Parent ratings of their child’s symptoms on the Inattention and Hyperactivity-Impulsivity scales of the Child Symptom Inventory-4 Rating scale (Gadow & Sprafkin, 1994, 1998). A score of 1.5 is considered clinically significant.

3Syndromatic Persistence: Defined as meeting full DSM-IV criteria for ADHD-I or ADHD-C (Biederman et al, 2010). In the ADHD-C group, 7 participants continued to meet full criteria for ADHD; of these, 3 met criteria on both hyperactivity/impulsivity and inattention symptoms, and 4 were now subthreshold for hyperactivity/impulsivity symptoms but continued to meet diagnostic criteria on inattention symptoms.

4Symptomatic Persistence: Participants who continued to show more than half of the symptoms required for a full diagnosis.

5.3.2 Tasks

Antisaccade and Prosaccade Tasks

For the two tasks, target movement was identical; only the instructions differed (“look toward the target when it appears” vs. “don’t look toward the target; look to the mirror position on the opposite side of the screen.”) The target was presented at the center of the screen for 1100, 1300 or 1500 ms. It then stepped to the left or right 9 degrees, with direction randomized. Subjects performed 15 trials twice in each of 4 runs for a total of 120 trials.

Predictive Saccade and Non-Predictive Saccade Control Tasks

The instructions were the same for both tasks (i.e., “Keep your eyes on the square,
don’t go ahead, don’t fall behind”). For both tasks, the target moved in steps of 9 degrees. In the predictive saccade task, the target moved at fixed intervals of 600ms from left to center to right and back to center in a repeating sequence. For the non-predictive saccade control task, the target moved at variable intervals (400, 600 or 800ms) with the direction of the target step from center randomized. Thus, for the predictive saccade task, the timing and direction of target movements were predictable, while for the non-predictive control task neither the timing nor the direction from center were predictable.

Fixation

A target was presented in the centre of the screen for 30s. This task was a non-saccadic control for all tasks.

5.3.3 Apparatus

Oculomotor data were recorded from the subject’s right eye for all but one subject. During image acquisition, the ISCAN fMRI Remote Eye Imaging System (ISCAN, Woburn, MA) was used to record eye movements. The eye was illuminated with an infrared source attached to the head coil (n=20) or mounted at the back of the scanner (n=3). A mirror angled at 45° was attached to the head coil and reflected the infrared image of the eye. This was captured by a video camera mounted at the back of the scanner bore. Visual stimuli were generated using E-prime and presented on an active-matrix projector running in 1024 x 728 mode at 60 Hz (light output 1000 ANSI lumens) that was viewed using a rear-projection system (Epson multimedia projector, EMP-8300, Meerbusch, Germany). The scanner, stimulus presentation and data acquisition were synchronized using a transistor-transistor logic (TTL) 5 volts signal sent
by the scanner to the E-Prime computer which in turn signaled the eye tracker to start recording at the start of each run. The beginning of each task and the stimuli were digitally encoded and included in the ISCAN data file. This system samples eye position at 60 Hz and can detect eye movements as small as 0.3 degrees in amplitude across 20° (horizontal range). A five point calibration was performed prior to each functional run.

**Image Acquisition**

A 3.0 tesla Magnetom TRIO (Siemens Medical Systems, Erlangen, Germany) whole-body high-speed imaging scanner was used to collect the images. Automated shimming procedures were used for all sequences, and scout images were obtained. A spoiled gradient-recalled echo pulse sequence [TR (repetition time) = 22 ms, TE (echo time) = 4.92 ms, flip angle = 25°] was used to acquire 3D high-resolution T1-weighed anatomical scans through the whole head. This yielded 176 slices with 1mm thickness and a nominal in-plane resolution of 1mm x 1mm (field of view (FOV) = 256 mm, matrix = 256 x 256). T2*-weighed functional images sensitive to blood-oxygen-level-dependent (BOLD) contrast were acquired using a single-shot gradient-recalled echo-planar imaging sequence (TR = 3000 ms, TE = 30, flip angle = 90°). Twenty-three 6mm thick axial-oblique slices were acquired and overlaid on the high resolution T1 anatomical scans of each subject, and positioning was checked on the parasagittal slice. Slice coverage was chosen so that the whole brain was scanned including the cerebellum. In-plane resolution for these images for all but one subject was 3.44 mm x 3.44 mm x 6 mm (FOV = 220 mm, matrix = 64 x 64). For the remaining subject, the in-plane resolution was 5 mm x 5 mm (FOV 320 mm, matrix = 64 x 64). During each of the 4 runs, 120 measurements of
3-s duration were acquired in ascending order (slices were interleaved: odds then evens). Therefore, a total of 480 scans were acquired for each subject. To minimize the impact of motion, a 3D prospective acquisition correction (PACE) for head motion (Thesen, Heid, Mueller, & Schad, 2000) was used during functional scans.

5.3.4 Procedures

Participants were habituated to the scanner environment in a mock scanner. They were also introduced to the abbreviated task instructions used in the scanner and practiced performing each task. Participants were then scanned in the MRI with eye movements monitored with an MRI-compatible system (ISCAN Ltd., Woburn, MA, USA). Eye movement recordings during scanning were not available or not scorable for 4 participants (one Control, one ADHD-I and two ADHD-Cs). During scanning, the head was stabilized with ear cushions and a positioning stabilizer integrated into the head coil equipment. In addition, when head size allowed, a vacuum cushion was used. All participants wore earplugs to attenuate scanner noise.

In the MRI, anatomical scans were acquired first, then the four functional runs. In each functional run, participants performed the 2 experimental tasks, the matched control tasks and fixation. Tasks were presented in palindromic order (ABCDEEDCBA), and order was counterbalanced across subjects using a digram-balanced Latin square to ensure that each task appeared at least once in each position, and to ensure that each task preceded and followed each of the other four tasks at least once. Each task was presented twice for 30 seconds in each run. Each run lasted 6 minutes (5 minutes of testing, plus instruction screens and time between the tasks).
5.3.5 Analysis

Data Analysis

Eye Movement Data Preprocessing

The oculomotor data acquired during the fMRI session were treated similarly to eye movement data acquired during Experiments 1, 2 and 3 except that the data were outputted to Excel files.

Image Processing

Individual anatomical MRI images were transformed into 3D Talairach space (Talairach & Tournoux, 1988) using a three-dimensional image cross-correlation algorithm (Collins, Neelin, Peter, & Evans, 1994) where the MRI is resampled by a linear transform to match the target volume (a database of 152 MRI volumes transformed to Talairach space through identification of neuroanatomical landmarks).

Preprocessing of functional data included a motion-correction where all time points were co-registered using a routine developed at the Montreal Neurological Institute. The third scan of each run was used as the reference. These data were then smoothed using a low-pass filter with a 6mm full-width at half-maximum (FWHM) Gaussian Kernel. Slices in which a subject displayed more than 1 mm of motion in x, y and/or z directions were excluded from the analyses. One run from one participant in each group was excluded from the imaging analyses due to motion artifact. Estimated motion parameters in x, y and z directions did not differ between the groups (all p’s > 0.45).
**Statistical Analysis**

Functional Imaging Data Analyses

For each subject, the differences in BOLD signal between task pairs were calculated within each run and then averaged across the four runs using fMRISTAT (Worsley, Liao, Grabove, Petre, Ha, & Evans, 2000). Images reflecting activity differences for each individual were then transformed into the standard Talairach stereotaxic space (in the same manner as for the anatomical images) and resampled at a higher resolution (2 x 2 x 2 mm). Group activation maps were generated for each of the three groups and overlaid on high resolution 3D average anatomical scans.

Two regions of interest -- the frontal eye fields and the supplementary eye fields -- were established *a priori* based on previous imaging studies (e.g. Gagnon et al, 2002; O’Driscoll et al, 1995; O’Driscoll, Benkelfat, Florencio, Wolff, Joober, Lal, & Evans, 1999; O’Driscoll et al, 2000). These regions of interests were defined using Talairach coordinates (**FEF**: X: -20 to -40 mm for left hemisphere and 20 to 40 mm for the right hemisphere, Y: 5 to -15 mm, Z: 40 to 60 mm; **SEF**: X: 0 to +/-12, Y: 10 to -20, Z: 44 to 66 mm (Gagnon et al, 2002; review by Grosbras, Lobel, Van de Moortele, LeBihan, & Berthoz, 1999)). The search volumes (33.84 (FEFs) and 33.05 (SEFs) resolution elements or resels) created by these definitions yielded significance thresholds of *t*=4.0.

Significance thresholds for activation (i.e. differences between the experimental task and the control task) in other areas were established using the minimum peak activation given by random fields theory and a Bonferroni correction using a search volume of 1000 mm$^3$ (Worsley, Marrett, Neelin, Vandal, Friston, & Evans, 1996), i.e. a peak activation $> 4.79$. We expected all groups to show some activation in task-related
regions during task performance because even impaired performance involves a large majority of correct responses. Thus, for the analyses comparing degree of activation between groups, the significance threshold was set to 3.17 (p<.001 uncorrected) to increase the power to detect differences.

**Correlations with Performance:**

To identify variation in neural activation that might underlie performance deficits on the antisaccade task, we used two approaches. In the first approach, we identified brain areas significantly activated by Controls and showing some activation (t>2.0 within vector distance ≤ 1 cm) in the two ADHD groups. Correlational analyses were subsequently run between activation in these regions and antisaccade error rate. We required that all groups show some activation for the region to be used in the correlational analysis because otherwise regions activated by chance in the Control group could create correlations with performance since the Controls also had few antisaccade errors. Although this approach is insensitive to error differences in regions truly activated only in Controls, the fact that both ADHD groups had ≥ 80% correct on antisaccades suggests that brain regions necessary for successful antisaccade performance should show some evidence of activation. In the second approach, we used between-group statistical maps (e.g., Controls minus ADHD-Cs on the antisaccade minus prosaccade subtraction) to identify regions where the magnitude of task-related activation differentiated the groups. For regions that differentiated between the groups in the statistical map and also showed evidence of at least some activation in the ADHD groups (t>2.0), the magnitude of activation at the peak was extracted for each participant and the
correlation of the magnitude of activation with performance (i.e., antisaccade errors) was evaluated using Pearson’s r. To ensure the correlations were not driven by leavers we excluded datapoints with excessive influence on the correlation using Cook’s Distance (SPSS 18) (Plaxco, Simons, & Baker, 1998).

To identify areas that might underly the clinical symptoms of ADHD, we looked for associations between activation and parametric variation in parent ratings of symptom severity. Areas where activation differentiated between the Controls and ADHD groups were identified. The relationship between symptom severity and activation in these areas was assessed with Pearson’s r. Since the areas of interests were those that had lower activation in the ADHD groups than Controls and the ADHD groups had by definition higher symptoms we did not run the correlations across Controls and ADHD groups. Instead we evaluated the correlations within the ADHD groups only.

**Predictive Saccade–Non-Predictive Saccade Control Tasks subtraction:**

We approached this between task comparison in the same way as for the antisaccade-prosaccade subtraction. No activation differences were found between the predictive saccade and non-predictive control task (see results below). Therefore further analyses of task-related activation were not conducted.

The alpha level for the analyses was set at 0.05. Data are reported as the means ± standard deviations.

Behavioral analyses were done using SPSS 18.0 (SPSS for Windows, Rel. 18.0. 2009).
5.4 RESULTS:

5.4.1 Antisaccade Performance:

In the scanner, there was a significant main effect of Group (F(2,22) = 8.25, \( p = 0.002 \)) on antisaccade error rates. Both the ADHD-C (\( t(20) = -3.24, p = 0.004 \)) and unexpectedly the ADHD-I (\( t(20) = -3.62, p = 0.002 \)) participants made more errors in the scanner than Controls. The two ADHD groups did not differ from each other (\( t(20) = -0.36, p = 0.72 \)) (Figure 5.1).

**Figure 5.1. fMRI Antisaccade Errors.**

There was a main effect of Group (F(2,22) = 8.25, \( p = 0.002 \)) with both ADHD groups making significantly more errors than Controls in the scanner. Two Control participants are represented with one triangle at 11% error, two ADHD-I participants are represented with one triangle at 21% error and two ADHD-C participants are represented with one triangle at 12% error. (One ADHD-I participant and one ADHD-C participant yielded eye movement data that were too noisy to score, and the eye-tracker was not available for one ADHD-C participant and one Control). Group means are represented by horizontal bars.
5.4.2 Antisaccade-Related BOLD Activation (Antisaccades – Prosaccades):

Compared to prosaccades, antisaccades significantly activated frontal-subcortical circuitry as well as parietal areas implicated in attention-shifting (Table 5.2, Figures 5.2-5.6). In Controls, large activations were observed in FEFs bilaterally. The ADHD-I group did not activate right FEFs significantly. In left FEFs, Controls activated two distinct peaks, one in the canonical FEF location and one about 1cm more dorsal (dorsal FEFs, reported separately in Table 5.2). In all three groups, activation in the canonical left FEF region exceeded 4.0. Controls also had large peaks in right superior parietal cortex, left precuneus, putamen and in cerebellum (Lobules VI and IX); lesser but significant activation was also observed in SEFs. The ADHD groups activated similar regions to Controls although the activation in left precuneus, putamen and cerebellum failed to reach significance in both ADHD groups. Activation in the SEF also failed to reach significance in the ADHD-I group; the ADHD-C group did activate a dorsomedial region of area 6 (Table 5.2), but the location was 13mm dorsal of the Control peak. Finally, ADHD-C participants activated two areas not activated in Controls, postcentral gyrus in the region of the motor strip eye field (Gagnon et al, 2002; Tehovnik, Sommer, Chou, Slocum, & Schiller, 2000) and supramarginal gyrus.
**Table 5.2 Antisaccade Minus Prosaccade Areas of Activation**

<table>
<thead>
<tr>
<th>Regions of Activation</th>
<th>Controls</th>
<th>ADHD-Is</th>
<th>ADHD-Cs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>Dorsal FEFs R</td>
<td>24</td>
<td>-14</td>
<td>61</td>
</tr>
<tr>
<td>FEFs R</td>
<td>23</td>
<td>-12</td>
<td>53</td>
</tr>
<tr>
<td>Dorsal FEFs L</td>
<td>-22</td>
<td>-12</td>
<td>66</td>
</tr>
<tr>
<td>FEFs L</td>
<td>-22</td>
<td>-12</td>
<td>56</td>
</tr>
<tr>
<td>SEFs¹</td>
<td>-8</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>Motor Strip Eye Fields</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior Parietal R</td>
<td>16</td>
<td>-66</td>
<td>56</td>
</tr>
<tr>
<td>Superior Parietal L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus L dorsal</td>
<td>-10</td>
<td>-56</td>
<td>52</td>
</tr>
<tr>
<td>Precuneus R dorsal</td>
<td>8</td>
<td>-60</td>
<td>60</td>
</tr>
<tr>
<td>Supramarginal Gyrus R</td>
<td>52</td>
<td>-44</td>
<td>28</td>
</tr>
<tr>
<td>Putamen R</td>
<td>28</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Cerebellar Lobule VI</td>
<td>-34</td>
<td>-48</td>
<td>-30</td>
</tr>
<tr>
<td>Cerebellar Lobule IX¹</td>
<td>-28</td>
<td>-46</td>
<td>-52</td>
</tr>
</tbody>
</table>

ADHD-Is, Attention Deficit Hyperactivity Disorder-Inattentive type; ADHD-Cs, ADHD-Combined
Coordinates and t values that are bolded are significant.
¹ Locations of activation in the region are >1cm apart.
Figure 5.2. *Right FEFs (Antisaccade Minus Prosaccade).*

The slice with the highest activation in this region for each group is shown (see Table 5.2). Significance threshold was 4.0 for this *a priori* region. In ADHD-Is, activation did not reach threshold. Antisaccade related activation of right FEFs significantly differentiated Controls from both groups (see Table 5.3).

Figure 5.3. *“SEFs” (Antisaccade Minus Prosaccade).*

Activation is shown at the dorsomedial slice with the highest SEF activation in each group (for coordinates, see Table 5.2). Significance threshold was 4.0 for this *a priori* region. The peak in the ADHD-I and ADHD-Cs groups is ≥1 cm dorsal to the canonical SEF location (Grosbras et al, 1999). The peak in Controls and ADHD-Cs reached the significance threshold, but the peak in ADHD-Is did not.
**Figure 5.4. Right Superior Parietal Cortex (Antisaccade Minus Prosaccade).**

Activation in right medial superior parietal cortex is shown at the dorsomedial slice with the highest activation for each group (for coordinates see table 5.2). The peaks in this region were significant in Controls and ADHD-Is but just missed the significance threshold in ADHD-Cs. Controls activated this region significantly more than ADHD-Cs (see Table 5.3). ADHD-I activation fell between Controls and ADHD-C’s, with no difference from the Controls but significantly greater activation than ADHD-Cs (see Table 5.3).

**Figure 5.5. Left Precuneus (Antisaccade Minus Prosaccade).**

Activation in left precuneus is shown at the slice of highest activation for each group. Controls significantly activated left precuneus; in ADHD-I activation fell just short of the corrected threshold, while in ADHD-Cs the activation was not significant (see Table 5.2). The difference between groups in left precuneus was largest at x = -8, y = -52, z = 56. ADHD-C participants activated this region significantly less than Controls (see Table 5.3). Other group comparisons did not reach significance threshold.
Figure 5.6. Right Putamen (Antisaccade Minus Prosaccade).

Activation in right putamen is shown at the slice of highest activation for each group. Controls significantly activated right putamen; in both ADHD groups the activation was not significant (see Table 5.2). The difference between groups in right putamen was largest at $x = 30, y = 2, z = 10$. ADHD-I participants activated this region significantly less than Controls and the difference between ADHD-C participants and Controls was a trend level (see Table 5.3).

5.4.3 Group Differences in Antisaccade-Related Activation:

We compared Controls and the two groups of ADHD participants on antisaccade-related activation (antisaccade minus prosaccade) using, as *a priori* regions of interest, the areas activated by antisaccades in Controls (Table 5.2). ADHD-C’s differed from Controls in right FEFs, right superior parietal cortex, left precuneus and cerebellar lobule VI (Table 5.3). ADHD-Is differed from Controls in right FEFs, right putamen and left cerebellar lobule VI. Activation in right superior parietal cortex was the only area to differentiate the two ADHD groups with ADHD-Is showing greater activation than ADHD-Cs (Table 5.3).
Table 5.3. *Group Differences in Antisaccade-Related Activations*<sup>1</sup>

<table>
<thead>
<tr>
<th>Controls vs. ADHD-C’s</th>
<th>Coordinates</th>
<th>T value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>FEF R</td>
<td>20</td>
<td>-12</td>
</tr>
<tr>
<td>Superior Parietal R</td>
<td>16</td>
<td>-66</td>
</tr>
<tr>
<td>Precuneus L</td>
<td>-8</td>
<td>-52</td>
</tr>
<tr>
<td>Putamen R</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Cerebellar Lobule VI L</td>
<td>-34</td>
<td>-48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Controls vs. ADHD-I’s</th>
<th>Coordinates</th>
<th>T value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>FEF R</td>
<td>20</td>
<td>-6</td>
</tr>
<tr>
<td>Putamen R</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Cerebellar Lobule VI L</td>
<td>-34</td>
<td>-42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD-I’s vs. ADHD-C’s</th>
<th>Coordinates</th>
<th>T value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>Superior Parietal R</td>
<td>20</td>
<td>-58</td>
</tr>
</tbody>
</table>

ADHD-C’s, Attention Deficit Hyperactivity Disorder-Combined; ADHD-I’s, ADHD-Inattentive

<sup>1</sup>Magnitude of Activation in Antisaccade-Prosaccade.

*<sup>t</sup> > 3.17 = p < 0.001 uncorrected (see Methods).

<sup>ns</sup>: non-significant.

5.4.4 Relationship between Antisaccade-Related Activation and Antisaccade Performance

The correlation between antisaccade-related activation and antisaccade errors was assessed for the peaks of activation in Controls in Table 5.2 that also showed some activation in the two ADHD groups (see Methods), as well as for the areas where activation had differentiated the groups in Table 5.3. Magnitude of activation was correlated with antisaccade performance in dorsal parietal lobe (Figure 5.7 & 5.8) bilaterally and showed a trend in left dorsal FEFs (Figure 5.9) (Table 5.4). Higher activation was associated with lower antisaccade error rates.
Table 5.4 Correlations Between Activation and Antisaccade Errors

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>x</th>
<th>Y</th>
<th>Z</th>
<th>r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Parietal R&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>16</td>
<td>-66</td>
<td>56</td>
<td>-0.64</td>
<td>0.001</td>
</tr>
<tr>
<td>Precuneus L&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-8</td>
<td>-52</td>
<td>56</td>
<td>-0.61</td>
<td>0.002</td>
</tr>
<tr>
<td>Dorsal FEFs L&lt;sup&gt;1&lt;/sup&gt;</td>
<td>-22</td>
<td>-12</td>
<td>66</td>
<td>-0.41</td>
<td>0.053</td>
</tr>
</tbody>
</table>

<sup>1</sup>Peak from Control group activation in antisaccade-prosaccade comparison (see Table 5.2);  
<sup>2</sup>Peak where activation significantly differentiated Controls from one of the ADHD groups (see Table 5.3).

Correlations were run only if all groups showed activation in the area (i.e., coordinates of activation >2.0 were within 1 cm in the three groups).

Figure 5.7. Activation in Right Superior Parietal and Antisaccade Errors*.

Activation in right superior parietal lobe (x = 16, y = -66, z = 56) was significantly correlated with antisaccade errors (r = -0.64, n = 22, p = 0.001).

*Sample size was different due to the exclusion of a lever in the correlation.
**Figure 5.8. Activation in Left Precuneus and Antisaccade Errors.**

Activation in left precuneus (x = -8, y = -52, z = 56) was significantly correlated with antisaccade errors ($r = -.61, n = 23, p = .002$).

**Figure 5.9. Activation in Left Dorsal FEFs and Antisaccade Errors.**

Activation in left dorsal FEFs (x = -22, y = -12, z = 66) was correlated with antisaccade errors ($r = -.41, n = 23, p = .053$).
5.4.5 Clinical Correlates of Brain Activation

Of the regions where activation significantly differentiated Controls from ADHD participants (Table 5.3), only left precuneus was significantly correlated with parental ratings of symptom severity within ADHD participants. Symptoms of inattention ($r(17) = -.68, p = 0.003$) and symptoms of hyperactivity ($r(16) = -.73, p = .002$) were linearly related to the magnitude of activation in left precuneus (Figures 5.10 & 5.11) with the higher activation associated with lower symptom ratings.

**Figure 5.10 Activation in Left Precuneus and Symptoms of Inattention.**

![Activation in left precuneus and symptoms of inattention](image)

Activation in left precuneus ($x = -8, y = -52, z = 56$) was related to symptoms of inattention in the ADHD groups ($r = -.68, p = 0.003$). Higher activation in this area was associated with lower parent ratings of symptoms of inattention.

---

1 For the correlations between parent ratings of ADHD symptoms and activation, sample size varies slightly since analyses were conducted excluding levers.
Figure 5.11 *Activation in Left Precuneus and Hyperactivity/Impulsivity.*

Activation in left precuneus (x = -8, y = -52, z = 56) was related to symptoms of hyperactivity/impulsivity (r = -.73, p=.002) with the higher the activation in this area, the lower the parent ratings of symptoms of hyperactivity/impulsivity.

5.4.6 Predictive Saccades-Related Changes in BOLD Activation

The purpose of the fMRI scans of predictive saccades was to determine whether any activation differences between groups obtained in the antisaccade task would be found as well in a task where performance between groups did not differ. However, no region differentiated significantly between predictive saccades and non-predictive saccades in Controls. This was likely due to changes made in adapting the tasks to the scanner. Specifically, in order for the control task to match the predictive saccade task in number of saccades per scan, fixation times at each location were shortened (400-800ms). This made following the target more challenging, a change that fostered predictive behaviour even when the target direction was not predictable. Thus behaviour in the
control task shifted from being visually guided to being predictive, effectively eliminating activation differences between the two conditions.
5.5 DISCUSSION:

We investigated the neural underpinnings of executive functions in subtypes of ADHD. Our main findings are that: 1) both ADHD subtypes had significantly elevated antisaccade error rates and significantly reduced activation of frontal-subcortical circuitry compared to Controls; 2) the ADHD-C group also had significantly reduced activation in dorsal parietal cortex in comparison to both Control and ADHD-I participants; 3) antisaccade error rate was related to activation in dorsal parietal cortex (left precuneus and right superior parietal lobe) and left dorsal FEFs; and 4) across the ADHD groups, parent ratings of inattention and hyperactivity were significantly related to activation in left precuneus.

The current study is the first to evaluate the neural basis of antisaccade deficits in ADHD with fMRI and the first to investigate differences in neural activation between the ADHD subtypes with respect to Controls. One previous study compared neural activation in the ADHD subtypes but did not include a Control group (Solanto et al., 2009). Without a healthy reference, it was not possible to know whether differences in activation between the ADHD groups represented inefficiency (overactivation) in one group or hypoactivation in the other.

We found evidence that the two subtypes have both common and distinct neural substrates. For example, both ADHD groups activated FEFs significantly less than Controls. However, the ADHD-C group also had lower activation found in dorsal parietal lobe (left precuneus and right superior parietal, both in BA 7). The involvement of these additional regions in the ADHD-C group may reflect greater neural involvement associated with the presence of symptoms of hyperactivity/impulsivity, or the greater
severity of symptoms in the ADHD-C group. With more members of this group showing syndromatic persistence (Table 5.1), we may have had more power to detect the neural correlates of their impairments.

The reduced activation in FEFs and the correlation between FEF activation and antisaccade error rates are consistent with an important role for FEF activity in antisaccades. That FEFs play a crucial role in antisaccade performance (Guitton et al, 1985; Sumner, Edden, Bompas, Evans, & Singh, 2010) is suggested by both human lesion (Guitton et al., 1985) and brain-imaging studies (Curtis & D’Esposito, 2003; Doricchi, Perani, Incoccia, Grassi, Cappa, Bettinardi et al, 1997; Johnston & Everling, 2008; O'Driscoll et al., 1995; Sweeney et al., 1996) and from studies of non-human primates (Everling & Munoz, 2000; Schlag-Rey, Amador, Sanchez, & Schlag, 1997). Single-unit firing in FEFs differentiates between antisaccades and prosaccades and between correct antisaccades and antisaccade errors (e.g., Everling & Munoz 2000). Although in single-unit studies of non-human primates, firing in FEF pyramidal cells is lower in antisaccades than prosaccades, in neuroimaging studies of humans, FEF activation is higher in antisaccades (Brown, Goltz, Vilis, Ford, & Everling, 2006; Brown, Vilis, & Everling, 2007; Connolly, Goodale, Desouza, Menon, & Vilis, 2000; Connolly, Goodale, Menon, & Munoz, 2002; Connolly, Goodale, Goltz, & Munoz, 2005; Curtis & D’Esposito, 2003; DeSouza, Menon, & Everling, 2003; Ford, Goltz, Brown, & Everling, 2005; Kimmig, Greenlee, Gondan, Schira, Kassubek, & Mergner, 2001). These differences are thought to reflect the different signal sources in the two methods, with single unit studies reflecting the firing of pyramidal neurons while BOLD signals reflect local field potentials that tap as well intracortical processing, such as the activity of
interneurons that inhibit pyramidal firing (Ford, Gati, Menon & Everling, 2009; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001, but see Lee, Durand, Gradinaru, Zhang, Goshen, Kim, et al, 2010). Recently, GABA concentrations in FEF have been significantly correlated with antisaccade performance, consistent with the notion that neurochemical inhibition in FEF is critical for correct antisaccades (Sumner et al, 2010). The findings in the current study, that the degree of FEF activation is related to antisaccade error rate is consistent with the notion that FEF activity influences the success of saccade inhibition.

Our data are also consistent with FEF involvement in ADHD. Structural studies of premotor cortex, the area of frontal cortex where FEFs are located (Paus, 1996), have suggested abnormalities in ADHD. Specifically, ADHD children have been reported to have reduced premotor cortex grey matter volumes (Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Shaw, Lerch, Greenstein, Sharp, Clasen, Evans, et al, 2006) and delayed attainment of peak cortical thickness in this area (Shaw, Eckstrand, Sharp, Blumenthal, Lerch, Greenstein, et al, 2007). Premotor cortex volume, and frontal eye field volume within premotor cortex, have been reported to be negatively correlated with antisaccade error rates in other clinical populations (Boxer, Garbutt, Rankin, Hellmuth, Neuhaus, Miller, et al, 2006; Buschman & Miller, 2009; Ettinger, Kumari, Chitnis, Corr, Crawford, Fannon, et al, 2004). Further, FEFs have been implicated in the strategic control of attention (Corbetta et al, 1998; Corbetta & Shulman, 2002; Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Juan, Shorter-Jacobi, & Schall, 2004; Schall, 2004; Thompson, Biscoe & Sato, 2005; Wardak, Ibos, Duhamel, & Olivier, 2006) an area of reliable deficit in ADHD (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005;
Willcutt et al, 2005). Thus, the activation differences in FEFs found here between the ADHD groups and Controls may relate not only to deficits in oculomotor inhibition, but also to impairments in attention.

Our findings are consistent with involvement of frontal-subcortical circuitry in both ADHD subtypes, as differences were found not only in FEFs but also in right putamen and in cerebellar hemispheres. Several previous studies have reported activation of right putamen during antisaccades in healthy controls (e.g., O’Driscoll et al, 1995; Sweeney et al, 1996). The observation here that Controls activated putamen but neither ADHD group did is consistent with some earlier reports of putaminal hypoactivation in ADHD (Cao et al, 2008; Rubia et al, 2005, 2009) and adds to this literature by indicating that striatal abnormalities play a role in both subtypes. Cerebellar hemispheres are activated during tests of inhibition (Liddle, Kiehl, & Smith, 2001; Mostofsky, Schafer, Abrams, Goldberg, Flower, Boyce, et al, 2003; Rubia, Smith, Woolley, Nosarti, Heyman, Taylor, & Brammer, 2006; Rubia, Smith, Taylor, & Brammer, 2007) including the antisaccade task (Luna, Thulborn, Munoz, Merriam, Garver, Minshew, et al, 2001). Cerebellum is reciprocally connected with motor areas in precentral gyrus (Kelly & Strick, 2003), including the FEFs (Lynch, Hoover, & Strick, 1994). A developmental fMRI study of antisaccades found that recruitment of lateral cerebellum and right FEFs during antisaccades increases with age, such that children and adolescents show smaller activation differences between antisaccades and prosaccades than adults (Luna et al, 2001). Structural studies of cerebellar development in ADHD have suggested that volumetric reductions in cerebellar hemispheres diminish with age (Mackie, Shaw, Lenroot, Pierson, Greenstein, Nugent, et al, 2007). Thus the differences here between
both ADHD groups and Controls may reflect a delay in the maturation of neural circuitry of cerebellum supporting antisaccades and response inhibition.

There is now a growing body of evidence implicating deficits in brain structures outside frontal-subcortical circuitry in the pathophysiology of ADHD (Cherkasova & Hechtman, 2009). We found robust evidence for parietal involvement in ADHD-C, with two dorsal parietal areas, left precuneus and right superior parietal lobe (adjacent regions in Brodmann area 7), activated significantly less in ADHD-C participants than Controls. Lower activation in both these regions correlated with higher antisaccade errors. Further, lower activation in left precuneus was correlated with higher parental ratings of inattention and hyperactivity/impulsivity.

The decreased dorsal parietal activation observed here could reflect deficits in the “dorsal attentional network” in ADHD (e.g. Silk, Vance, Rinehart, Egan, O’Boyle, Bradshaw, & Cunnington, 2005). The dorsal attentional network includes structures that are at the interface of cognition and motor control, including the frontal eye fields and posterior parietal cortex (Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). There are strong reciprocal connections between the frontal and parietal areas in this network (Andersen, Snyder, Bradley, & Xing, 1997; Goldman-Rakic, 1988). For example, precuneus has reciprocal connections to FEFs and dorsolateral prefrontal cortex, and efferent projections to superior colliculus, areas strongly implicated in antisaccade performance (Cavada & Goldman-Rakic, 1989; Cavanna & Trimble, 2006; Petrides & Pandya, 1984; Goldman-Rakic, 1988; Leichnetz, 2001). Superior parietal peaks have been found in several previous functional imaging studies of antisaccades (Brown et al, 2007; Curtis & D’Esposito, 2003; DeSouza et al, 2003; Doricchi et al,
1997; Matsuda, Matsuura, Ohkubo, Ohkubo, Matsushima, Inoue, et al, 2004; O’Driscollet al, 1995). Thus the regions of the dorsal attentional network where we see differences between ADHD-C and Controls have been strongly implicated in antisaccade performance. The structures of this network support not only attention but aspects of strategic motor control, including movement inhibition, planning and selection (Andersen & Cui, 2009; Cavanna & Trimble, 2006; Luna & Sweeney, 2004), which may be more compromised in ADHD-C than ADHD-I and could possibly account for the difference in superior parietal cortex activation between the subtypes.

The pattern of results in dorsal precuneus in BA 7 is essentially the opposite of that observed in a ventral area of precuneus on the border of posterior cingulate (BA 23/31). The latter region has been implicated in ADHD (Cao, Zang, Sun, Sui, Long, Zou, & Wang, 2006; Castellanos, Margulies, Kelly, Uddin, Ghaffari, Kirsch et al, 2008; Uddin; Kelly, Biswal, Margulies, Shehzad, Shaw, Ghaffari et al, 2008) and in the default mode network (Greicius, Krasnow, Reiss, & Menon, 2003; Raichle, MacLeod, Snyder, Powers, Gusnard, & Shulman, 2001). The posterior cingulate/ventral precuneus shows task-related suppression of activity, and failure of suppression in this network is associated with task errors and attentional lapses (Eichele, Debener, Calhoun, Specht, Engel, Hugdahl et al, 2008; Weissman, Roberts, Visscher, & Woldorff, 2006). The default mode network is hypothesized to support introspective thought, which constitutes intrusions or lapses in goal-focused behaviour. Our findings in dorsal precuneus are essentially the reverse of those reported in the literature for posterior cingulate/ventral precuneus; we found high task-related activation, with higher activation associated with fewer errors and less severe symptoms of inattention and hyperactivity/impulsivity. The
connectivity of the parietal cortex includes strong connections between areas 23/31 and dorsal area 7 (Cavanna & Trimble, 2006). Activity in these regions has been reported to be negatively correlated (Fransson, 2005; Fox, Snyder, Vincent, Corbetta, Van Essen, & Raichle, 2005). Activation of the “task-positive” parietal regions may suppress activity in “task-negative” areas to reduce task-irrelevant thoughts that interfere with strategic allocation of attention, both in the scanner and in everyday life (Broyd, Demanuele, Debener, Helpf, James, & Sonuga-Barke, 2009; Fox et al, 2005; Fransson, 2005).

It was surprising that the ADHD-I group was impaired on the antisaccade task given that their performance in the laboratory sessions in early adolescence (Experiment 1) and at follow-up (Experiment 3) was not significantly different from that of Controls. We believe the difference was accounted for by differences in how the task was administered in the laboratory and scanner sessions. Laboratory conditions were aimed at obtaining the participants' optimal performance. The testing environment was quiet with two experimenters in the room, one seated immediately next to the participant to facilitate on-task behaviour. If the participants made 3 consecutive antisaccade errors, the task instructions were repeated by the experimenter. Thus, behaviour received fairly tight external monitoring, consistent with our goal of identifying deficits that would be evident regardless of the situation and were not attributable to failure to “try.” In the MRI, the testing conditions were noisy and there were no adjacent adults providing close supervision and feedback; indeed the participants were alone in the scanner room, had difficulty interacting with the technician due to scanner noise, and some had difficulty maintaining appropriate levels of arousal due to being solitary in a recumbent position. Thus, the scanner performance likely tapped real-world deficits in self-regulating level of
arousal and on-task behaviour, deficits that in ADHD-I may be temporarily overcome with close supervision by an interactive, on-task adult.

Our findings must be considered in the context of the study’s limitations. First, our sample size was relatively small. Nonetheless, it is similar to or larger than many previous functional imaging studies of ADHD (for review see Bush, Valera, & Seidman, 2005) and, importantly, was sufficient to detect task-related activation and between-group differences. In the current study, we did not obtain the expected activations during predictive saccades compared to the non-predictive saccade task. We believe that this absence of findings reflected adjustments in the task parameters for the scanner that diminished behavioural differences between the predictive and control tasks. Specifically, to ensure that the motor demands of the two tasks were identical in the scanner, we increased the pace of target movement in the non-predictive saccade task. Difficulty tracking the faster unpredictable target movements, and the shortness of fixations generally, enhanced predictive behaviour in the control task and likely eliminated activity differences between the predictive and control conditions. Finally, as expected in any long-term follow-up of people diagnosed with ADHD in childhood, a significant portion of our participants did not meet full criteria for the disorder in late adolescence. Thus, some regions where between-group differences were not found could yield differences in groups diagnosed in adulthood. Nonetheless, the purpose of this study was to look at the functional neuroanatomy of ADHD in adolescence in a sample diagnosed in childhood. As about half of individuals diagnosed with ADHD in childhood no longer meet full criteria in late adolescence -- but continue to have significant symptoms and difficulty in adaptive functioning -- (Faraone, Biederman, &
Mick, 2006), the current study provides information on the neural structures involved in a group with a representative adolescent outcome.
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Chapter Six: General Discussion
6.1 SUMMARY OF MAIN FINDINGS

A series of experiments were designed to investigate similarities and differences in the Inattentive and Combined subtypes of ADHD. Executive oculomotor tasks were used in all four experiments because these tasks have been well-established to depend on frontal-subcortical circuitry, the circuitry primarily implicated in the pathophysiology of ADHD.

In Chapter Two, we evaluated whether ADHD-Inattentive (ADHD-I) and ADHD-Combined (ADHD-C) participants had similar or different executive oculomotor profiles in early adolescence. We found that, compared to Controls, ADHD-C participants were impaired in motor inhibition (as evidenced by increased antisaccade errors) and motor planning (reduced proportion of predictive saccades), but not in task-switching (no difference in switch cost was observed). ADHD-I participants were unimpaired on the tasks. These findings indicated that the neurocognitive profiles of the two subtypes differ, suggesting by extension that their neural substrates differ as well.

Chapter Three examined the effects of methylphenidate -- the most common pharmacological treatment for ADHD -- on executive oculomotor tasks in the two subtypes. We observed that methylphenidate improved motor inhibition (i.e., decreased antisaccade errors) and motor planning (i.e., increased the proportion of predictive saccades), but did not reduce switch cost. The magnitude of the improvement was similar in the ADHD-I and ADHD-C groups, suggesting that methylphenidate is effective in both. These results support the current clinical practice of prescribing methylphenidate for children diagnosed with ADHD-I and ADHD-C (Barbaresi, Katusic, Colligan, Weaver, Leibson, & Jacobsen, 2006; Barkley, DuPaul, & McMurray, 1991; Gorman,
In Chapter Four, we studied the longitudinal course of executive functioning in the two subtypes. While there is an extensive literature reporting declines in symptoms of hyperactivity during adolescence, few longitudinal studies have investigated whether executive function deficits remain or remit during development (Biederman, Petty, Fried, Boyle, Spencer, Seidman, Gross, Poetzl, & Faraone, 2007; Biederman, Petty, Doyle, Spencer, Henderson, Marion, Fried, & Faraone, 2008; Hopkins, Perlman, Hechtman, & Weiss, 1979; Fischer, Barkley, Smallish, & Fletcher, 2005; Hinshaw, Carte, Fan, Jassy, & Owens, 2007). The participants who took part in the first two experiments were followed up, on average, 5.5 years later and administered the same battery of executive oculomotor tasks. In addition, participants took part in a time reproduction task and provided information on two measures of adaptive functioning (i.e., number of grades repeated and number of arrests). Both subtypes showed improvements in clinical symptoms and executive functioning from early to late adolescence. Nonetheless, while ADHD-C participants were no longer impaired in motor planning, they continued to be impaired in motor inhibition compared to Controls. They were also impaired in time reproduction, over-estimating the duration of short time intervals. ADHD-I participants were unimpaired on the tasks. In terms of adaptive measures, more ADHD participants of both subtypes had been arrested than Controls and the number of arrests was correlated with antisaccade error rates. The longitudinal stability of antisaccade errors and their relationship to adaptive outcome is consistent with the notion of disinhibition as a core deficit of ADHD.
In Chapter Five, we studied the neural substrates of disinhibition in ADHD using fMRI. Unexpectedly, both ADHD subtypes showed significantly elevated antisaccade error rates in the scanner and did not differ from each other. In terms of differences in neural activation from Controls, both ADHD groups showed lower activation of frontal-subcortical circuitry. The ADHD-C’s also had lower activation of precuneus and superior parietal cortex than Controls and lower activation in superior parietal cortex than the ADHD-I group. Activation in left precuneus was associated with antisaccade error rate and with parental ratings of symptom severity.

Below we discuss some of these findings in relation to the major themes and research questions of the thesis.

6.2 HOW THE INATTENTIVE & COMBINED SUBTYPES ARE SIMILAR & DIFFERENT

6.2.1 Executive Functioning

Laboratory measures of executive functions in early adolescence yielded different profiles for the two subtypes. Direct comparisons showed that ADHD-C’s made significantly fewer predictive saccades than the ADHD-I’s and had a larger proportion of individuals impaired on the antisaccade task. In late adolescence, the ADHD-C’s no longer differed from the ADHD-I’s on motor planning but continued to have more individuals impaired on the antisaccade task. The persistence of the inhibitory deficits across time, even with the diminution of parent-rated symptoms, supports the notion of motor disinhibition as a core deficit of ADHD (Barkley, 1997).
The ADHD-I participants did not show deficits on our laboratory measures of executive functioning at baseline nor at follow-up but had similar adaptive outcomes as the Combined group (elevated grade repetitions and arrests). A possible explanation for the discrepancy between adaptive outcomes and lab performance relates to how the laboratory tests were administered. Our goal in designing the laboratory testing was to compare the optimal performance of each group so that deficits identified would be those present even when participants were interested and cooperative. To do this, testing was done with two testers in the room, one to run the eye movement equipment and one to engage directly with the participant to maximize on-task behaviour. Thus, the situation was highly structured, and participants were encouraged to persist and given frequent breaks. In retrospect, this approach may have differentially benefited the ADHD-I group; at follow-up, they were tested twice, first in the laboratory in these optimal conditions, and months later in the scanner under suboptimal conditions. In the scanner, but not in the lab, the ADHD-I group showed significantly elevated error rates compared to Controls. In the scanner, participants were alone in the gantry, they could not hear feedback from the experimenter due to scanner noise, and they were recumbent in the dark, creating, for some participants, difficulty maintaining appropriate levels of arousal. The decline in performance between the laboratory and scanner sessions in the ADHD-I group suggests that this group may have benefited more from the environmental supports than children with the Combined subtype. It also suggests that without these supports (potentially in many real-life situations), inhibitory deficits exist in the ADHD-I group and may contribute to their diminished adaptive outcomes relative to Controls. In consideration of this possibility, I consulted the literature on behavioural treatments for
ADHD.

Behaviour modification programs are effective in the treatment of ADHD (DuPaul & Eckert, 1997; Fabiano, G.A., Pelham, Coles, Gnagy, Chronis-Tuscano, & O’Connor, 2009; Pelham & Fabiano, 2008). Typically, these programs implement consistent behavioural contingencies in the child’s environments (e.g., home, school, recreational settings). One effect of these measures is that they increase structure and supervision around the child and provide social feedback, characteristics that were present in our testing environment. Anecdotally, some parents in the study described their sons’ benefitting from being placed in small classes, or in the front row of the class, or from one-on-one tutoring, all interventions that increase structural and social support for on-task behaviour. Whether the subtypes differ in their ability to benefit from behavioural interventions remains to be clarified; a literature search yielded no study that has compared the effectiveness of non-pharmacological interventions in the subtypes. The findings in the present dissertation suggest that closer structural and social support for on-task behaviour may benefit children with the Inattentive subtype, possibly by overcoming difficulties with fluctuating attention, motivation and arousal, or difficulties in self-monitoring, deficits that are not as easily overcome in the Combined group.

6.2.2 Neural Pathways

Two major hypotheses of the neuroanatomical substrates of ADHD that are relevant to the current thesis are the frontal-subcortical hypothesis (e.g., Seidman, Valera & Makris, 2005) and the right parietal hypothesis (e.g., Voeller & Heilman, 1988). The frontal-subcortical hypothesis -- originally the frontal hypothesis -- was initially
suggested by observations that children with hyperkinetic syndrome shared
commonalities with patients with frontal lobe lesions (Levin, 1938) (e.g., disinhibition,
motor restlessness, distractibility, inattention). In recent years, structural neuroimaging
studies (for review, see Castellanos, 1997; Durston, 2003; Seidman, Valera, & Makirs,
2005; Valera, Faraone, Murray, & Seidman, 2007) and functional imaging studies
(Durston, 2003; Durston, Tottenham, Thomas, Davidson, Eigsti, Yang, Ulug, & Casey,
2003; Rubia, Overmeyer, Taylor, Brammer, Williams, Simmons, & Bullmore, 1999;
Rubia, Taylor, Smith, Oksannen, Overmeyer, & Newman, 2001; Vaidya, Austin,
Kirkorian, Ridlehuber, Desmond, Glover, & Gabrieli, 1998) combined with
neuropsychological investigations (e.g., Barkley, Grodzinsky, & DuPaul, 1992; Douglas,
1999; Pennington and Ozonoff, 1996; Shue and Douglas, 1992; Willcutt, Doyle, Nigg,
Faraone, & Pennington, 2005) have provided compelling evidence in support of a frontal-
subcortical hypothesis of ADHD. Because dopamine is a major neurotransmitter in this
circuitry, this hypothesis is also supported by evidence on the mechanism of action of
stimulants (Shaywitz, Klopper, & Gordon, 1978; Spencer, Biederman, Madras, Faraone,
Dougherty, Bonab, Fischman 2005) and by evidence of abnormal reward response in
ADHD (Holroyd, Baker, Kerns, & Muller, 2008; Iaboni, Douglas, Ditto, 1997), both of
which implicate dopamine. The right parietal hypothesis was initially proposed because
of the difficulties ADHD individuals have with arousal and attention. Hypoarousal and
attentional deficits are frequent characteristics of right parietal damage (Mesulam, 1981;
Voeller, 1991; Voeller & Heilman, 1988; Posner & Petersen, 1990). Structural and
functional neuroimaging investigations (Castellanos, Lee, Sharp, Jeffries, Greenstein,
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Filipek, Semrud-Clikeman, Steingrad, Kennedy, & Biederman, 1997; Makris Makris, N., Biederman, J., Valera, E.M., Bush, Kaiser, Kennedy, Caviness, Faraone, & Seidman, 2007; Rubia, Smith, Brammer, Toone, & Taylor, 2005; Rubia, Halari, Smith, Mohammed, Scott, Giampietro, Taylor, & Brammer, 2008; Shaw, Eckstrand, Sharp, Blumenthal, Lerch, Greenstein, Clasen, Evans, Giedd, Rapoport, 2007; Vaidya, Bunge, Dudukovic, Zalecki, Elliott, & Gabrieli, 2005) as well as neuropsychological studies (e.g., Aman, Roberts, & Pennington, 1998; Snow, 1990; Voeller & Heilman, 1988) have implicated parietal areas in the pathophysiology of ADHD. However, the volume of research on parietal function remains relatively small. Because we did not hypothesize greater parietal dysfunction in the ADHD-C group, any explanation is necessarily speculative. However, our findings do suggest greater involvement of dorsal parietal cortex in ADHD-C than ADHD-I or possibly greater involvement of this region in adolescents with syndromatic persistence.

6.2.3 Treatment Response and Treatment in Relation to Course

Both subtypes showed significant improvement in executive functioning on methylphenidate, consistent with previous findings (e.g., Barkley et al, 1991; Stein et al, 2003). Nonetheless, participants from the ADHD groups had more arrests and had repeated more grades than Controls. Given the early implementation of pharmacological interventions, one might have expected adaptive outcomes to be better.

In the literature, stimulants reliably improve academic performance (Advokat, 2009; Ingram, Hechtman, & Morgenstern, 1999). However, more than 30 years of research on stimulants have yielded little evidence that these drugs increase the long-term
academic achievement of individuals diagnosed with ADHD in childhood (Advokat, 2009). Specifically, in the short-term, stimulants improve daily classroom performance (e.g., ability to remain in seat and complete school work); in the long-term, children diagnosed with ADHD in childhood who received stimulant treatment fare about the same academically as those who did not receive treatment (Carlson & Bunner, 1993; Smalley & Jarvelin, 2007; Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007).

Typically, there is a high rate of medication discontinuation in adolescence (Sleator, Ullman, & von Neumann, 1982), a time of important and increasing academic demands. This may, in part, account for poorer academic outcome in ADHD despite early medication treatment. In our ADHD sample, all participants were taking methylphenidate in early adolescence; by late adolescence, few (3 Inattentive and 3 Combined participants) continued to do so, and those that did were generally taking it only periodically (e.g., when taking exams). Several participants reported that their decision to stop medication was essentially a rejection of the authority position that there was something wrong with them. It is possible that combining medication either with educational interventions that allow the individual to see medication as a tool (rather than an authority-imposed personality-changing intervention) or with behavioral strategies that could continue to benefit the individual once medication is discontinued, may be important to changing long-term outcomes.

6.3 LIMITATIONS

The research presented in this dissertation must be considered in the context of its limitations. First, the longitudinal design, which has some major advantages over cross-sectional designs, also has disadvantages. For example, while participants were selected to be essentially free of comorbid disorders at study entry, the criterion for inclusion at
follow-up was having participated in early adolescence, and co-morbidity was a feature of the clinical picture in late adolescence. This co-morbidity complicates the interpretation of the data since it is possible that results were influenced in part by past or current drug use. Nonetheless, recreational drug use did not differ across our three groups. Further, not excluding on this basis also increased the representativeness of this late adolescent sample since marijuana, the only illicit drug regularly used by our participants, has been found to have been used by up to half of grade 12 students (Eaton, Kann, Kinchen, Shanklin, Ross, Hawkins, Harris, Lowry, McManus, Chyen, Lim, Brenner, & Wechsler, 2008).

A second limitation is that because our sample was diagnosed in childhood and was followed up irrespective of current clinical status, our results do not necessarily inform our understanding of people diagnosed with ADHD as adults. Since several of our participants no longer met full criteria for the disorder, the severity of symptoms in our sample at follow-up is lower than what would be observed in a group diagnosed as adults. In addition, there may be other differences between samples diagnosed in childhood and samples diagnosed in adulthood, simply because help-seeking in adulthood constitutes a different form of selection than help-seeking by parents for children.

Third, our sample showed some attrition that may have impacted the findings. Those lost to follow-up (1 Combined, 3 Inattentives) did not differ from other members of their group in terms of symptom severity or IQ as measured at baseline. However, 3 of the 4 ADHD participants lost to follow-up were in the highest socioeconomic status. We cannot rule out the possibility that the non-participation of these individuals affected our results; however, socioeconomic status was found to be unrelated to outcome measures in
follow-up participants (p’s > .5).

Finally, all of our ADHD participants were treated with stimulant medication at the time of their initial participation. Between-subjects differences in medication dose and length of exposure to stimulant medication may have impacted to some extent baseline performance as well as brain development in adolescence (for review see Andersen, 2005). The effect of these medication variables on our findings is unknown.

6.4 SUMMARY

The series of experiments outlined in this dissertation provide new information on the longitudinal course of executive functions and on the neural bases of the ADHD subtypes. Our data suggest that among executive functioning deficits, inhibitory dysfunction is a compelling target of intervention; while motor planning deficits resolved in adolescence, inhibitory deficits persisted and were related to adaptive outcome. The longitudinal data are relevant to treatment, both in showing short-term efficacy, where executive functions in both subtypes improved on methylphenidate, and long-term outcome, where the ADHD groups had poorer adaptive functioning than Controls despite treatment. The findings further shed light on the relationship between symptoms, executive functions and adaptive outcome and between symptoms and neural activity. Our data suggest similar frontal-subcortical involvement in both subtypes of ADHD and greater dorsal parietal involvement in ADHD-C and in symptom expression.
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