SELECTIVE INHIBITION:

LIFESPAN DEVELOPMENT, ATTENTION-DEFICIT/HYPERACTIVITY

DISORDER and EFFECTS OF STIMULANT MEDICATION

by

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Selective Inhibition: Lifespan Development, Attention-Deficit/Hyperactivity Disorder and Effects of Stimulant Medication.

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ABSTRACT

A modification of the stop-signal procedure was used to investigate selective inhibition.

Subjects performed a visual choice reaction time task and attempted to selectively inhibit

their response to this task when hearing one of two randomly presented tones (1000 Hz,

250 Hz). Normal development of selective inhibition was assessed in a community

sample of 317 subjects, aged 6 to 82 years. Selective inhibition was also measured in a

group of 59 children with ADHD and compared to community controls. Lastly, the

effects of stimulant medication (MPH) were investigated in 28 of the children with

ADHD in an acute, placebo-controlled, randomized, crossover trial with three fixed doses

of MPH. Findings are discussed with regards to the maturation and decay of selective

inhibition across the life span, the consistency of purported inhibition deficits in ADHD

and the impact of MPH on this unique and highly cognitively demanding construct in

children with ADHD.

Acknowledgements

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List of Abbreviations

ADHD	Attention-Deficit/Hyperactivity Disorder
DSM-IV	Diagnostic and Statistical Manual – Fourth Edition
GoRT	Go-Signal Reaction Time (ms)
MPH	Methylphenidate (Ritalin)
P(I/N)	Percent Inhibition given the Nonselected stop-signal
P(I/S)	Percent Inhibition given the Selected stop-signal
SDGoRT	Standard Deviation of Go-Signal Reaction Time (ms)
SSRT	Stop-Signal Reaction Time (ms)
%CGR	Accuracy of go-task responding as percentage of Correct Go-signal Responses
%EARLY	Percentage of Early (invalid) Responses

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CHAPTER 1

Introduction

Attention-Deficit/Hyperactivity Disorder

Prevalence and Significance

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common

behavioural disorder of childhood, affecting 3 to 5 percent of school-age children

(American Psychiatric Association [APA], 1994; Szatmari, Offord, and Boyle, 1989).

According to the *Diagnostic and Statistical Manual – Fourth Edition (DSM-IV)* (APA,

1994), a diagnosis of ADHD requires the following criteria: specifically defined

symptoms of inattention and/or hyperactivity/impulsivity; onset before seven years of

age; impairment from symptoms in two or more settings and clear evidence of clinically

significant impairment in social, academic, or occupational functioning (APA, 1994).

Children with ADHD are impaired in multiple settings, including at school, at home and

with peers. Although ADHD is predominantly regarded as a childhood disorder,

symptoms of ADHD can persist well into adulthood, often adversely effecting academic,

vocational, social-emotional, and psychiatric outcomes (Hechtman and Weiss, 1983;

Greene, Biederman, Faraone, Sienna, and Garcia-Jetton, 1997). In addition, those with

ADHD also exhibit substantially greater use of medical care in multiple delivery settings

(Leibson, Katusic, Barbaresi, Ronsom, and O'Brien, 2001).

Behavioral and Cognitive Characteristics

ADHD is a highly heterogeneous disorder. The current classification system for

diagnosis, the DSM-IV, identifies three different subtypes of ADHD: predominantly

Inattentive, predominantly Hyperactive/Impulsive, and Combined subtypes. Within the

population of children with ADHD, the relative subtype distribution is estimated to occur

as follows: Combined (50-60% of ADHD cases), Inattentive (20-30%) and

Hyperactive/Impulsive (10-20%) (Faraone, Biederman, and Friedman, 2000; Faraone,

Biederman, Webber, and Russell, 1998; Wolraich, Hannah, Pinnock, Baumgartel, and Brown, 1996; Lahey, et al., 1994). Although children with these ADHD subtypes demonstrate markedly different behavioural profiles, past research has not demonstrated cognitive or academic differences in these subtypes (Warner-Rogers, Taylor, Taylor, and Sandberg, 2000). In addition, the heterogeneity of ADHD is evidenced by the majority of children with ADHD meeting criteria for at least one additional psychiatric disorder (as reviewed in Tannock, 1998). The most frequently comorbid diagnoses seen in children with ADHD include oppositional defiant disorder, conduct disorder, anxiety disorders, mood disorders and learning disabilities (Biederman, Newcorn, and Sprich, 1991).

Current models of ADHD are founded on neuropsychological theories of impaired functioning of the frontal lobes, in particular the prefrontal cortex (Goldman-Rakic, 1987; Shallice, 1982). It has been suggested that the cognitive difficulties experienced by children with ADHD are accounted for by deficits in the executive functions (Barkley, 1997; Pennington and Ozonoff, 1996). Executive functions are high-level cognitive processes that coordinate other cognitive processes involved in perception, action, and thought (Tannock, 1998). Impairments in these executive functions can range from subtle impacts on the parameters of other processes, to dramatic, cascading effects on subordinate functions throughout the human information processing system (Schachar, Mota, Logan, Tannock, and Klim, 2000). Although the precise definition and measurement of executive functions remains elusive, the components of inhibition (stopping of a motor response) and working memory (holding of information used to guide subsequent actions) have been identified as being suitable and important for scientific investigation (Eslinger, 1996).

Neurobiology

Neuroimaging studies have provided information on which brain regions malfunction in children with ADHD, perhaps accounting for behavioural symptoms seen in the disorder. Regions of the prefrontal cortex, the cerebellum, and the basal ganglia have been shown to be smaller in children with ADHD compared to normal control children (as reviewed by Himelstein, Schulz, Newcom, and Halperin, 2000; Tannock, 1998). Interestingly, brain regions implicated in the cognitive process of inhibition are similar to those associated with ADHD. For example, using functional magnetic resonance imaging (fMRI) and event-related potentials (ERPs), inhibition has been mapped to specific brain regions, including the right frontal and prefrontal cortices (Casey et al., 1997; Pliszka, Liotti, and Woldroff, 2000; Rubia et al., 2001), bilateral frontal areas, head of the caudate and putamen (of the basal ganglia) (Vaidya et al., 1998), right middle and inferior frontal gyri, frontal limbic area, anterior insula, and the inferior parietal lobe (Garavan, Ross, and Stein, 1999).

Stimulant Treatment

Stimulant medication (primarily Methylphenidate (MPH)) is the most widely used treatment for children with ADHD. MPH is prescribed to over 90% of children diagnosed with ADHD in the United States (Kimko, Cross, and Abernathy, 1999). MPH is a lipid soluble agent that rapidly crosses the blood-brain barrier. It has a short half-life of 2-3 hours, its duration of action is 1-3 hours and peak plasma concentrations are typically attained within 2 hours of dosing (Kimko et al., 1999). MPH is known to influence dopaminergic, noradrenergic and serotoninergic neurotransmitter systems (Solanto, 1998). One pathway of MPH action in the brain is through blocking the re-uptake

mechanism of the dopamine transporters, increasing the amount of extracellular

dopamine available to bind to its receptors (Volkow et al., 2001). Dopamine is an

important neurotransmitter involved in executive control processing that has a high

density of receptors in the prefrontal cortex and basal ganglia (Solanto, 1998), brain

structures that have been shown to be both deficient in ADHD, as well as intricately

involved in the process of cognitive inhibition. As a result, elevated dopamine levels in

the synaptic clefts of these brain structures are believed to be associated with the

beneficial effects of MPH on cognitive processes including inhibition. Management of

overt behavioural problems is the primary reason for stimulant treatment, with estimates

of 80 to 85% of children with ADHD placed on MPH treatment experiencing reduction in

behavioural problems (Quay, 1997). In addition, MPH has also been shown to improve

various cognitive functions, including that of inhibition (Tannock, Schachar, Carr,

Chajczyk, and Logan, 1989; Tannock, Schachar, and Logan, 1995a).

Inhibition

Inhibition has been implicated as an important contributor to a variety of child

psychopathologies and impulsivity disorders (Gray, 1987; Patterson and Newman, 1983).

For instance, children with externalizing disorders are often characterized by

underinhibited and impulsive behaviour, whereas children with internalizing disorders

may show symptoms of overinhibition (Oosterlaan and Sergeant, 1996). Specifically,

inhibition deficits have been implicated in assorted disinhibition disorders, Tourette's

syndrome, obsessive-compulsive disorder, and ADHD (Garavan et al., 1999). Moreover,

inhibition is a central concept to theories of development and aging that interpret

cognitive difficulties of young children and the elderly as deficits in inhibitory processing

(e.g., Bjorkland and Harnishfegger, 1990; Hasher and Zacks, 1988; Kramer, Humphrey,

Larish, and Logan, 1994). The general concept of inhibition appears in many different

guises and is measured in a variety of ways in different literatures (e.g., Dagenbach and

Carr, 1994; Kramer, Humphrey, Larish, and Logan, 1994; Nigg, 2000). The inhibition of

interest in this thesis is conceptualized as one of several, internally generated acts of

control in the repertoire of a higher-order executive system that regulates the operations

of the human information processing system and permits self-regulation (Goldman-

Rakic, 1987; Logan, 1985; Shallice, 1982). It is defined as the ability to suddenly and

completely stop a planned or ongoing thought and action (Logan, 1994). This behavioural

inhibition encompasses three interrelated processes: inhibition of the initial pre-potent

response to an event; stopping of an ongoing response; and interference control (the

protection of this delay from disruption by competing events) (Barkley, 1997). This act of

behavioural control is required in many real-life situations in which an individual's

planned or ongoing actions are suddenly rendered inappropriate by unanticipated events

or changes in the immediate environment. Examples of common everyday behaviours

that involve inhibition include not crossing the road when a car suddenly turns the corner,

checking a swing in a baseball at bat when the pitch is outside of the strike zone and

withholding an inappropriate social response.

ADHD and Behavioural Inhibition

The precise etiology of ADHD remains unclear. However, there is converging

evidence that poor inhibition may be a fundamental characteristic of this disorder and that

impairments in inhibition lead to secondary impairments in many areas of behavioural

and cognitive functioning. For example, it has been argued that ADHD is fundamentally a disorder of a developmental problem in self-control, and that deficits in attention are a secondary, and not universal characteristic of ADHD (Barkley, 1997). Furthermore, it is this poor inhibition that leads to secondary impairments in working memory, self-regulation, reconstitution (i.e., the ability to reconstruct behaviour) and internal speech. From another perspective, it is postulated that poor inhibition in children with ADHD arises from an imbalance between two opposing systems: a behavioural activation system activated by reward and a behavioural inhibition system activated by punishment (Gray, 1982). Children with ADHD are thought to have under active behavioural inhibition systems, resulting in poor responsiveness to conditioned stimuli such as punishment or non-reward, which accounts for proposed inhibitory problems in ADHD (Quay, 1997). Lastly, Schachar, Tannock, and Logan (1993) suggest that an inefficient inhibition process in children with ADHD results in the impulsive behaviours often apparent in this childhood disorder.

Method and Measures

Investigations of the underlying cognitive deficits in ADHD have increasingly employed laboratory tasks purported to measure specific cognitive constructs, including behavioural inhibition, impulsivity and attention. As a result, inhibition has been extensively studied in the laboratory and is operationalized as the suppression of a prepotent response. Although there is no single test for measuring inhibition in the literature, the stop-signal task (Logan and Cowan, 1984) is a widely popular, theoretically motivated and empirically validated task that has been used to assess inhibition both developmentally across the lifespan (Williams, Ponesse, Schachar, Logan, and Tannock,

1999) and in children with ADHD (see review by Oosterlaan, Logan and Sergeant, 1998). The stop-signal task is designed to measure one core aspect of behavioural inhibition: stopping an ongoing response.

The Stop-Signal Task (Logan and Cowan, 1984)

This paradigm involves two concurrent tasks: a response execution (going) task and a response inhibition (stopping) task. The response execution task is a choice reaction time task that requires subjects to discriminate between the go stimuli "X" and "O" presented on a computer screen. The response inhibition task, which occurs randomly and infrequently (typically on 25% of go-task trials), involves the presentation of a stop-signal in the form of an auditory tone that signals the subject to inhibit his go trial response for that particular trial. The stop-signal task is designed so that the response execution task is directly racing with the response inhibition task. A subject's ability to successfully inhibit on a given stop trial is dependent on whether he can finish the response inhibition task before the response execution task. Hence, the latency of response to the go signal (Go-signal Reaction Time: GoRT) and the latency of response to the stop-signal (Stop-Signal Reaction Time: SSRT) are the primary experimental parameters of inhibition.

The Race Model

The race between the response execution and the response inhibition tasks is based upon a "horse race" model of inhibition which has been developed formally and shown to account quantitatively for all of the data in stop-signal experiments (Logan and Cowan, 1984). This model is based on the principle that the response execution process and the response inhibition process are independent and race to finish first with each

presentation of a stop-signal. Based on this race model, failure to inhibit could result from either the subject responding too slowly to the stop-signal or, conversely, responding too quickly to the go signal, or both.

Dependent Measures of the Stop-Signal Task

GoRT can be measured directly as the amount of time from when the go signal is presented to the subject to the execution of the response. SSRT, however, cannot be measured directly as subjects either inhibit or fail to inhibit with the presentation of the stop-signal. Although it is known that if subjects successfully inhibit on a given stop-signal their SSRT must have been faster than their GoRT and vice-versa if they are unable to inhibit, the inhibition response does not provide an observable response with a measurable latency of inhibition. An estimation of SSRT is therefore required. Various methods have been used to calculate SSRT (Logan. 1994).

In the tracking version of the stop-signal task (Logan. Schachar and Tannock. 1997), the timing of the stop-signal is varied each stop trial, making it sometimes very easy and sometimes very difficult to inhibit. Specifically, the amount of time between the presentation of the response execution signal (i.e., the letter "X" or "O") and the presentation of the stop-signal (referred to as the stop-signal delay) is continuously altered in 50 ms intervals to handicap the race between response execution and response inhibition one way or the other. For instance, if the subjects successfully inhibit to the stop-signal on a given trial, the stop-signal delay is increased by 50 ms and decreased by 50 ms if they respond. The 50 ms tracking procedure is used to yield a stop-signal delay at which the subjects are able to successfully inhibit to the stop-signal 50% of the time. At this point, the probability of successful inhibition is 50% and the race between the

response inhibition and response execution tasks is, on average, "tied". Here, the mean stop-signal delay represents the point at which response inhibition is just as likely as response execution to win the race and the process that ultimately wins on any given trial is due to random variation. This mean stop-signal delay also represents the mean point in time at which the response inhibition process finishes and can therefore be used to estimate response inhibition speed (SSRT). Therefore, on the basis of GoRT, stopping success (P(I/S)) and stop-signal timing (mean delay), SSRT can be calculated by subtracting the mean stop-signal delay (at which P(I/S) approximates 50%) from the mean response execution speed (GoRT).

Additional variables can be measured from the stop-signal task and can be used as complementary indicators of task performance. These include the subjects' accuracy in responding to the go signal (the percentage of time they correctly responds to the "X" or the "O" - %CGR), their variability of response execution (the standard deviation of their response execution speed - SDGoRT), and the percent inhibition given the selected stop-signal tone (P(I/S)).

Advantages of The Stop-Signal Task

Other measures have also been used to measure inhibition in ADHD research. For instance, the go/no-go reaction time task requires subjects to respond to a certain category of stimuli but not respond to the other (e.g., Filipovic, Jahanshaha, and Rothwell, 1999; Overtoom et al., 1998). Similarly, the Conners' Continuous Performance Task (Conners, 1995) requires the subject to interrupt a continuous motor response by demanding a response of pressing the spacebar for every letter presented on a computer screen except for the letter X (McGee, Clark, and Symons, 2000).

The advantages of the stop-signal task and its underlying assumptions over other measures of inhibition are numerous. In contrast to other neuropsychological measures of response inhibition, the stop-signal task allows more precise measurement of the underlying processes involved. The stop-signal task allows for a clear definition of the conditions that trigger the act of control (the presentation of the stop-signal) and the changes that result from executing the act (inhibition of the response). Also, the model provides a method for measuring the internal stopping process speed (SSRT) even though successful inhibition produces no overt, quantifiable behaviour. Although SSRT does not provide all of the information measured in the stop-signal task, it is a highly informative measure of inhibition, as changes in SSRT characterize important differences between groups of individuals (e.g., Oosterlaan and Sergant, 1998a) and individuals tested under different conditions (e.g., MPH effects on SSRT: Tannock et al, 1995a). Moreover, the stop-signal task provides a way of measuring inhibition (SSRT) that controls for any concurrent differences in the speed of response execution (GoRT). This is important since a slower response execution process is easier to stop than a faster one at an equivalent stop-signal delay (Logan, 1994). Since development is known to affect the speed of the response execution and inhibition processes (Williams et al., 1999), the ability to disentangle the effects of the response execution task on the response inhibition task using this paradigm is valuable.

Stop-Signal Inhibition and ADHD

Schachar and Logan (1990) first used the stop-signal task to measure inhibition in children with ADHD and found task deficits unique to ADHD children. Specifically, children with ADHD were slower to inhibit (i.e., longer SSRTs) than normal controls.

were less frequently able to successfully inhibit when presented with the stop-signal (smaller P(I/S)) but did not differ in their response execution speed (GoRT). A meta-analysis of inhibition studies in children with ADHD conducted by Oosterlaan et al. (1998) found that children with ADHD were generally slower to both stop and go than normal controls, with the magnitude of the effect size for response inhibition (Cohen's d = 0.64) demonstrated as significantly greater than that for response execution (Cohen's d = 0.49). Similar results were found between children with conduct disorder and normal children with a smaller effect size reported, suggesting that poor inhibition may not be unique to ADHD.

Attempts to further investigate the specificity of an inhibition deficit in ADHD using various cohorts of children with ADHD have recently been undertaken. For instance, both Nigg (1999) and Schachar et al. (2000) have examined the performance of DSM-IV diagnosed ADHD children on the basic stop-signal task. Nigg (1999) compared DSM-IV ADHD combined type children to matched normal comparison children and found that a deficit in SSRT in children with ADHD remained significant, replicating the effect size of d = 0.6 previously found in the metanalysis (Oosterlaan et al, 1998). Schachar et al. (2000) found that children with ADHD had significantly impaired inhibition when compared with normal controls, children with conduct disorder and children with both ADHD and comorbid conduct disorder. By contrast, a reading disorder effect on inhibition was found in a sample of children with ADHD, where children with ADHD plus comorbid reading disorder exhibited inhibition deficits of children with ADHD in an additive fashion (Purvis and Tannock, 2000). Thus, several studies of inhibition in ADHD have questioned the role of inhibition as a unique cognitive marker

for ADHD. In addition, no studies to date have examined DSM-IV ADHD subtype differences in inhibition.

Other research has focused on experimental modifications of the stop-signal task to examine inhibition in children with ADHD. By manipulating aspects of the stop-signal task, different aspects of inhibition can be investigated beyond simple replications of the stop-signal task. For instance, the effect of a motivational deficit underlying the demonstrated inhibition deficit in children with ADHD was examined using reward contingencies and response cost contingencies with concurrent stop-signal task performance (Oosterlaan and Sergeant, 1998b). In another experimental manipulation, Logan and Burkell (1986) complicated the stop-signal task by requiring subjects to perform a unique response execution task following response inhibition (i.e., responding to the stop-signal by pressing a third button). The application of this change task to children with ADHD yielded interesting results. First, children with pervasive ADHD had slower SSRTs compared to normal controls. In addition, children with ADHD were slower than normal controls to re-engage (i.e. respond to the stop-signal by performing a unique response execution task) (Schachar, Tannock, Mariott, and Logan, 1995). However, complicating the response demands in the change task did not slow either mean response execution or response inhibition speed for children with ADHD compared to previous basic stop-signal task findings. No experimental manipulation of the stop-signal task to date has influenced inhibition speeds in children with ADHD, or in normal controls.

Selective Inhibition

It is possible to conceptualize inhibition on a continuum from simple (i.e.,

nonselective – inhibit to any and all inhibition stimuli) to more demanding (e.g., selective

– inhibit to only selected stimuli). Whereas simple inhibition requires individuals to stop

an ongoing action when definitively rendered inappropriate. selective inhibition requires

an additional quick discriminatory decision as to when it is appropriate to continue versus

stop whenever a stop-signal is presented.

A variant of the stop-signal task can be used to measure selective inhibition. The

response inhibition (stopping) task can be made more complex. much like the response

execution (going) task has been made more complex (Logan and Burkell. 1986: Schachar

et al.. 1995; Tannock et al.. 1995a for the change task). The inhibition task can be made

more complex at the perceptual end by requiring discrimination between more than one

stop-signal. or it can be made more complex by requiring discrimination among various

responses. some of which should be inhibited and others of which should not (DeJong et

al.. 1995).

This thesis examines the perceptual aspect of selective inhibition by adding a

second stop-signal to the basic. nonselective stop-signal task. Each of the auditory stop-

signals (the selected stop-signal. and the nonselected stop-signal) is presented on 20% of

trials. Subjects are instructed to inhibit their response execution whenever presented with

the designated stop tone and to continue to respond to trials in which the non-designated

stop-signal tone is presented (Figure 1.1). In addition to measuring the percent inhibition

given the selected stop-signal tone (P(I/S)), the percent inhibition given the nonselected

Figure 1.1

A cartoon schematic of the selective stop-signal task
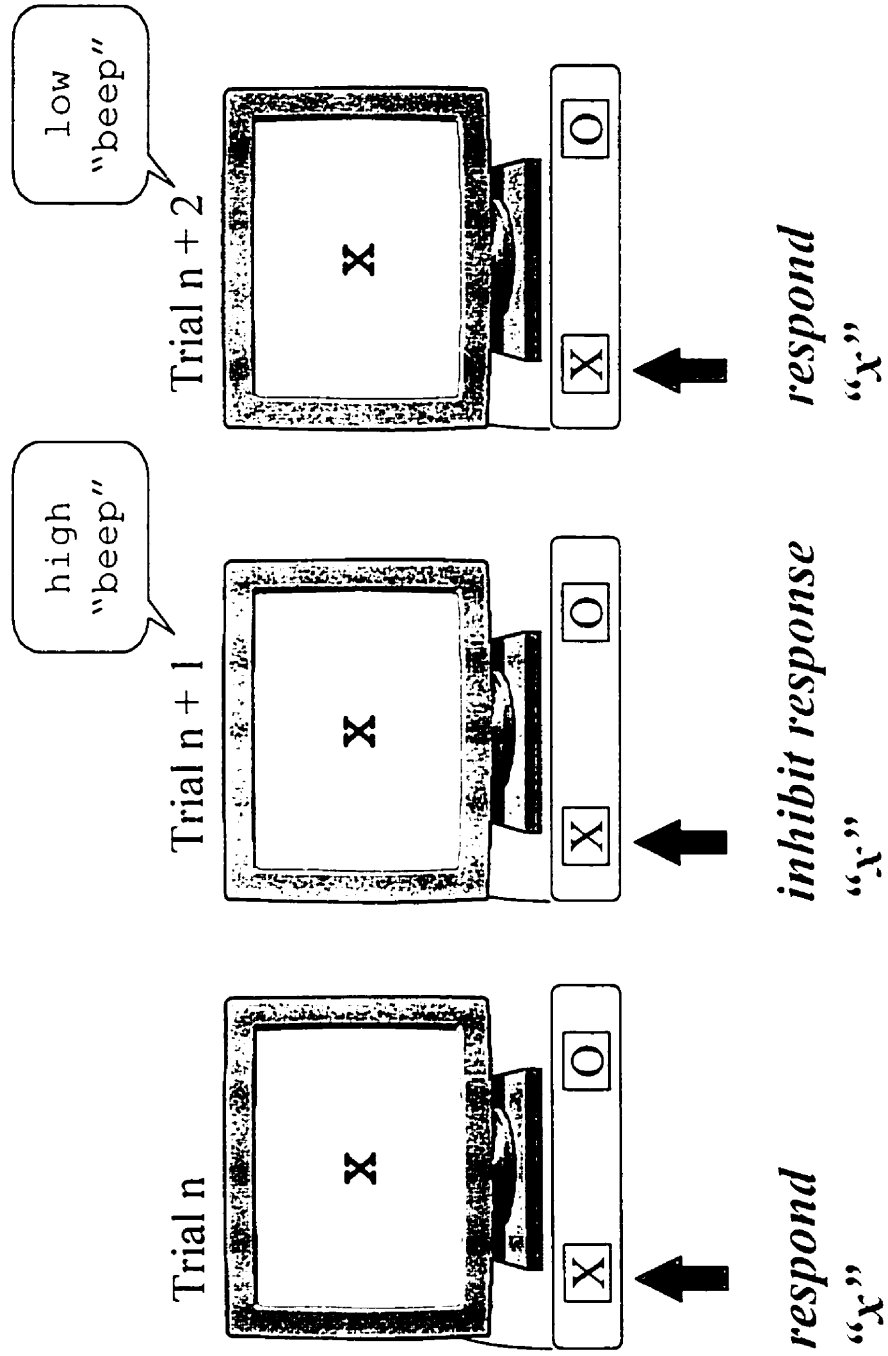
stop-signal tone can also be calculated (P(I/N)). This provides a measure of how well the subject is able to successfully discriminate between stop-signal tones and successfully execute the correct response. This is the first experimental manipulation of the stop-signal task designed to examine perceptual selective inhibition. Studies to date on selective inhibition have been limited to examining the motor end of selective inhibition and have been restricted to adult subjects (De Jong, Coles, Logan, and Gratton, 1990; DeJong et al., 1995; Logan, Kantowitz, and Riegler, 1986; Van Der Veen, Van Der Molen, and Jennings, 2000). No study to date has examined this construct across the entire lifespan or in children specifically.

Rationale for Present Study

To date, studies on inhibition in children with ADHD have focused primarily on nonselective inhibition where subjects were required to halt their responding whenever presented with an inhibitory stimulus. This automatic, "inhibit-all" process, however, does not address the impact of the quick discriminatory process often required in deciding whether or not the inhibition of a response is appropriate given particular circumstances. The studies presented in this thesis will be the first to examine selective inhibition using a novel adaptation of the stop-signal task. This novel experimental manipulation of the stop-signal task is in line with other work involving manipulations of the stop-signal task in order to better understand the proposed inhibition deficit in ADHD (e.g., Oosterlaan and Sergeant, 1998b, Tannock et al., 1995a). Selective inhibition is a unique cognitive construct that may represent the delicate and flexible inhibition process

frequently used to discriminate between potential inhibitory stimuli and determine subsequent responding.

The research will be presented as two separate chapters. The chapters will report on our findings of the development of selective inhibition across the lifespan, and selective inhibition in children with ADHD both on and off stimulant medication. Chapter 2 presents data from a large scale, cross-sectional study examining the development of selective inhibition in 317 subjects, aged 6-82 years. The goal of this study is to examine changes in selective inhibition throughout the lifespan. If selective inhibition is a more challenging and unique task than nonselective inhibition, then it is hypothesized that the development of selective inhibition will follow robust and unique lifespan trends in both response execution and selective response inhibition.

Chapter 3 presents a research study examining selective inhibition in children with ADHD. In this study, the selective inhibition of 59 children with ADHD is compared to that of 59 age-matched community control children. In addition, stimulant medication (MPH) effects on the selective inhibition of a subset (n=28) of the children with ADHD are examined in an acute, placebo-controlled, crossover trial with three fixed doses of MPH. Since children with ADHD exhibit a specific impairment in response inhibition, it is hypothesized that these children will exhibit significant impairments in selective inhibition, a more challenging type of response inhibition. In addition, the impact of DSM-IV ADHD subtypes will be examined on inhibition performance. If impulsivity is associated with poor inhibition, as theory would predict (Barkley, 1997), the Hyperactive/Impulsive and Combined DSM-IV ADHD subtypes will evidence greater deficits in inhibition than the Inattentive subtype. Lastly, since MPH has been

shown to improve nonselective inhibition, marked improvements in selective inhibition are predicted with MPH.

A general discussion will follow to draw overall conclusions and trends within the two chapters. Also, the discussion will include limitations of the research, directions for future research of inhibition studies both developmentally and within specific psychopathologies and lastly the theoretical and clinical implications of the research contained in this thesis.

Footnote

[1] This thesis is comprised of two manuscripts prepared for journal submission. In making each of these self-contained, overlap of the text of some of the chapters was unavoidable.

CHAPTER 2

The Development of Selective Inhibition Across the Life Span

Abstract

Objective: A modification of the stop-signal task was used to investigate the development of selective inhibition. **Method:** A group of 317 subjects. aged 6 to 82 years, performed a visual choice reaction time (go) task and attempted to selectively inhibit their response to the go task when hearing one of two randomly presented tones (1000 Hz. 250 Hz). each presented on 20% of trials. Measures of response execution and inhibition were assessed using reaction times to the go (GoRT) and selective stop (SSRT) signals. respectively. **Results:** Results in this study indicated that SSRT gets faster with increasing age throughout childhood. with pronounced slowing across the adult years. In addition. strong evidence was obtained for age-related speeding in GoRT throughout childhood. with marked slowing throughout adulthood. Subsequent hierarchical regression analyses illustrated that the age-related changes in selective inhibition could not be simply explained by overall slowing or speeding of responses. **Conclusions:** Findings are discussed in regard to the decay and maturation of selective inhibition across the lifespan.

Inhibition is a central concept to theories of development and aging that interpret

cognitive difficulties of young children and the elderly as deficits in inhibitory processing

(e.g., Bjorkland and Harnishfegger, 1990; Hasher and Zacks. 1988; Kramer et al.. 1994).

Moreover, deficient inhibition is central to current theories of psychopathology and

impulsivity (e.g.. Barkley, 1997; Gray, 1987; Patterson and Newman. 1993; Quay, 1997).

The general concept of inhibition appears in many different guises and is measured in a

variety of ways in different literatures (e.g., Dagenbach and Carr. 1994: Kramer et al..

1994). The present study focuses on the type on inhibition that is manifest in the stop-

signal task (Lappin and Eriksen. 1966; Logan and Cowan. 1984; Logan Cowan. and

Davis. 1984; Ollman. 1973; Osman, Kornblum. and Meyer. 1990; Vince. 1948). This

type of inhibition is conceptualized as one of several internally generated acts of control

in the repertoire of a higher-order executive system that regulates the operations of the

human information processing system and permits self-regulation (e.g.. Goldman-Rakic.

1987; Logan. 1985; Shallice. 1982). It is defined as the ability to stop (suddenly and

completely) a planned or ongoing thought and action (Logan. 1994). This central act of

control is required in many real-life situations in which an individual's planned or

ongoing actions are suddenly rendered inappropriate by unanticipated events or changes

in the immediate environment (e.g., a batter in a baseball game must halt his swing in

order to adjust to a pitch that has just broken out of the strike-zone).

One clear advantage of using the stop-signal task over other neuropsychological

measures of inhibition (e.g., Matching Familiar Figures Test. Go-NoGo Task. Conners'

Continuous Performance Test) is that the underlying model provides a way of measuring

the latency of the internally generated act of control (stop-signal reaction time - SSRT)

even though successful inhibition produces no overt behaviour. In the stop-signal task,

SSRT is the primary performance variable and indicates the speed of the inhibition

process. SSRT does not provide all the information yielded by the stop-signal task, but is

highly informative because changes in SSRT characterize important differences between

groups of individuals (e.g., impulsive adults have longer SSRTs than non-impulsive

adults: Logan et al., 1997) and between individuals tested under different conditions (e.g.,

stimulant medication improves SSRT compared to placebo in children with ADHD:

Tannock, et al., 1989: Tannock et al., 1995a).

Research using the stop-signal paradigm to date has focused primarily on non-

selective or basic inhibition, which involves the inhibition of any and all responses

whenever a stop-signal occurs (e.g., May and Hasher, 1998, Ridderinkof, Band, and

Logan, 1999; Williams et al., 1999). In comparison, selective inhibition is a more

cognitively demanding process requiring the inhibition of some responses without the

inhibition of others (Logan et al., 1986: DeJong et al., 1995). For example, subjects

engaged in a choice reaction time task could be presented with a stop-signal that requires

the inhibition of responses to one stimulus but not to the other. In everyday life, selective

inhibition is often required when driving. For instance, unexpected road conditions (e.g.,

a patch of ice versus a physical obstruction) require the driver to quickly decide whether

it is better to keep driving or to halt. Such adaptive acts of control depend on an intricate

interplay between activation and inhibition, affording a much more flexible inhibition

than nonselective inhibition. The present study investigates selective inhibition.

Developmental change in the speed of responding is well documented, using a

wide variety of reaction time tasks (e.g., Cerella and Hale, 1994; Hale, 1990: Kail, 1993).

Generally, response speed increases throughout childhood, reaching a peak in early

adulthood, then decreases gradually throughout adulthood (Hale, 1990, Williams et al.,

1999). Until recently, developmental change in inhibition was unclear. The relatively few

studies available yield only limited evidence of age-related speeding of response

inhibition processes throughout childhood (Band, 1996; Jennings, Van der Molen,

Pelham, Debski, and Hoza, 1997; Oosterlaan and Sergeant, 1997; Schachar and Logan,

1990) and of age-related slowing across adulthood (Kramer et al., 1994, May and Hasher,

1998). By contrast, a recent study of lifespan changes in inhibition revealed marked

speeding of inhibition processes across childhood through adolescence with only limited

evidence of slowing in older adults (Williams et al., 1999). Consistent with previous

research, clear evidence of age-related speeding of response execution throughout

childhood and adolescence and marked slowing throughout adulthood was found

(Williams et al., 1999). Previous studies with the stop-signal task provide a possible

explanation for this unexpected limited evidence of slower go task responding in the

older adults. Kramer et al. (1994) and May and Hasher (1998) used more complex go

tasks and observed a more marked slowing of SSRT throughout adulthood in comparison

to the study conducted by Williams and colleagues (1999) (by an average of 90 ms vs. 20

ms). They suggested that an overall increase in cognitive demands could have resulted in

greater difficulty controlling the stopping process, particularly in the elderly.

The current study investigated the impact of increased task complexity on

developmental changes in inhibition by using a variant of the stop-signal task to measure

selective inhibition. The stop-signal task can be made more complex, much like go tasks

can be made more complex. It can be made more complex at the perceptual end by

requiring a discrimination between more than one presented stop-signal, and it can be made more complex at the motor end by requiring discrimination among responses (some of which should be inhibited and others of which should not be inhibited; DeJong et al.. 1995). The present study examined the *perceptual* aspect of selective inhibition by adding a second tone to the basic stop-signal task and instructing subjects to inhibit response execution whenever presented with the designated or selected stop-signal tone. and continue to respond to trials during which the nonselected stop-signal tone is presented. Studies to date on selective inhibition are limited and have been restricted to adult subjects (DeJong et al.. 1990, 1995; Logan et al.. 1986; Van Der Veen et al.. 2000). No study to date has examined this construct in children or across the entire lifespan.

The present study was designed to investigate selective inhibition in a community sample comparable to that used in a previous developmental study of simple inhibition in terms of age (6-81 year olds). demographics and recruitment source (Ontario Science Centre; Williams et al.. 1999). Our goal was to ensure adequate statistical power for the investigation of age-related changes in selective inhibition. We predicted that the observed latencies of response execution in the selective stop-signal task and the developmental changes in their latency would be comparable to those observed in other developmental studies using a similar response execution task (e.g.. Ridderinkof et al.. 1999; Williams et al.. 1999). By contrast. we predicted a more marked slowing of SSRT. or response inhibition across adulthood using the selective stop-signal task due to the increased cognitive demands at hand prior to inhibiting a response (i.e.. requiring subjects to discriminate between stop-signals and attempting to inhibit to one signal and continue responding to the other).

Method

<u>Subjects</u>

Throughout a two-week testing period in July 1998, 328 visitors to the Ontario

Science Centre (Toronto, Canada) were recruited for participation. Of these individuals,

11 (3 %) were excluded from analyses because of extreme scores (three or more standard

deviations from the mean) on the two primary outcome variables (6 for GoRT and 5 for

SSRT), leaving data collected from the remaining 317 subjects for analysis. Volunteers

with hearing, vision, or motor function impairments and those who did not speak at least

some English or French could not participate as the study design was not adapted for

such special needs. In addition, individuals who were on medication or who had a self-

disclosed psychiatric illness were also excluded.

The subjects ranged in age from 6 to 82 years. There were 157 males and 160

female subjects. As shown in Table 2.1, the gender distribution across the seven age

groups was fairly uniform. As might be expected of visitors to a science centre, the

majority of subjects had a reasonably strong educational background: Virtually all of the

subjects under 17 years of age were currently attending school; 23% of the young adults

had completed secondary school and 65% completed some form of postsecondary

education; and most of the adults had completed some postsecondary education (80% of

the mid-adult group, 90% of the older adult group, and 47% of the seniors group).

English was the most common language used by subjects with 83% of subjects citing it

as their primary language spoken at home. Other languages used as the main form of

communication at home included French (4%), Chinese (3%), Spanish (2%), Italian (1%)

and German (1%). Accordingly, a wide range of ethnic groups was represented in the sample.

<u>Apparatus and Stimuli</u>

Five stand-alone, IBM compatible, desktop computers were used to present the stimuli. Each of these five testing units was provided with adjustable padded headphones through which two distinct auditory signals could be presented without hindrance from potential background noise. In addition, each computer was connected to a handheld response box (14 cm x 8.5 cm x 3.5 cm) that contained three single-pole double-throw buttons. These buttons were arranged on the top of the box in a linear formation with the two outermost buttons individually labeled with the visual stimuli for the go task.

The visual stimuli for the go task were the uppercase letters "X" and "O", presented in the center of the screen for 1000 ms. Each go-task stimulus was preceded by a 500-ms fixation point, also presented in the center of the screen. Two 500 ms auditory tones (1000 Hz, 250 Hz) were generated by the computer, each presented on approximately 20% of trials and delivered through headphones at a comfortable volume for listening. One of these two tones was designated as the selected stop-signal tone; the nonselected tone was to be ignored. The stop-signal delay (i.e., the interval between the presentation of the go signal and the stop-signal) was changed dynamically after each designated stop-signal trial based on the performance of the subject (Logan et al., 1997). Stop-signal delay was initially set at 250 ms and was adjusted in 50 ms steps in the following manner: The delay increased by 50 ms if the subject inhibited successfully to the selected stop-signal (making it harder to inhibit on the next stop-signal trial) and decreased by 50 ms if the subject failed to inhibit (making it easier to inhibit on the next

selected stop-signal trial). This online tracking system of success in selective inhibition was designed to force a "tie" finish between response execution and response inhibition. Thus, the goal of the tracking algorithm was to allow subjects to successfully inhibit responding to the response execution task on approximately 50% of the selected stop-signal trials. This was necessary for the estimation of SSRT, which is calculated from the mean stop-signal delay subtracted from the mean GoRT (see Appendix of Williams et al.. 1999). Mean response execution speed (i.e.. GoRT) was calculated based on the response speeds during those trials in which an auditory tone (both selected and nonselected) was absent.

The experimental task comprised of 192 trials divided into 6 32-trial blocks. There were an equal number of "X"s and "O"s presented in each block. The auditory tone stimuli (1000 Hz. 250 Hz tones) were presented on 12 (i.e.. 38%) of the visual go signal trials (distributed randomly in each block of 32 trials): 6 (19%) were 1000 Hz and 6 (19%) were 250 Hz tones. Each tone was presented half of the time with an "X" and half of the time with an "O". The order in which the trials were presented was randomized separately for each subject. Once started. the program ran continuously presenting one trial every 3.0 seconds.

Two questionnaires were administered. One consisted of 14 demographic items including date of birth, gender, handedness. educational level. languages spoken at home. computer knowledge, health, accident history, learning difficulties and prescribed medication. This questionnaire was used in a previous study on the development of nonselective inhibition (Williams et al., 1999). The second questionnaire comprised of age-appropriate versions of the Nowicki-Strickland Internal-External Locus of Control

Inventory. This was used as a measure of generalized expectancies for internal versus

external control of reinforcement among individuals. Data generated from these Locus of

Control scales are not presented in the current paper, since there was no evidence of any

relationship between self-reported locus of control and any aspect of performance on the

selective inhibition task: rather those data will be the focus of a subsequent paper.

Procedure

Located within the Laser Lab at the Ontario Science Centre, the testing area was

secluded and divided into two separate areas: one for the completion of consent forms

and questionnaires and the other for the completion of the stop-signal task. The initial

portion of the experiment was done in the first area of the testing space and consisted of

each subject reading and signing a consent form, as well as completing the demographic

and personality questionnaires (approximately 10 minutes in length). An accompanying

parent or guardian completed child questionnaires.

An experimenter accompanied each subject to the computer testing area in order

to complete the selective stop-signal task. Subjects were tested individually and the

experimenter read a uniform set of instructions, operated the computer and monitored the

subject's progress from start to completion of the computer task (approximately 20

minutes in length). Each subject completed one practice block before commencing six

test blocks. Subjects were told that they would see a fixation point followed by one of

two letters ("X" or "O") and that their task was to respond to the letter (by pressing the

appropriate response button) as quickly as possible without making mistakes. Also, they

were told that although they were to respond to the presented letters as quickly as

possible, when the selected stop-signal tone was presented. (either the higher 1000 Hz or

the lower 250 Hz sounding of the two auditory tones), they were to attempt to halt

responding during that given trial. They were instructed not to wait for the auditory tones

as they occurred randomly. Mean GoRT was displayed at the end of the practice block.

The selection of the designated stop-signal was counterbalanced so that approximately an

equal number of subjects in each age group inhibited selectively to the high tone and to

the low tone.

Following the completion of the practice block, the stop-signal delay was reset to

250 ms prior to the onset of the first test block. Mean GoRTs were displayed at the end of

each test block in order to allow the subjects to rest, as well as to enable the experimenter

to monitor response execution task performance and restate instructions so that subjects

maintained relatively consistent GoRTs across the six experimental blocks.

Statistical Analysis

Due to the number of trials required by the tracking algorithm of the stop-signal

task to adjust the stop-signal delay to the point where the subject is successfully

inhibiting on 50% of stop trials, performance on the first block of the selective stop-

signal task was excluded from analyses, leaving five test blocks for analysis. In addition,

the total number of trials in which an early anticipatory (invalid) response (i.e., a

response within 200 ms of the onset of each response trial) was computed and then

excluded from further analyses. These anticipatory responses could occur on either

response execution or response inhibition trials. An examination of the stability of

performance in SSRT and GoRT across the five experimental blocks was conducted as a

reliability check of the data obtained by the selective stop-signal task. Subjects were then

divided into seven different age groups based on their stage in the life cycle in order to

allow for comparisons with data from previous studies (e.g.. Kramer et al., 1994:

Schachar and Logan, 1990; Williams et al., 1999). Response execution task accuracy

was examined as a check on the validity of response execution performance and accuracy

of selective inhibition (assessed by the percent inhibition given the nonselected stop-

signal (P(I/N)) was inspected across the different age groups, using an analysis of

variance (ANOVA) approach. The effect of time on task performance was examined by

comparing mean values of the outcome measures on the first two blocks of the task

versus that of the last two blocks. ANOVAs were used to determine how age affected the

execution and selective inhibition of prepotent responses (the dependent variables being

GoRT and SSRT. respectively). Subsequent trend analyses followed in order to

investigate the hypothesis that SSRT and GoRT would have curvilinear (quadratic)

relationships with age. Planned comparisons of mean GoRTs and SSRTs for young adults

(18-29 years) versus seniors (60-82 years) were performed to investigate whether the

developmental trends in adulthood for selective inhibition would differ to those

previously observed in nonselective inhibition (Williams et al.. 1999). A hierarchical

regression analysis was used to examine the curvilinear relationships observed between

age and the two criterion variables (SSRT and GoRT) and to compare developmental

trends. Lastly, secondary analyses on the effects of age on additional aspects of selective

stop-signal task performance, including response variability, ability to inhibit,

performance accuracy and proportion of early (invalid) responses, were conducted using

one-way ANOVAs.

Results

Reliability Check

Reliability coefficients were computed for the main dependent variables (SSRT

and GoRT) across the five experimental blocks used in the analyses for both the entire

data set and for each age group. Overall, $\alpha = 0.93$ for SSRT and $\alpha = 0.97$ for GoRT. The

coefficients across all of the age groups were also consistently positive and high.

The data found in Table 2.1 shows that subjects of all ages performed with

proficiency in regard to correctly responding to go signals (i.e., the letters "X" and "O"):

The mean accuracy of responding was 96.2% (SD = 5%). In addition, the mean percent

inhibition given the selected stop-signal was 49.1% (SD = 6.6%), indicating that the

tracking method was robust across the lifespan (i.e., inhibiting on ~50% of selected stop-

signal trials). The mean percent inhibition given the nonselected stop-signal was 4.1%

(SD = 8.2%), indicating that subjects were able to discriminate between the selected and

nonselected stop-signals.

Repeated-measures ANOVAs comparing mean performance on the first (blocks 2

and 3) and second (blocks 5 and 6) halves of the experimental task across the seven age

groups were conducted to examine the effects of time on task, as well as potential time by

age interactions. These analyses confirmed that time did not influence SSRT (F(1) = .639,

p = .43), GoRT (F(1) = 2.06, p = .15), SDGoRT (F(1) = 3.31, p = .07), percent inhibition

given the selected (F(1) = 1.67, p = .20) or nonselected (F(1) = .001, p = .98) stop-

signals. Mean go task accuracy, however, was found to decrease with time (F(1) = 5.54, p

= .019). No significant time by age interactions were found on any of the performance

variables. The failure to detect a slowing of GoRT and an overall change in mean SSRT

Table 2.1

Description of age groups, and related means and standard deviations (SD) for the dependent variables.

				%EARLY		SSRT[a]		GoRT[a]		SDGoRT		P(I/S)		P(I/N)		%CGR	
Age	Description	n	%Female	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
6-8	Early Childhood	40	55	0.74	1.37	456	230	645	239	201	75	49	10.6	6.6	13.4	92.1	6.0
9-12	Mid-Childhood	62	40	0.68	1.50	336	159	462	122	125	42	48	6.4	3.0	5.4	93.8	6.2
13-17	Adolescence	54	65	0.37	1.23	261	111	390	91	100	34	48.4	4.2	2.2	4.2	95.9	4.8
18-29	Young Adulthood	48	52	0.26	0.49	248	132	378	69	97	43	48.2	5.1	2.8	5.4	98.0	2.6
30-44	Mid-Adulthood	65	51	0.11	0.41	230	120	433	95	108	37	50	4.1	5.1	9.7	98.1	3.1
45-59	Older Adulthood	23	39	0.75	2.29	232	122	494	146	128	38	47.8	9.7	6.2	8.2	98.1	4.2
60-82	Seniors	25	44	0.23	0.54	329	133	634	185	173	94	54.3	5.7	5.0	9.0	98.5	1.6
6-82	Total	317	50	0.42	1.20	295	164	470	163	127	61	49.1	6.6	4.1	8.2	96.2	5.0

%EARLY = Percentage of early (invalid) responses (calculated out of the total 192 trials)
SSRT = Stop-signal reaction time (ms)
GoRT = Go-signal reaction time (ms)
SDGoRT = Standard deviation of go-signal reaction time (ms)
P(I/S) = Percent inhibition given the selected stop-signal
P(I/N) = Percent inhibition given the nonselected stop-signal
%CGR = Accuracy of go-task responding as percentage of correct go-signal responses
[a]Mean stop signal delay may be calculated from data presented, since SSRT= GoRT - Delay, it follows that Delay = GoRT - SSRT

over the duration of the experimental task indicates that subjects did not adopt a deliberate strategy of waiting for the occurrence of a stop-signal, which would have posed a threat to the assumptions of the horse-race model underlying the stop-signal task (e.g., Logan and Cowan, 1984).

Developmental Change

Mean scores and standard deviations for performance variables overall, as well as within each of the seven age groups, are presented in Table 2.1. Factorial ANOVAs with age and sex as between-subject variables revealed no significant sex differences for SSRT or GoRT. Accordingly, only the age variable was included in subsequent analyses of SSRT and GoRT data.

Response Inhibition (Stopping)

One-way ANOVAs revealed a significant overall age effect for SSRT. $F (6, 310) = 13.007$, $p < .001$ (see Figure 2.1). Significant quadratic ($p < .001$) and linear ($p < .001$) trends for the relationship between SSRT and age group were demonstrated.

As evident from the data shown in Table 2.1, young children (6-8 years) were approximately 120 ms slower in stopping than older children (9-12 years), and young adults (18-29 years) were about 80 ms faster than the oldest group of adults (60-82 years). As expected, the planned contrast between young adult (18-29 years) and seniors (6-82 years) was significant, $t (71) = 2.49$, $p < .05$, as was the planned contrast between young children (6-8 years) and older children (9-12 years), $t (100) = 2.87$, $p < .001$.

Figure 2.1 – Group means (inner symbol) and standard error of the mean (outer bars) for stop-signal reaction time (SSRT) and go-signal reaction time (GoRT) for the seven age groups.
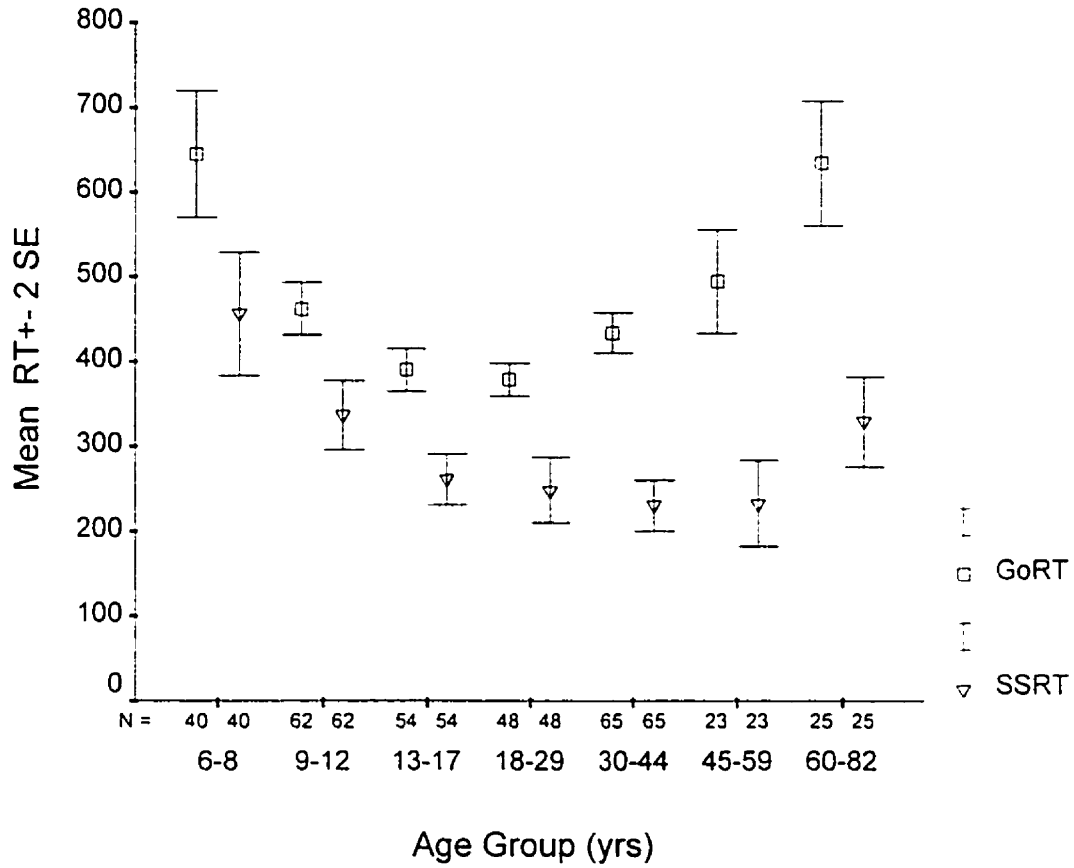
Response Execution (Going)

The one-way ANOVA revealed a significant main effect for age on GoRT, $F (6, 310) = 25.16$, $p < .001$ (see Figure 2.1). Subsequent trend analyses revealed a significant quadratic relationship ($p < .001$) between GoRT and age group. Planned comparisons revealed significant differences in GoRT between the young adult and older adult groups, $t (71) = 8.45$, $p < .001$. Specifically, the young adults (18-29 years) were about 250 ms faster than the seniors (60-81 years). These findings indicate that the speed of response execution becomes faster throughout childhood but then slows significantly across the adult years (see Table 2.1).

Regression Analyses

The results of the regression analyses are summarized in Table 2.2. Hierarchical multiple regression analysis was used for several reasons. First, two analyses were undertaken to confirm the developmental trends found in SSRT and GoRT (see Table 2.2, Analyses A and B). The statistical significance of the beta weights (standardized regression coefficients) was interpreted in this respect. For both analyses, age was entered as the first predictor, and on the subsequent step, the quadratic function of age was entered as the second predictor. As expected, the quadratic function of age was a significant predictor of SSRT, $\beta = 1.31$, $t (314) = 6.61$, $p < .001$, and GoRT, $\beta = 1.80$, $t (314) = 9.62$, $p < .001$ (see Figure 2.2).

Table 2.2

Hierarchical regression analyses predicting stop-signal reaction time (A,C) and go-signal reaction time (B)

Analysis/Steps	Cumulative R	F for R	R^2Change	F Change	B	t for B
A. Stop-signal reaction time						
1. Age	.18	10.86**	.03	10.86**	-1.44	-7.30***
2. Age^2	.39	28.02***	.11	43.71***	1.31	6.61***
B. Go-signal reaction time						
1. Age	.14	5.99*	.02	5.99*	-1.60	-8.55***
2. Age^2	.49	50.11***	.22	92.49***	1.80	9.62***
C. Stop-signal reaction time						
1. GoRT[a]	.10	2.85	.01	2.85	-0.06	-0.95
2. Age	.22	7.90***	.04	12.84***	-1.56	-6.99***
3. Age^2	.39	18.97***	.11	39.21***	1.41	6.26***

Note Analyses were conducted using the entire sample (ages 6-82, N=317) unless otherwise specified.

[a] Go-signal reaction time

* $p<.05$, ** $p<.01$, *** $p<.001$

Figure 2.2 – Scatter graph of stop-signal reaction time (SSRT) and go-signal

reaction time (GoRT) as a function of age
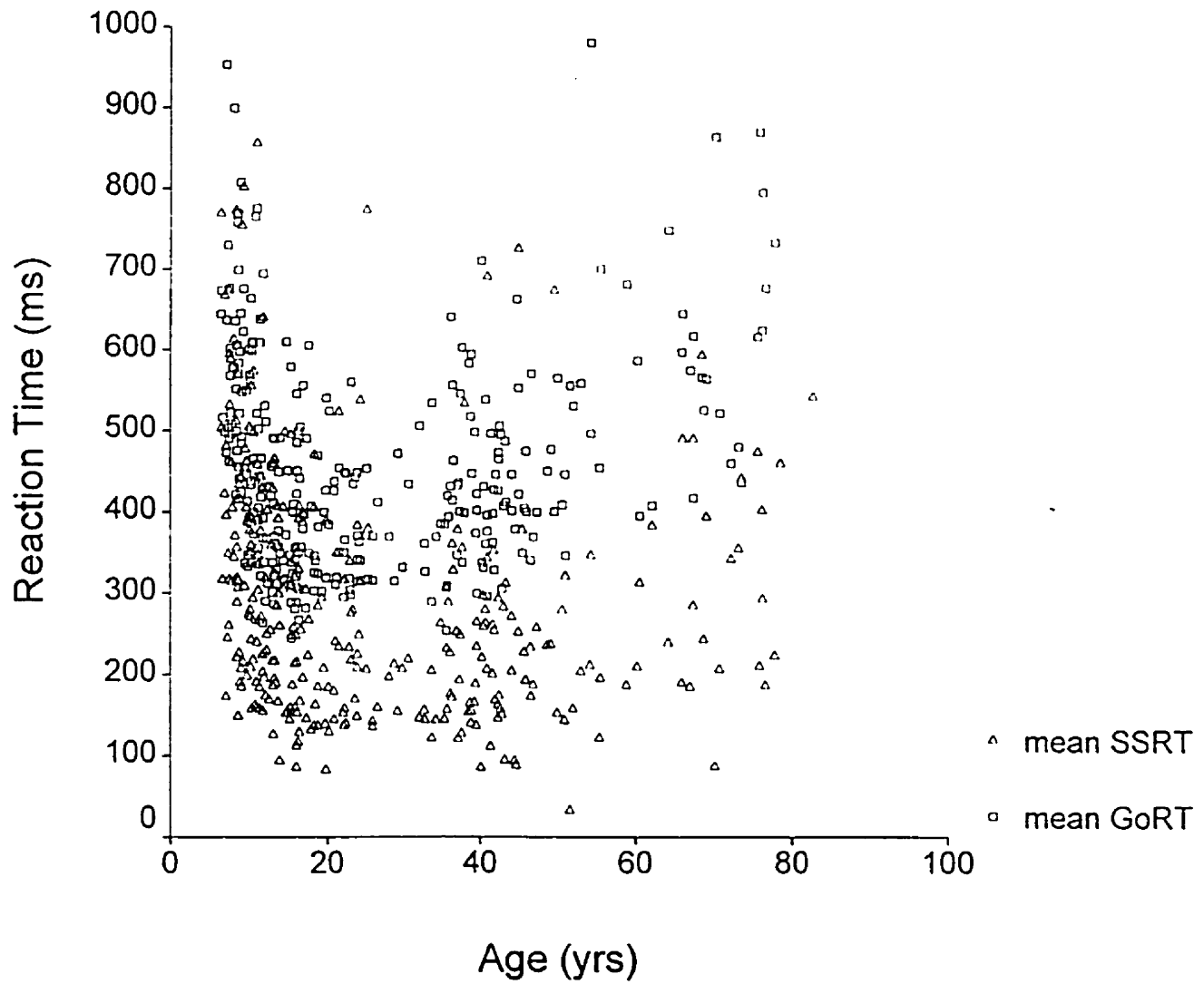
Second. further analysis of the data was conducted to determine whether the age-related change in SSRT was distinct from the age-related change in GoRT or whether SSRT changed with age in the same manner as GoRT (Table 2.2. Analysis C). Accordingly. variables were entered into a regression equation in a hierarchical procedure with SSRT as the dependent variable. GoRT was entered first (to first remove the effect attributable to the speed of responding). followed by age: the quadratic function of age was entered as the last step. This hierarchical approach permitted an examination of the significance of the unique variance added to the equation by the quadratic function of age. over and above that which could be accounted for by GoRT and age (i.e.. the significance of the change in explained variance on the final step). After the variance associated with the GoRT and age had been accounted for. the quadratic function of age added a significant amount of unique variance. $R^2\Delta = .11$. $F\Delta (1,313) = 39.21$. $p < .001$.

Additional Measures of Performance

One-way ANOVAs among the seven age groups on other outcome measures of the selective stop-signal task were also conducted. The proportion of early (invalid) responses (%EARLY) was found to significantly differ among the age groups ($F = 2.28$. $p = .036$). Also. significant differences among the age groups were found in variability of response execution speed ($F = 24.02$. $p < .001$). percent inhibition given the selected stop-signal ($F = 3.6$. $p = .002$). and given the nonselected stop-signal (P(I/N)) ($F = 3.11$. $p = .006$) and overall accuracy of response execution (%CGR) ($F = 13.42$. $p < .001$). Subsequent post-hoc analyses revealed that the older adults (60+ yrs) had a higher overall mean percent inhibition to the selected tone than all of the other age groups. and that both the youngest (6-8 yrs) and the oldest (60+ yrs) age groups had significantly greater

variability in GoRT than all of the other age groups. In addition response execution

accuracy increased throughout the life span, with post-hoc analyses identifying the

children (6-12 yrs) as being significantly less accurate than the adolescents and adults.

Discussion

The present study was designed to characterize developmental changes in the

ability to selectively inhibit a prepotent course of action. Accordingly, we used a

modification of the well-established stop-signal task to measure this type of inhibition in

a large community sample of individuals ranging in age from 6 to 82 years. The task used

in the present study was unique from previous versions of the stop-signal task (e.g.,

Kramer et al., 1994; May and Hasher, 1998; Ridderinkof et al., 1999; Williams et al.,

1999) in that we used a choice response execution reaction time task but altered the

response inhibition task so that both response execution and response inhibition

comprised a fixed choice reaction time task. The central findings are threefold. First,

developmental differences in the ability to selectively inhibit prepotent responses were

evidenced across the lifespan. Second, the abilities to selectively inhibit and execute

prepotent responses were found to follow differential developmental trends. Lastly, the

developmental trends found in selective inhibition are unique from those found by others

in the inhibition literature.

Results generated from this study indicated that response execution and selective

response inhibition follow different developmental trends. Although both SSRT (our

primary measure of selective inhibition) and GoRT (our primary measure of response

execution) improved throughout childhood and diminished throughout adulthood, the

developmental trends were less pronounced for the selective inhibition of prepotent

responses than for their execution (Figures 2.1 and 2.2). We observed a marked

difference in the effect size for the relationship between age and response execution (the

$P^2\Delta$ indicated that 22% of the variability in GoRT was explained by age) relative to that

between age and SSRT (only 11% was explained by age). The contrast observed in the

strength of the age effect between response execution and selective inhibition suggests

that the developmental trends may differ.

In addition, the notion of different developmental trends for the two processes is

supported by the results of the hierarchical multiple regression analysis, which indicated

that the significant age-related change in selective inhibition was distinct from the age-

related change found in response execution. Specifically, we found that the quadratic

function of age was a significant predictor of selective inhibition after accounting for the

variance attributable to response execution. That is, after partialing out any relationship

between selective inhibition and response execution, the pattern of change in inhibition

over the lifespan was still characterized by a quadratic function ($P^2\Delta = .11$).

The uniqueness in developmental trends for selective inhibition versus execution

of prepotent responses (for both adults and children) lends support to the underlying

theory of the stop-signal task, which posits that the processes governing the inhibition of

a speeded response are independent from those governing its execution (Logan. 1994).

Evidence of very strong age-related trends for response execution and less pronounced

trends for the inhibition of the ongoing action provided by the current study and in

previous research (e.g.. Band. 1996; Jennings et al.. 1997; Schachar and Logan. 1990;

Williams et al., 1999) is inconsistent with the hypothesis that speeded information

processing is mediated by a single global mechanism (e.g., Cerella and Hale, 1994; Kail, 1993). A number of alternative explanations are possible. First, it is possible that the ability to withhold a planned action is one of the earliest emerging control processes (executive functions) and one that is also preserved the longest (Barkley, 1997; Welsh and Pennington, 1988). This developmental pattern would make sense from an evolutionary perspective, given the significance of inhibition for survival. Further investigation of selective inhibition and execution of prepotent responses is clearly warranted, extending the study of developmental change into the preschool years, and using a longitudinal rather than a cross-sectional design.

A second perhaps related explanation for the unique observed developmental trends in selective response inhibition and execution is that the balance between individual differences and developmental differences may vary across cognitive measures. For example, given that the reliabilities of the measures of selective inhibition and response execution were comparable, the difference in strength of the age-related effects suggests that factors other than age are more strongly related to variance in the selective inhibition measure. Perhaps individual differences in selective inhibition remain fairly stable across age, whereas individual differences in response execution change across age. This could not be directly tested in the current study but indicates an avenue for further investigation.

Furthermore, due to the nature of the selective stop-signal task, constant cognitive demands on working memory (i.e., having to remember which tone goes with which response) and on set-shifting modalities of differential responses are placed on the subject. Since these cognitive demands have been shown to develop throughout

childhood and deteriorate throughout adulthood (e.g., Anderson, Craik, and Naveh-Benjamin, 1998; Kane, Hasher, Stoltzfus, et al., 1994; Chiappe, Hasher and Siegel, 2000) and since they impact more on the inhibition process (i.e., having to detect the presence of an auditory tone, discriminating between the pitch of the tone and finally matching the tone heard to the appropriate response) versus the execution process (i.e., simply matching visually presented stimuli to the appropriate response execution), it is possible that it is the high impact of the cognitive processes involved in selectively inhibiting responses which are driving the age-related effects observed.

Although differences in subjects tested precludes a direct comparison of our results with those of other developmental studies using similar inhibitory tasks, some similarities and differences can be inferred and provide context to the present study's findings. Specifically, Kramer et al. (1994), May and Hasher (1998) and the current study demonstrated a more marked slowing of SSRT in later adulthood than that shown in Williams et al. (1999). It should be noted that the response execution tasks used by Kramer et al. and May and Hasher were more complicated than that used in Williams et al.. That is, Kramer et al.'s response execution task included a response compatibility component and May and Hasher required the participant to judge whether an item (e.g., CHAIR) was a member of a particular category (e.g., FURNITURE). In comparison, the response execution task used in Williams et al. only required that the subject respond to the letters "X" and "O" and attempt to inhibit responding whenever an auditory stop-signal was presented. The present study was unique in design from all three of these studies in that it used a different response inhibition (i.e., stop) task. That is, the present study required the participant to discriminate between the designated stop-signal tone and

another similar auditory tone while executing a response whereas the Williams et al. response inhibition task presented only one possible auditory stop tone and required the cessation of response execution whenever that auditory tone was presented. The overall increase in cognitive demands in the present. Kramer et al., and May and Hasher studies may have given rise to greater difficulty in controlling the inhibition process, particularly in the elderly.

We found evidence of strong developmental trends throughout the lifespan for the execution of prepotent responses. That is, response execution speed (GoRT) increased throughout childhood and then gradually decreased (slowed) throughout adulthood. resulting in a U-shaped function (Figure 2.1). These findings are consistent not only with previous studies using the stop-signal task but with a substantial body of literature demonstrating developmental improvement in response speed in childhood and progressive slowing throughout adulthood on a wide variety of speed response tasks (Cerella. 1990; Kail. 1991. 1993). In addition. the developmental trend of response execution observed in the present study was found to be highly similar to that of Williams et al. (1999).

Future studies on the development of selective inhibition in comparison to other types of inhibition are clearly warranted. For instance. a direct comparison of selective inhibition as measured by the stop-signal task in comparison with nonselective inhibition. or a comparison of selective inhibition as perceptually defined in the current study (i.e.. requiring the discrimination between auditory tones) versus motor-based selective inhibition (i.e., requiring the selection of the appropriate motoric response) would enhance our understanding of this complex cognitive process.

Finally, the results of the present study indicate that the stop-signal task provides a robust measure of selective inhibition across a wide age span. Subjects from primary school age through senior citizenship, both female and male, were able to complete the task, respond to go signals with high levels of accuracy, and selectively inhibit their prepotent response to the extent predicted by the tracking procedure used to adjust stop-signal delays (i.e., 50%). The lifespan data provided by our study may serve as a reference base for applied research examining neuropsychology and psychopathology (e.g., to test models and theories proposed to explain cognitive aging or various disorders such as Parkinson's disease, Alzheimer's disease, schizophrenia, and attention-deficit/hyperactivity disorder).

CHAPTER 3

Characterizing Selective Inhibition in Children with Attention-Deficit/Hyperactivity Disorder On and Off Stimulant Medication

Abstract

Objective: To investigate selective inhibition in children with attention-deficit/hyperactivity disorder (ADHD) both on and off methylphenidate (MPH) using the novel selective stop-signal task. Selective inhibition is a challenging stopping process that requires discrimination between stop-signals. **Methods:** Selective inhibition in a group of 59 clinic referred, DSM-IV diagnosed ADHD children is compared to that of 59 children from a community based comparison sample; MPH effects on selective inhibition are assessed in a subset of the ADHD sample that participated in an acute, randomized, placebo-controlled, crossover trial with three fixed doses of MPH. In the selective stop-signal task, subjects performed a visual choice reaction time response execution task and attempted to selectively inhibit their response when hearing *one* of two randomly presented stop-signals, with each tone presented on 20% of trials. Measures of response execution and inhibition were assessed using reaction times to the response execution and selective stop-signals, respectively. **Results:** Children with ADHD performed more poorly than controls on the majority of task parameters: they exhibited more anticipatory (invalid) responses, with less accurate and more variable responses on the response execution task; as well as a slower selective inhibition process. MPH improved speed of both inhibition and response execution processes, as well as reduced variability of response execution and decreased nonselective inhibition. **Discussion:** On the one hand, findings are consistent with purported inhibition deficit in ADHD, but on the other hand, suggest that neither the impairment itself, nor MPH effects, were restricted to inhibition.

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common developmental psychiatric disorders diagnosed in childhood. According to current theory, the essential impairment in this disorder is a deficit involving response inhibition (Barkley, 1997). Inhibition (i.e., response inhibition) is a self-generated, higher-order executive function that refers to the ability to stop (completely and suddenly) a planned course of action (Logan and Cowan, 1984). It is an important cognitive ability required in everyday life (Logan, 1994) and may be a potential marker for ADHD (Schachar et al., 1993; Barkley, 1997).

Deficits in this type of inhibition can be seen most clearly using the stop-signal task (Logan and Cowan, 1984), in which subjects are required to intentionally inhibit their responses. Subjects are engaged in a reaction time task (e.g., discriminating between visual stimuli), and occasionally, they are presented with an auditory stop-signal that requires them to inhibit their response to the current stimulus. This task permits direct measurement of how quickly one can execute a response and an estimate of how quickly one can inhibit the estimated prepotent response.

Although children with ADHD have been demonstrated to have poor inhibition in comparison to normal control children (e.g., Nigg, 1999; Purvis and Tannock, 2000; Schachar and Logan, 1990; Schachar et al., 2000; Schachar et al., 1995), these findings warrant further investigation. For instance, although both Quay (1997) and Barkley (1997) have posited that deficits in motor inhibition processes are associated with the DSM-IV ADHD Combined subtype, differences in inhibition among the ADHD subtypes have not been examined. Also, some studies of inhibition have found that ADHD children are slower in response execution, as well as in inhibition tasks, suggesting that

the performance decrement may reflect a general speed-of-processing deficit rather than a specific deficit in inhibition (Oosterlaan et al., 1998; Tannock, 1998). By contrast, other studies have found no differences in response execution with large differences in response inhibition (e.g. Schachar et al., 2000) or larger differences in response inhibition than in execution (e.g. Oosterlaan et al, 1998), both of which are contrary to the general speeding hypothesis. Finally, it is unclear whether inhibition is specific to ADHD since deficits in inhibition have been linked with other disruptive disorders (e.g., Oosterlaan et al., 1998) and with reading disorder (Purvis and Tannock, 2000).

Stop-signal studies in ADHD research have thus far focused on nonselective inhibition whereby subjects were to inhibit any and all responses whenever a stop-signal occurred (e.g., Nigg, 1999; Purvis and Tannock, 2000; Schachar and Logan, 1990; Tannock et al., 1989). This nonselective inhibition does not afford very sophisticated cognitive control in that all responses are shut down whenever a stop-signal is presented (DeJong et al., 1995). The present study takes a novel approach to the study of inhibition in children with ADHD by using a variant of the stop-signal task to measure selective inhibition. A second tone was added to the basic stop-signal task and subjects were instructed to inhibit response execution whenever presented with the designated or selected stop-signal tone, and continue to respond to trials during which the nonselected stop-signal tone was presented. The second tone increased the perceptual complexity of the stop-signal task by requiring subjects to discriminate between selected and nonselected stop-signals with each presentation of an auditory stop-signal, prior to executing an inhibitory response.

The stimulant methylphenidate (MPH) is currently the most widely used treatment for children with ADHD, exerting pronounced effects on reducing the core behavioural symptoms (hyperactivity, impulsivity, inattentiveness) (see National Institutes of Health Consensus Statement, 2000, or Schachar, Tannock, Cunningham, 1996). In fact, reported behavioural improvement is estimated in 80% to 85% of children with ADHD treated (Quay, 1997). Although the primary objective of MPH treatment is aimed at this management of overt problem behaviour, understanding the effects of MPH on underlying cognitive processes (especially inhibition) is also critical.

Psychostimulant medication such as MPH is believed to activate self-regulatory or control processes, thereby ameliorating the fundamental inhibition deficit in children with ADHD (Barkley, 1997; Douglas, 1999). Reported stimulant trials have demonstrated empirical support for this theory. For example, MPH effects on response inhibition using the basic stop-signal task were investigated and significant speeding of the inhibitory process was found, suggesting an improvement in response inhibition (Tannock et al., 1989). In addition, since improvements in response inhibition were greater at the higher dose (1.0 mg/kg) than at the lower dose (0.3 mg/kg), the beneficial effect of MPH on response inhibition was related to dose.

By contrast, a non-linear dose relationship was reported in Tannock et al. (1995a). Specifically, a high dose (0.9 mg/kg) was found to be less effective in improving response inhibition than lower doses (0.3, 0.5 mg/kg). This latter study used a more complicated version of the basic stop-signal task (change task) that required children to inhibit their response to a primary task and immediately execute a response to a secondary task when given a signal to do so. Accordingly, results from this study are in

agreement with the theory that stimulants such as MPH may impair higher order

cognitive functioning at high doses (Sprague and Sleator, 1977; Solanto, 2000a). A

separate interesting finding in both of these aforementioned studies is the concomitant

evidence of improvement in aspects of performance (i.e. response execution speed) other

than that of response inhibition with MPH. This suggests that perhaps effects not specific

to inhibition were occurring or that stimulants enhanced an underlying mechanism

common to both response inhibition and execution.

In the present study, the primary objectives were to determine whether children

with ADHD exhibited deficient selective inhibition and whether MPH enhanced selective

inhibition in children with ADHD. A pronounced deficit in selective inhibition in

children with ADHD in comparison to community controls was expected because the

stop-signal task was made more complex than it has been in previous research. Similarly.

because of the added complexity of the selective inhibition process. it was predicted that

performance on the selective stop-signal task would discriminate between ADHD

subtypes (i.e., the Combined subtype would evidence greater deficits in inhibition than

the primarily Inattentive subtype). Also. since the results of previous studies examining

stimulant effects on nonselective inhibition have demonstrated global improvements in

response inhibition and execution with MPH. similar results are predicted with stimulant-

influenced performance on the selective inhibition task.

Method

<u>Subjects</u>

<u>Study 1 ADHD vs. Normal Controls</u>

The first study comprised of an ADHD sample of 59 children (50 boys, 9 girls) ranging in age from 6.37 to 12.91 years (M = 8.67, SD = 1.41), who were referred for assessment of problems relating to attention, behaviour and learning to an outpatient neuropsychiatry clinic in an urban, pediatric hospital. Exclusionary criteria included a full-scale intelligence quotient (IQ) score of less than 80, any evidence of neurological dysfunction, poor physical health, uncorrected sensory impairments, or a history of psychosis. All 59 clinical participants received a confirmed diagnosis of ADHD based on the protocol described below. Of the 59 DSM-IV diagnosed children with ADHD in our sample, 15 (25%) of these children were subtyped as Inattentive, 8 (14%) as Hyperactive/Impulsive and 36 (61%) as Combined. Seventeen (29%) subjects were classified as having a concurrent reading disorder, 22 (39%) were diagnosed with a comorbid conduct disorder and 16 (27%) were identified as having a comorbid oppositional defiant disorder. The clinical characteristics of the different ADHD subtypes are presented in Table 3.1.

Data from community control comparison children were derived from a large sample in our study of selective inhibition across the lifespan (Bedard et al., submitted). In that study examining the effects of development on selective inhibition, 317 subjects, aged 6 to 82 years, were tested individually at an urban science museum over a two-week period. From the 102 children aged 6-12 years tested throughout this period, 59 children were selected to match the clinical ADHD sample case by case based on age (and gender where possible). In situations in which a clinical subject could be matched with more

Table 3.1

Description of ADHD Sample by DSM-IV ADHD subtype

Sample Characteristic	Inattentive (n=15)	Hyperactive/Impulsive (n=8)	Combined (n=36)
Age, mean (SD)	8.0 (0.9)	7.5 (1.4)	8.4 (1.6)
% Females	20	25	14
Full Scale IQ, mean (SD)[a]	103 (12.4)	98.4 (6.6)	107 (12.2)
Teacher-based:[b]			
# Inattentive Symptoms	6.4 (1.3)	3.5 (1.9)	5.9 (1.6)
# Hyp/Imp. Symptoms	2.9 (1.2)	4.1 (3.1)	5.0 (2.4)
Parent-based:[b]			
# Inattentive Symptoms	5.6 (1.8)	4.1 (1.0)	6.2 (1.6)
# Hyp/Imp. Symptoms	4.4 (2.1)	6.5 (1.9)	6.4 (2.0)
Comorbid diagnoses (% participants)			
Reading disability	13	38	33
Conduct disorder	29	50	40
Oppositional defiant disorder	63	13	29

Some comorbidity data was unavailable [a]*Data from 1 Inattentive child, 1 Hyperactive/Impulsive child, & 1 Combined child missing;* [b]*Data from 1 Inattentive child & 1 Combined child missing; Conduct Disorder: data from one Inattentive child missing; Oppositional Defiant Disorder: data from three subjects missing*

than one child in the community sample, the matched pair was constructed by random selection among the potential matches. This community sample consisted of 37 boys and 22 girls ranging in age from 6.44 to 12.13 years (M = 8.89, SD = 1.47).

Stimulant effects on selective inhibition were examined in a subsample (N=28) of the children with ADHD described above (26 boys, 2 girls), who ranged in age from 6 to 12 years (M = 8.87, SD = 1.32). These children were recruited from children who had been referred specifically for evaluation of their responses to stimulant treatment or for whom stimulant medication had been recommended by the clinical diagnostic team (i.e.. all children participating in this MPH trial would have received MPH independent of this study). This subsample consisted of 10 children with DSM-IV Inattentive subtype, 4 children with DSM-IV Hyperactive/Impulsive subtype and 14 with DSM-IV Combined subtype. As the Hyperactive/Impulsive subtype consisted of only four children, they were not included in further subtype analyses. The subtype groups comprised children of similar age, gender and intelligence (see Table 3.2). As typical of clinical samples. 5(18%) of the ADHD clinic sample were classified as having a concurrent reading disorder. 9(32%) were diagnosed with a comorbid conduct disorder and 9(32%) were identified as having a comorbid oppositional defiant disorder. The demographic information for this subject group as a whole, as well as by their ADHD subtype. is provided as Table 3.2.

Table 3.2

Description of subset of ADHD Sample that participated in MPH trial by DSM-IV

ADHD subtype

	Total Sample (n=28)	Inattentive (n=10)	Hyperactive/ Impulsive (n=4)	Combined (n=14)
Age, mean (SD)	8.9 (1.4)	8.9 (0.8)	9.0 (1.5)	8.9 (1.7)
Range	6.37-11.96	7.10-9.75	7.67-10.75	6.37-11.96
% Females	7	10	25	0
Full-Scale IQ, mean (SD)	107 (12.7)	106 (14.2)	99 (6.1)	110 (12.6)
Teacher-based:				
# Inattentive Symptoms	6.2 (1.8)	6.3 (2.0)	4.7 (0.6)	6.5 (1.7)
# Hyp/Imp. Symptoms	4.6 (1.2)	2.9 (1.5)	5.3 (2.9)	5.7 (1.6)
Parent-based:				
# Inattentive Symptoms	5.4 (1.0)	5.7 (1.4)	4.3 (1.0)	5.6 (2.4)
# Hyp/Imp. Symptoms	5.1 (2.2)	4.3 (1.9)	7.3 (1.3)	4.9 (2.4)
Comorbid diagnoses* (% participants)				
Reading Disorder	18	10	50	14
Conduct Disorder	32	20	50	36
Oppositional Defiant Disorder	32	30	50	31

*Data from 1 inattentive child unavailable

Diagnostic Assessment

Clinical diagnosis of ADHD, using DSM-IV criteria, was based upon information

from semi-structured interviews conducted with parents (Parent Interview for Child

Symptoms-IV (PICS); Schachar, Ickowicz, and Wachsmuth, 1994) and the child's

classroom teacher (Teacher Telephone Interview-IV (TTI); Tannock and Schachar,

1994). The parent interview is based on the Schedule for Affective Disorders and

Schizophrenia for School-Aged Children – Present and Lifetime Version interview

(KSADS-PL: Kaufman et al.. 1997) with an expanded ADHD module, covering the

child's development and current behavior with a particular focus on the symptoms of

ADHD, oppositional defiant disorder and conduct disorder. A trained clinician rated the

presence/absence and severity of each of the DSM-IV symptoms based on descriptions of

the child's behavior in various situations, as elicited from the informant. The TTI

followed the same basic format as the PICS; it covered all of the DSM-IV symptoms of

ADHD, oppositional defiant disorder and conduct disorder in detail, but it also screened

for internalizing disorders such as generalized anxiety disorder. Reliability and validity

for the DSM-III-R version of both interviews is high (Schachar, Tannock, Marriott and

Logan, 1995); evaluation of the psychometric properties of the DSM-IV versions is

underway. Preliminary analysis on the DSM-IV version of the PICS indicates the Kappa

statistic for the ADHD diagnosis on the PICS was .84 for 32 cases. Kappas for individual

PICS symptoms ranged from a low of 0.51 for 'avoids work' to a high of 1.00 for 'waits

turn', 'quiet play', and 'intrudes'. Preliminary analyses on the DSM-IV version of the

TTI based on ten interviews resulted in inter-rater reliability based on a symptom level

ranging from 75% to 100% for the ADHD symptoms.

In addition, parents, teachers and children completed various standardized rating scales to provide supportive information. These measures included the Conners' Rating Scales – Revised (Conners, 1997), the Revised Ontario Child Health Study Scales (Boyle et al., 1987; Boyle, Offord, Racine, Fleming, Szatmari, and Sanford, 1993), the Revised Children's Manifest Anxiety Scale (Reynolds and Richmond, 1985), the Child Depression Inventory (Kovacs, 1992). All measures have been found to have acceptable psychometric properties. (e.g., Handbook of Psychiatric Measures: APA).

Among other measures, the Wechsler Intelligence Scale for Children – Third Edition (WISC-III: Wechsler, 1991), the reading subtest of the Wide Range Achievement Test – Third Edition (WRAT3: Wilkinson, 1993), and the Word Attack and Word Identification subtests of the Woodcock Reading Mastery Test – Revised (Woodcock, 1987) were administered during the initial assessment session. In the event that a psychologist had administered these tests within the past year, those results were obtained with consent from parents.

The DSM-IV does not specify an algorithm for combining information across informants. Accordingly, in this study the following `6/4` algorithm was used to classify ADHD subtype. The Inattentive subtype required at least 6 symptoms of inattentiveness on the PICS or TTI, with fewer than 6 symptoms of hyperactivity-impulsivity on both the PICS and TTI plus evidence of pervasiveness of symptomatology. Pervasiveness is defined operationally in this study as at least 4 symptoms of either inattentiveness or hyperactivity-impulsivity endorsed on each interview (i.e., a child could not receive a diagnosis of ADHD based on symptomatology restricted to home or school settings only). The Hyperactive/Impulsive subtype required at least 6 symptoms of

hyperactivity/impulsivity on the PICS and/or TTI, with fewer than 6 symptoms of

inattentiveness on the PICS or TTI. The Combined subtype required at least 6 symptoms

of inattentiveness plus 6 symptoms of hyperactivity/impulsivity on the PICS and/or TTI,

plus evidence of pervasiveness of symptomatology. Each child's diagnostic profile as

defined by the preceding research criteria was confirmed by a child psychiatrist, based

upon clinical review of all of the information gathered during the assessment.

Reading disorder was assessed using a definition of low-achievement in

standardized tests of single word and non-word reading (WRMT-R Word Attack, Word

Identification, WRAT3 Reading). Reading disorder was defined by scores of at least 1.5

SD below the mean for age on at least one of the three tests or if scores were at least 1.0

SD below the mean for age on at least two of the three tests. Conduct disorder and

oppositional defiant disorder were diagnosed using DSM-IV criteria.

The Selective Stop-Signal Task

Apparatus and Stimuli

A stand-alone, IBM compatible, desktop computer was used to present the

stimuli. Attached to the computer was a pair of adjustable padded headphones through

which two distinct auditory signals could be presented without hindrance from potential

background noise. In addition, the computer was connected to a handheld response box

(14 cm x 8.5 cm x 3.5 cm) that contained three single-pole double-throw buttons. These

buttons were arranged on the top of the box in a line formation with the two outermost

buttons individually labeled with the visual stimuli for the go task.

The visual stimuli for the go task were the uppercase letters "X" and "O",

presented in the centre of the screen for 1000 ms. Each go-task stimulus was preceded by

a 500-ms fixation point, also presented in the centre of the screen. Two 500 ms auditory

tones (1000 Hz, 250 Hz) were generated by the computer, each presented randomly on

approximately 20% of trials and delivered through headphones at a comfortable volume

for listening. One of these two tones was designated as the selected stop-signal tone: the

nonselected stop-signal tone was to be ignored. The stop-signal delay (i.e., the interval

between the presentation of the go signal and the stop-signal) was changed dynamically

after each selected stop-signal trial based on the performance of the subject (Logan et al.,

1997). Stop-signal delay was initially set at 250 ms and was adjusted in 50 ms steps in the

following manner: The stop-signal delay increased by 50 ms if the subject inhibited

successfully to the selected stop-signal (making it harder to inhibit on the next selected

stop-signal trial) and decreased by 50 ms if the subject failed to inhibit (making it easier

to inhibit on the next selected stop-signal trial). This online tracking system of success in

selective inhibition was designed to force a 'tie' finish between response execution and

response inhibition. Thus, the goal of the tracking algorithm was to allow subjects to

successfully inhibit responding to the go-task on approximately 50% of the selected stop-

signal trials. This was necessary for the estimation of stop-signal reaction time (SSRT)

(see Appendix of Williams et al., 1999).

The experimental task comprised 192 trials divided into six 32-trial blocks. There

were an equal number of "X"s and "O"s presented in each block. The auditory tone

stimuli (1000 Hz, 250 Hz tone) were presented on 12 (i.e., 38%) of the response

execution trials (distributed randomly in each block of 32 trials): 6 (19%) were 1000 Hz

and 6 (19%) were 250 Hz tones. Each of the stop-signal tones was presented half of the

time with an "X" and half of the time with an "O". The order in which the trials were

presented was randomized separately for each subject. Once started, the program ran continuously presenting one trial every 3.0 seconds. Measures of SSRT and GoRT were the primary outcome measures for this task.

Administration Procedure

Subjects were tested individually. The experimenter remained in the testing room with the subject, read a uniform set of instructions, operated the computer and monitored the subject's progress from start to completion of the computer task (approximately 20 minutes in length). Each subject completed one practice block before commencing the six test blocks. Subjects were told that they would see a fixation point followed by one of two letters ("X" or "O") and that their task was to respond to the letter (by pressing the appropriate response button) as quickly as possible without making mistakes. Also, they were told that although they were to respond to the presented letters as quickly as possible, when the selected stop-signal tone was presented they were to attempt to halt responding during that given trial. They were instructed not to wait for the auditory tones as they occurred randomly. GoRT was displayed at the end of the practice block. The selection of the designated stop-signal was counterbalanced so that approximately an equal number of subjects in both the clinical and the normal control groups inhibited selectively to the high tone and to the low tone. The examiners testing the children with ADHD were blind to child diagnosis and study hypotheses.

Drug Protocol

All 28 children participated in a five-day randomized double-blind placebo controlled crossover trial of MPH conducted in a pediatric hospital laboratory. Testing occurred over a period of five consecutive days, Monday through Friday, for

approximately three hours per session. In each session, participants completed the selective stop-signal task and other cognitive and academic measures (not reported here).

After baseline measures were obtained on the first day ('practice day'), each child received each of three doses of MPH (5 mg, 10 mg, and 15 mg for children who weighed under 25 kg; 10 mg, 15 mg, and 20 mg for those who weighed over 25 kg) and a placebo dose in a counter-balanced order so that approximately equal numbers of children received each of the possible drug condition orders. The two exceptions to this rule were that no directly ascending (i.e. P L M H) or descending (H M L P) medication orders were permitted because they would have made it difficult to interpret drug effects for the individual child, nor was one which began with the highest dose, due to a possible increased risk of side effects resulting from sudden challenge with high dose (Rapport et al., 1994). The examiner, psychiatrist, child and child's family were unaware of the medication condition for each trial day until trial completion. Placebo and active medication was prepared by the hospital pharmacist, powdered, and packaged in an opaque gelatin capsule to prevent identification of contents by colour, taste, or volume. Each child's medication was placed in an individually named and dated envelope to ensure accurate administration. The selective stop-signal task was administered two hours after ingesting the capsule containing MPH or placebo. The letters (i.e. response execution visual stimuli) presented on the screen varied for each day of the medication trial (Day 1: F D, Day 2: K R, Day 3: E P, Day 4: S Z, Day 5: C H) to eliminate potential practice effects on the response execution task. Also, the selected stop-signal tone was altered from subject to subject so that an equal amount of subjects were instructed to selectively inhibit to the high (1000 Hz) and low (250 Hz) tones, respectively (15

inhibited to the high tone and 13 to the low tone). The designated tone for each individual was kept constant across the five days of the medication trial.

In addition, a 3-point 16-item checklist for problem behaviour (10 items) and side effects (6 items) monitoring was developed based on clinical observations of frequently occurring problem behaviours and side effects during previous acute, medication trials in a laboratory setting (Tannock et al., 1989; 1995a; 1995b). Problem behaviours monitored included hyper pressing of the response buttons, fidgeting, talking, defiance and play, and side effects included drowsiness and observable tics. The examiner concurrently completed this checklist with the assessment of selective inhibition.

Statistical Analyses

Due to the number of trials required by the selective-stop-signal task to adjust the stop-signal delay to the point where the subject is successfully inhibiting on approximately 50% of selected stop-signal trials, performance on the first block of the selective stop-signal task was excluded, leaving five test blocks in the analyses. In addition, the total number of trials in which an early anticipatory (invalid) response (i.e., a response within 200 ms of the onset of each response trial) was computed and then excluded from further analyses. These anticipatory responses could occur on either response execution or response inhibition trials. An examination of the stability of performance in SSRT, GoRT and variability in GoRT across the five experimental blocks was conducted as a reliability check of the data obtained by the selective stop-signal task.

Performance on the selective stop-signal task between the ADHD clinic-based and community control samples was compared using a series of independent, parametric t-tests and calculations of effect size (Cohen's d). Performance on the selective-stop-

signal task between the ADHD subtypes sampled was examined using one-way analyses

of variance (ANOVAs), followed by measures of estimated effect size, as calculated by

eta-square (η^2). In addition, the proportion of individuals who displayed impaired SSRTs

(defined as a mean SSRT greater than one standard deviation of the mean SSRT for the

entire community control group) were compared using chi-square tests for (a) the

children with ADHD versus community controls, and (b) across the ADHD subtypes.

The primary set of analyses for the second half of the study examined the effects

of MPH on performance variables of the selective stop-signal task. First, a repeated-

measures ANOVA was conducted to examine the effects of MPH Dose (4 levels: the

repeated within-subjects factor) on the main dependent variables measured in the

selective stop-signal task. Since a previous study of MPH impact on the change task (a

manipulation of the basic stop-signal task) demonstrated that inhibition deteriorated with

higher doses of MPH (Tannock et al., 1995a), three focused F tests (contrasts or planned

comparisons with numerator df = 1) were applied to SSRT (the primary measure of

selective inhibition) in order to determine relationships in selective inhibition across the

four drug doses. The set of three contrasts used were the Helmert Planned Comparisons

approach (Comparison one: placebo vs. low, medium, and high dose; Comparison two:

low versus medium and high dose; Comparison three: medium versus high dose). The

shape of the dose-response curve of SSRT was defined by the pattern of findings across

the three contrasts. Secondly, the effects of dose (four levels: the repeated within-subjects

factor) on selective stop-signal task performance was examined by ADHD subtype (the

repeated between-subjects factor). Lastly, MPH effects on problem behaviours and

observed side effects during selective stop-signal task administration were analyzed with

a two-way ANOVA with repeated-measures across dose (four levels) for (a) the entire

sample, and (b) between ADHD subtypes (one between-subjects variable).

Results

Preliminary Checks on Data

The novel application of the selective stop-signal task was successful. For the

sample as a whole (59 children with ADHD, 59 community controls), the percent

inhibition given the selected stop-signal tone was 46% and the percent inhibition given

the nonselected stop-signal tone was 7%. This indicates that the sample as a whole was

able to successfully discriminate between auditory stop-signal tones, and successfully

inhibit to the selected stop-signal tone. Also, overall mean accuracy in response execution

was 90.5%, demonstrating that the children were able to match their response to the

stimuli presented. Reliability over three blocks was consistently high, with α = 0.93 for

SSRT, α = 0.95 for GoRT, and α = 0.80 for SDGoRT.

Selective Inhibition in Children with ADHD vs. Community Controls

Performance on the primary outcome measures of the selective stop-signal task by

the children with ADHD versus the community control group is summarized as Table

3.3. In comparison to the community control group, children with ADHD had a

significantly higher percentage of invalid anticipatory responses (~6% of total presented

trials) than did matched community controls (< 1% of total presented trials). Also, the

children with ADHD had significantly poorer selective inhibition, as demonstrated by a

mean SSRT 120 ms slower than that of the community controls. Mean GoRT, however,

did not differ significantly between the groups. Other aspects of performance were

Table 3.3

Mean scores (± SD) for performance on the selective stop-signal task for the

ADHD sample and matched community controls

Variable	Control Group (N=59) M (SD)	ADHD Group (N=59) M (SD)	Group Difference (*p*)	Effect Size (*d*)
%Early [a]	0.9 (1.6)	5.5 (8.8)	p = .001	0.73
Response Inhibition SSRT (ms)	403 (187)	524 (236)	p = .002	0.57
P(I/S)	48.8 (9.6)	43.0 (10.7)	p = .002	0.57
P(I/N)	5.2 (11.3)	9.0 (14.4)	p = .11	0.30
Response Execution GoRT (ms)	587 (223)	·567 (158)	p = .58	0.10
SDGoRT (ms)	170 (69)	223 (93)	p = .001	0.65
%CGR	92.3 (6.3)	86.3 (9.3)	p < .001	0.76

[a] *Early responses may occur on any trial (i.e., those with and without a stop signal) and are excluded from all analyses and interpretation of GoRT, SSRT, SDGoRT, etc.*

%EARLY = Percentage of early (invalid) responses (calculated out of the total 192 trials)
SSRT = Stop-signal reaction time (ms)
GoRT = Go-signal reaction time (ms)
SDGoRT = Standard deviation of go-signal reaction time (ms)
P(I/S) = Percent inhibition given the selected stop-signal
P(I/N) = Percent inhibition given the nonselected stop-signal
%CGR = Accuracy of go-task responding as percentage of correct go-signal responses

significantly worse in the ADHD group compared to the community controls, including

impaired go task accuracy, a greater variability in response execution speed and a poorer

ability to inhibit to the selected stop-signal tone. Lastly, the mean difference in response

inhibition and execution speeds (calculated by subtracting mean SSRT from mean GoRT)

was much larger for the community controls (SSRT 180 ms faster than GoRT) than for

the ADHD group (SSRT only ~40ms faster than GoRT).

To further examine the specificity of a selective inhibition deficit in ADHD

children, we used a categorical approach to determine inhibition deficits in ADHD.

Impairment in selective inhibition was defined as a mean SSRT greater than one standard

deviation above that for the comparison community sample. The 8(14%) of the control

group that exhibited mean SSRTs at least one standard deviation above their group mean

(i.e., an SSRT or 589 ms or greater) was very similar to the 16% expected from a normal

distribution. However, a much larger proportion (36%, n = 21) of the children with

ADHD exhibited an SSRT that was at least one standard deviation above the mean for

the age matched normal group. The difference in proportion of each sample displaying

impaired selective inhibition was statistically significant (X^2 = 7.7, df = 1, p = 0.005).

Selective Inhibition Across the ADHD Subtypes

The clinical characteristics of the children within each of the three ADHD

subtypes are reported in Table 3.1. Mean scores, significance values and effect sizes of

the selective stop-signal task outcome variables among the three ADHD subtypes are

presented in Table 3.4.

Table 3.4

Mean scores (± SD) for performance on the selective stop-signal task for the

ADHD sample by DSM-IV ADHD subtype

Variable	Inattentive (n=15) M (SD)	Hyperactive /Impulsive (n=8) M (SD)	Combined (n=36) M (SD)	Group Difference	Effect Size (η^2)
%Early	4.7 (5.7)	8.9 (12.7)	5.1 (9.0)	p = .13	.02
Response Inhibition SSRT (ms)	480 (277)	403 (186)	569 (219)	p = .14	.07
P(I/S)	43.0 (11.5)	48.2 (5.0)	41.8 (11.1)	p = .31	.04
P(I/N)	6 (8)	18 (26)	8 (13)	p = .13	.07
Response Execution GoRT (ms)	545 (144)	604 (106)	568 (174)	p = .70	.01
SDGoRT (ms)	211 (90)	232 (95)	226 (96)	p = .85	.01
%CGR	86 (9)	88 (7)	86 (10)	p = .86	.01

Note: Non-parametric Kruskal-Wallis Test analyses showed nonsignificant differences between the ADHD subtypes across all performance variables

%EARLY = Percentage of early (invalid) responses (calculated out of the total 192 trials)
SSRT = Stop-signal reaction time (ms)
GoRT = Go-signal reaction time (ms)
SDGoRT = Standard deviation of go-signal reaction time (ms)
P(I/S) = Percent inhibition given the selected stop-signal
P(I/N) = Percent inhibition given the nonselected stop-signal
%CGR = Accuracy of go-task responding as percentage of correct go-signal responses

As this table indicates, no statistically significant differences among subtypes were found on any of the outcome measures. However, the Combined subtype had the slowest mean SSRT (569 ms), followed by the Inattentive (480 ms). The Hyperactive/Impulsive group had the best inhibition latency (402 ms), which was identical to that of the age matched community controls (see Table 3.3). In addition, the Hyperactive/Impulsive group also had the highest response execution accuracy and the best ability to inhibit to the selected stop-signal tone in comparison to the other ADHD subtypes. Differences in mean SSRT and GoRT among the subtypes were also of interest: the Hyperactive/Impulsive subtype had the largest difference with mean SSRT ~200 ms faster than mean GoRT, followed by the Inattentive with mean SSRT ~65 ms faster than mean GoRT, with the Combined group having identical mean going and stopping speeds.

To determine the relative proportion of children in each of the ADHD subtypes with impaired selective inhibition, mean SSRTs were compared with those of the community control group's mean SSRT. We determined the number of children in each subtype with SSRTs longer than one standard deviation for the community control group's mean SSRT (i.e. greater than 589 ms). The results were as follows: 4(27%) of the Inattentive subtype, 1(13%) of the Hyperactive/Impulsive subtype and 16(44%) of the Combined subtype had impaired selective inhibition relative to the community based comparison sample. The proportion of children displaying impaired selective inhibition was significantly different across the subtypes ($X^2 = 12.2$, df = 3, p = 0.007).

MPH Effects on Selective Inhibition

The means and standard deviations for the dependent variables of the selective-stop-signal task obtained for each of the three active treatment conditions and placebo are presented in Table 3.5. In addition, mean scores on the selective stop-signal task during baseline ('practice') day are also presented for comparison purposes in Table 3.5 (baseline values were not included in subsequent analyses). MPH had no effect in reducing the percentage of early (invalid) responses. which remained high (ranging from ~12% to ~8%) across all trial days.

Response Inhibition

MPH had an overall effect of accelerating the inhibitory process (contrast one for SSRT: $F(1) = 7.94$, $p < .01$). The dose effects for response inhibition. however, were non-linear. Contrast two for SSRT (low vs. medium. high doses). approached significance ($F = 3.428$, $p = .07$). indicating that there was a trend of relative slowing of the inhibitory process at higher doses (contrast 3 demonstrated no significant differences in SSRT between the medium and high dose ($F = 0.25$, $p = .62$)). At low dose. the inhibitory process was approximately 50 ms faster than the mean response inhibition latency of medium and high doses combined. and 150 ms faster than at placebo. Under the effect medium and high doses of MPH. mean SSRT remained approximately 100 ms faster than that of placebo demonstrating marked improvements in response inhibition latency across all of the drug doses when compared to placebo.

Table 3.5

Mean scores (± SD), repeated-measures ANOVA results, and effect sizes for performance on the selective stop-signal task for the

ADHD sample across the four drug days (placebo, low, medium, & high doses of MPH)

Variable	Drug Dose					ANOVA	Result	Effect Size
	Baseline(Day 1)	Placebo	Low	Medium	High	F-Value	P-Value	(η^2)
%Early	20.6 (21.2)	12.1 (12.3)	11.3 (18.1)	8.0 (10.8)	8.4 (11.4)	1.58	.215	.06
Response Inhibition								
SSRT (ms)	533 (229)	578 (314)	426 (234)	483 (221)	466 (222)	5.22	.006	.16
P(I/S)	43.35 (10)	42.02 (11)	41.15 (12)	43.10 (8)	44.70 (10)	1.05	.364	.04
P(I/N)	13.27 (16)	15.39 (19)	8.24 (15)	8.09 (13)	6.23 (11)	3.83	.028	.13
Response Execution								
GoRT (ms)	509 (107)	548 (140)	469 (163)	480 (115)	476 (143)	5.87	.003	.18
SDGoRT (ms)	226 (103)	275 (150)	189 (143)	174 (83)	156 (69)	12.10	.001	.31
%CGR	83 (8)	77 (12)	80 (14)	82 (12)	82 (14)	2.75	.064	.10

%EARLY = Percentage of early (invalid) responses (calculated out of the total 192 trials)
SSRT = Stop-signal reaction time (ms)   P(I/S) = Percent inhibition given the selected stop-signal
GoRT = Go-signal reaction time (ms)   P(I/N) = Percent inhibition given the nonselected stop-signal
SDGoRT = Standard deviation of go-signal reaction time (ms)   %CGR = Accuracy of go-task responding as percentage of correct go-signal responses

MPH was also shown to improve an additional aspect of selective inhibition performance: the ability to continue to respond to the go stimuli despite the presentation of the nonselected (i.e., distracter) stop-signal tone. P(I/N) was relatively high at placebo (15%) and significantly decreased with MPH (to levels of 8% at both low and medium and 6% at high). The percent inhibition given the selective stop-signal (P(I/S)), however, did not significantly improve with medication, remaining stable across drug doses (between 41% and 44%).

Response Execution

Beneficial effects of MPH on response execution measures were also observed (Table 3.5). Of primary focus, MPH was found to significantly increase speed of response execution (i.e., GoRT) and reduce variability of response execution speed (i.e., SDGoRT). At placebo dose, mean GoRT was found to be 548 ms, and improved by a range of 68 ms (Medium) to 80 ms (Low). Similarly, mean SDGoRT was 275 ms at Placebo and improved (i.e. decreased) by a range of 86 ms (Low) to 119 ms (High). It should be noted that MPH also improved overall accuracy (%CGR) (p = .06).

Lastly, the mean difference between stopping (SSRT) and going (GoRT) latencies did not appear to increase with drug, remaining similar across the drug days (ranged from 3 to 43 ms).

Overt Behaviour and Side Effects

Mean values for measures of overt problem behaviour and observed side effects for placebo and each of the three medication days are presented as Table 3.6.

Table 3.6

Mean scores (± SD), repeated-measures ANOVA results, and effect sizes for overt

behaviours and side effects observed during selective stop-signal task performance

across the four drug days (placebo, low, medium & high doses of MPH)

Variable	Drug Dose				ANOVA	Result	Effect Size (η^2)
	Placebo	Low	Medium	High	F-Value	p-Value	
Behaviour Total Score (max = 30)	11.9 (6.9)	4.5 (3.2)	5.0 (4.4)	4.0 (3.8)	26.7	.001	0.50
Side Effect Total Score (max = 18)	0.9 (1.2)	0.9 (1.2)	0.8 (0.9)	1.0 (1.3)	0.2	.888	0.01

Overall, drug reduced the number and severity of all overt problems behaviours

reported but did not significantly alter observable side effects, which appeared minimal

across the drug days.

Observed Trends in MPH Dose Response

Results from trend analyses for the primary variables of performance on the

selective stop-signal task, as well as overall problem behaviour and observed side effects

displayed during completion of the task, are presented as Table 3.7. Dose response trends

were found to be quadratic or linear for latency of response execution (GoRT) and

variability of response execution (SDGoRT) and fit best cubic or quadratic functions for

response inhibition (SSRT).

Table 3.7

Trend analyses of the relationships between MPH dose and cognitive and behavioural

measures of performance on the selective stop-signal task

Variable	Trend		
	Linear	Quadratic	Cubic
SSRT	3.91	6.61[c]	5.68[b]
GoRT	6.39[c]	11.68[a]	2.36
SDGRT	19.01[a]	8.36[a]	1.53
Problem Behaviours	32.45[a]	29.79[c]	11.11[b]
Side Effects	0.21	0.23	0.18

[a] $p < .001$, [b] $p < .05$, [c] $p < .01$

MPH Effects by ADHD Subtype

No significant effects of ADHD Subtype (Inattentive and Combined) on MPH

response regarding performance on the selective stop-signal task were demonstrated. In

addition, no ADHD subtype differences in MPH effects on problem behaviours or on side

effects were observed during administration of the selective stop-signal task.

Discussion

This is the first study to examine selective inhibition in children with ADHD using a novel experimental manipulation of the stop-signal task. The primary findings from the study are threefold: (1) children with ADHD were poorer to selectively inhibit than matched community controls, (2) there is no clear evidence that selective inhibition differed among the DSM-IV ADHD subtypes, and (3) MPH improved selective inhibition in children with ADHD.

On average, children with ADHD were 120 ms slower to selectively inhibit than community controls. The effect size of this difference in inhibition speed is consistent with that found in previous studies comparing nonselective inhibition speeds in children with ADHD versus normal controls (Nigg et al., 1999; Oosterlaan et al., 1998; Schachar et al., 2000). This indicates that the present study's manipulation of the stop-signal task produced differences in inhibition consistent to those previously reported in the literature: clearly, children with ADHD experienced greater difficulty in inhibiting to the selected stop-signal than did community controls.

The experimental manipulation of the stop-signal task used to measure selective inhibition was evidently successful. In the selective stop-signal task, the response inhibition task was made more complex by requiring the initial perceptual discrimination between different stop-signals while the response execution task remained unchanged relative to the basic, nonselective stop-signal task (Logan, 1984). Results indicate that this version of the stop-signal task was indeed successful at challenging the subjects' inhibition process while having little impact on their response execution. Mean SSRTs were greater for both the children with ADHD and community controls than those

previously reported using simpler response inhibition tasks while response execution

(GoRT) speeds remained very similar (see Nigg et al.. 1999; Purvis and Tannock. 2000

for nonselective SSRT means). In addition. subjects were able to selectively inhibit to the

selected stop-signal tone. as evident by percent inhibition to the selected and nonselected

stop-signal tones, respectively.

Interestingly. despite the increased challenge of the inhibition process. mean

SSRT remained faster (180 ms) than mean GoRT for the community controls. as has

been previously shown with nonselective inhibition in children both with and without

ADHD (Nigg. 1999; Purvis and Tannock. 2000; Schachar et al.. 2000). However. this

was not the case for the children with ADHD who had SSRTs very similar to their

GoRTs in the selective stop-signal task. In addition. MPH did not separate SSRT and

GoRT in these children. as will be discussed later. The significance of this unexpected

pattern of findings for SSRT and GoRT in children with ADHD is unknown and needs

further investigation.

Although the selective stop-signal task was successful in stressing the inhibitory

process in children with ADHD. it was no more successful than the nonselective stop-

signal task in capturing a greater proportion of children with ADHD with impaired

inhibition relative to controls. That is. the 36% of the ADHD sample found to have

impaired selective SSRT was equivalent to the proportion of the ADHD sample

previously found to have impaired nonselective SSRT using the same categorical

approach in classifying impairment (Purvis and Tannock. 2000).

The selective inhibition data among the ADHD subtypes is highly intriguing and

suggestive of potential subtype differences in inhibition. Although the continuous

approach used to examine selective inhibition among the ADHD subtypes found

insignificant differences, two clear patterns emerged in this data. First, although small in

number, the Hyperactive/Impulsive subtype looked unimpaired relative to the Combined

subtype in selective inhibition. Second, the Inattentive subtype appeared impaired in

selective inhibition compared to the community controls. Both of these observations

directly challenge the theoretical relationship between poor inhibition and high

impulsivity in ADHD (Barkley, 1997; Schachar and Logan, 1990; Tannock et al., 1993).

Moreover, the categorical approach used to investigate differences in the proportion of

children with impaired SSRT revealed significant differences among the subtypes.

Specifically, the Combined subtype had the greatest proportion of children with impaired

SSRT (44%) whereas the Hyperactive/Impulsive subtype had the smallest proportion of

children with impaired SSRT (13%), identical to the proportion of impaired children in

the community control group. Therefore, although the present data on subtype differences

in selective inhibition is inconclusive, most likely to due to small sample size and

inadequate power, findings are provocative and highlight directions for future research in

the field of inhibition and ADHD.

In this study, children with ADHD showed poorer performance on a number of

parameters in addition to selective inhibition when compared with community controls.

For instance, children with ADHD showed increased variability and poorer accuracy of

response execution, as well as a greater total number of invalid anticipatory responses

than controls. This suggests that the cognitive deficit in children with ADHD may not be

limited to inhibition, as previously suggested. Perhaps difficulty encountered on the

selective stop-signal task by children with ADHD is reflective of a more general deficit in

information processing or of other cognitive processes used during the task. such as the demands continuously placed on working memory in remembering which stop-signal tone requires inhibition of the go task response.

Stimulant medication (MPH) improved selective inhibition in children with ADHD. With respect to dose response, the fastest mean selective SSRT was observed at the lowest dose of MPH with slight decreases in inhibition speed noted at the higher doses. When compared to other stimulant effect studies on inhibition using different manipulations of the stop-signal task, the present study's inhibition dose response more closely resembled the non-linear dose improvements seen in inhibition using a stop-signal task with a complicated response execution (Go) task (Tannock et al., 1995a) than that of linear dose improvements observed using the basic stop-signal task (Tannock et al. 1989). This decline in inhibitory performance on the more cognitively challenging tasks with MPH is in accordance with the theory that stimulants such as MPH may impair higher order cognitive functioning at high doses (Sprague and Sleator. 1977; Solanto. 2000a). Improvements in overt problem behaviours observed with MPH indicate that, in general, the medication trial worked as intended. Also, since an increase in side effect severity and frequency paralleling the decrease in SSRT speed was not evident, the decline in selective inhibition observed with higher doses of MPH can not be attributed to side effects resulting from the stimulant medication.

No difference in MPH effects on selective inhibition was found between the Inattentive and Combined subtypes. This is not surprising since there was no difference in selective inhibition between these subtypes off medication and suggests that MPH does not differentially effect response inhibition between these two DSM-IV ADHD subtypes.

Future studies examining stimulant effects on the selective inhibition of all three DSM-IV

subtypes would provide more conclusive evidence on subtype response to MPH since

sample sizes here were limited.

The significance of the unexpected pattern of overlapping SSRT and GoRT

speeds in the children with ADHD in the present study is unknown. Moreover, although

MPH had an overall beneficial effect on performance, it still could not address this

processing difficulty in children with ADHD. Perhaps children with ADHD are

particularly impaired in dealing with unpredictable stimuli, especially when it requires an

attentional and response shift, and MPH does not help this set shifting.

Interestingly, children with ADHD showed improved performance not only in

selective inhibition, but also in speed and variability of response execution when given

MPH. Thus, MPH may influence global cognitive processes, such as attentional capacity

or working memory, that are deficient in children with ADHD and result in

improvements in aspects of response inhibition, as well as response execution.

Alternatively, MPH may influence a number of distinct executive functions including

response inhibition and those involved in the selection, execution or maintenance of an

optimal response strategy (Tannock et al., 1989).

Limitations of the present study must be considered in interpreting the findings.

The recruitment methodology of our community sample of community controls did not

permit collection of some types of data such as IQ or psychiatric profiles. Thus, we

cannot confirm that the community sample was free of psychopathology or was of

comparable intellectual ability to the children with ADHD. Also, due to our MPH study

sample characteristics, only two of the three DSM-IV ADHD subtypes (Inattentive and

Combined) were considered in the MPH effects on selective inhibition subtype analysis. In the first half of this study, the Hyperactive/Impulsive subtype, however, did demonstrate intriguing selective inhibition data off medication that should be explored in future research with a larger sample size.

A categorical approach for comparing the proportion of subjects with impaired inhibition in children with ADHD and community controls was used because normalized (standardized) selective stopping data does not exist. Many authors have suggested that inhibition tasks could be used to help diagnose children with ADHD and quantitate their degree of impairment. Accordingly, it was hypothesized that a selective inhibition task may be better able to differentiate children with ADHD from normal controls. However, the categorical approach used in this study did not provide better discrimination between children with ADHD and community controls on the selective stop-signal task than had been previously observed in nonselective inhibition (Purvis and Tannock, 2000). Future studies with large sample of children with ADHD using receiver-operator curve analyses (ROC) might provide precise impairment cut-off scores of inhibition.

A future study that directly assesses differences between selective and nonselective inhibition in the same group of children with ADHD would provide insight into the relationship between nonselective and selective inhibition. This type of study might provide information about the impact of particular cognitive functions, such as working memory, in different types of inhibition.

In addition, studies comparing the performance of children with ADHD and other psychiatric or cognitively-impaired groups on the selective stop-signal task are required in order to ascertain whether deficits in selective inhibition are: (a) restricted to only

children with ADHD, (b) characteristic of a disorder which is commonly seen comorbid with ADHD, or (c) evident only in a circumscribed group of children with ADHD.

In summary, this novel study was highly successful in examining selective inhibition in children with ADHD both on and off stimulant medication. Results generated from this study clearly demonstrate impairment in selective inhibition in children with ADHD compared to community controls, as well as indicate potential differences in selective inhibition among the ADHD subtypes. The present study's findings both compliment and build on the existing ADHD inhibition literature and validate the use of the selective-stop-signal task for future studies examining response inhibition in childhood psychopathology.

CHAPTER 4

Discussion and Future Directions

This thesis investigated an essential self-regulatory function, inhibition, which interacts with initiatory (excitatory) processes to permit the finely tuned control of thought and action. Previous research on inhibition has focused primarily on simple, nonselective inhibition, which requires the execution of an inhibitory response whenever a stop-signal is presented. By contrast, this thesis investigated selective inhibition, which provides a more precise form of control by requiring the additional discrimination between stop-signals prior to the execution of an inhibitory response. Nonselective inhibition is known to develop progressively from childhood to adulthood (Band et al., 1999; Ridderinkof et al., 1999; Williams et al., 1999), to be impaired in neurodevelopmental disorders such as ADHD (Schachar et al., 1995; 2000), and to be enhanced by stimulant medications including MPH (Tannock et al., 1989, 1995a). Little is known about selective inhibition. Thus, the goals of this research were to determine (a) whether selective inhibition follows a similar developmental pattern across the lifespan to that demonstrated for simple inhibition of a motor response (i.e., all-or-none decision about responding or non-responding); (b) whether selective inhibition is impaired in children with ADHD, in addition to whether the DSM-IV ADHD subtypes differ in this type of control process; and (c) whether it is enhanced by stimulant medication (MPH) which is one of the primary treatment modalities for ADHD.

Development of Selective Inhibition

The first study (Chapter 2) examined selective inhibition in a large community sample ranging in age from 6 to 82 years. Results showed that the speed of selective inhibition increased throughout childhood, with pronounced slowing across the adult years. This slowing in inhibition speed for the elderly appeared greater than previously

demonstrated using a nonselective inhibition task (Williams et al., 1999). In addition,

strong evidence was obtained for age-related speeding of response execution throughout

childhood, with marked slowing throughout adulthood. However, methodological

differences (e.g., different probability of stop-signal occurrence) precluded a direct

comparison between the development of selective and nonselective (Williams et al.,

1999) inhibition. Hierarchical regression analyses provided evidence that slowing or

speeding of response execution could not explain the age-related changes in the speed of

selective inhibition. This suggests that performance on the selective inhibition task was

not influenced by performance on the response execution task. Furthermore, these results

indicate that the experimental manipulation of the stop-signal task was successful in the

measurement of selective inhibition as findings remained robust across the lifespan.

Selective Inhibition in ADHD

The first study reported in Chapter 3 examined selective inhibition in a clinical

sample of children with a confirmed diagnosis of ADHD. Selective inhibition in children

with ADHD off medication was compared to that of age-matched community controls.

Results provide strong evidence that selective inhibition is impaired in children with

ADHD. Also, there was also no clear evidence of differences in selective inhibition

among the DSM-IV ADHD subtypes. Additional aspects of selective stop-signal task

performance were also impaired in children with ADHD in comparison to the community

controls. These results suggest that impairment in children with ADHD may not be

restricted to selective inhibition per se.

Selective inhibition is more cognitively demanding than nonselective inhibition as

it involves an additional stage of processing in order to discriminate between potential

stop-signals and recall which particular stop-signal requires the inhibition of a response.

Consequently, we anticipated that virtually all of the ADHD sample would exhibit

impaired inhibition on the selective stop-signal task. However, the selective stop-signal

task, much like the nonselective stop-signal task (Purvis and Tannock, 2000), only

identified approximately one third of the children with ADHD tested as having impaired

inhibition relative to the comparison sample. A recent study by Crosbie and Schachar (in

press) reported a significantly higher rate of family history for ADHD in children with

ADHD with poor inhibition compared to those with good inhibition and concluded that

stop-signal task performance could serve as a phenotypic marker for genetic analyses of

ADHD. A more rigorous investigation of this issue should be conducted using the

selective inhibition method together with a family study (i.e., interviewing and testing the

parents) rather than family history, which relies solely on parents' retrospective recall.

Children with ADHD evidenced difficulty in their early response preparation on

the selective stop-signal task. This is the only experimental manipulation of the stop-

signal task to measure anticipatory responses, providing information on the total

proportion of early, invalid responses executed prior to the presentation of the response

execution stimuli. Previous studies have examined reaction time distributions for children

with ADHD compared to normal controls (Leth-Steenson, Elbaz, and Douglas, 2000;

Sonuga-Barke, Saxton, and Hall, 1998). The latter study demonstrated that hyperactive

children displayed a systematic tendency to respond before the response window

occurred (Sonuga-Barke et al., 1998). Leth-Steenson et al. (2000) demonstrated that

children with ADHD could be distinguished from normal controls because they had

abnormally large numbers of long reaction times, although they did not in fact differ in

median reaction time. Differences at the other tail of the distribution of reaction times in the Leth-Steenson et al. (2000) study were unclear as the tail appeared to be artificially truncated, probably resulting from an exclusion of early responses from analysis. Results from this thesis are in agreement with previous research in that children with ADHD had significantly more early, invalid responses than community controls and suggest that ADHD may be associated with problems at both tails of the reaction time distribution. Children with ADHD appeared more likely than community controls to be both too fast and too slow in reaction time. In addition, this large proportion of early anticipatory responses was one of the few performance variables not improved by MPH. Children with ADHD clearly have fundamental problems in the early preparation of their responses, perhaps in the initial co-ordination or timing of their motor responses, that MPH does not beneficially alter. These anticipatory responses need to be further studied in children with ADHD. as well as in children with other psychopathologies. and they should not removed or excessively trimmed from reaction time data without initial examination. Also. future studies measuring these early (invalid) responses using concurrent neuroimaging techniques may provide further information on the formation and execution of these early responses.

MPH Effects on Selective Inhibition in ADHD

The second half of Chapter 3 examined the impact of stimulant medication (MPH) on the selective inhibition of children with ADHD. This was assessed in a double-blind, placebo-controlled. crossover trial with three fixed doses of MPH. Results indicated that MPH beneficially improved speed of selective inhibition, as well as various aspects of response execution performance. The dose response of inhibition speed was

non-linear in shape: fastest mean inhibition speed occurred at low dose with slight

(nonsignificant) slowing of mean inhibition speed observed at higher MPH doses. A

future study examining the effects of even higher MPH doses than those used in this

study would provide clearer evidence of the selective inhibition dose response in children

with ADHD. Also, this study is limited in that it only investigated acute effects of a

single dose of MPH at each dose level. MPH effects generated may be an artifact of the

acute challenge presented each dose level, resulting in an unclear idea of how findings

generalize to longer-term treatment with stimulants.

Although MPH is the primary pharmacological treatment for children with

ADHD, other drugs are also commonly used in the treatment of ADHD. For instance,

dextro-amphetamine (dexedrine) is another psychostimulant that acts on the dopamine

and norepinephrine systems and exerts similar behavioural improvements to MPH in

children with ADHD. Future studies examining the impact of other psychostimulants

(e.g., Adderall, pemoline), nonstimulants (clonidine, guanfacine), tricyclic

antidepressants (TCAs) and nonTCAs (e.g., buproprion and selective serotonin reuptake

inhibitors [SSRIs]) used in the pharmacological treatment of ADHD are recommended.

Such research would provide more clinical information on: (a) how these drugs

potentially uniquely influence selective stop-signal task performance, (b) the

characteristics of children with ADHD that respond to specific pharmacological

treatments over others, and (c) the traits of children with ADHD that fail to respond to

any pharmacological treatment at all.

Lastly, no information exists on the degree to which performance on the selective

stop-signal task accurately reflects the behaviour or problems that tend to occur in natural

settings. Barkley (1991) suggests that ecological validity for laboratory-based measures

of ADHD should be evaluated using behaviour that is of greatest concern to the child's

teachers and parents. The ecological validity of the selective stop-signal task could be

established through several additional studies. First, comparing selective inhibition in

children with ADHD from both additional cohorts of normal control children and

children with other psychiatric problems would establish the specificity of selective

inhibition deficits in children with ADHD. Also, future studies replicating the sensitivity

of selective inhibition in children with ADHD to stimulant medication effects would

strengthen the selective stop-signal task's ecological validity, given that stimulants are

known to produce improvement in parent and teacher ratings of behaviour (Nichols and

Wachsbush, submitted). Finally, the ecological validity of the selective stop-signal task

could be evaluated by directly correlating performance on the selective inhibition task

with measures of behaviour in natural settings and with parent and teacher ratings of

ADHD symptoms. It would also be interesting to investigate whether or not performance

on selective stop-signal test in childhood is predictive of driving behaviour, or

athleticism, or other real-life tasks requiring selective inhibition of particular responses

over others.

Overall Discussion

This study provides compelling evidence for poorer selective inhibition at the

extreme ends of the lifespan relative to young and middle-aged adults, as well as in

children with ADHD relative to age-matched community controls. Also, MPH was found

to improve selective inhibition in children with ADHD. Explanations for these trends in

the data remain speculative, but indicate the potential for future avenues of exploration.

For instance, perhaps the poor selective inhibition evidenced in this thesis is due

to low underlying levels of dopamine, which result in decreased efficiency in the brain

systems used in inhibition that are reliant on dopamine availability. The brain dopamine

system is particularly vulnerable to age, and in the human brain, significant losses over a

normal lifespan have been reported for several of the dopamine receptors (as reviewed by

Volkow et al., 2000). Furthermore, research has demonstrated that in healthy elderly

people, the decline in D2 dopamine receptors is associated with disrupted performance in

neurocognitive tasks related to frontal lobe function such as the Wisconsin Card Sorting

Test and the Stroop Interference Test (Volkow, Gur, Wang, et al., 1998b). Recently, the

first link between age-related declines in brain dopamine activity and frontal and

cingulate brain region metabolism was reported (Volkow et al., 2000). Although little

research to date has examined developmental changes in dopamine levels in the very

young, this decrease in available dopamine in the elderly could explain why selective

inhibition deteriorated in the elderly (Chapter 2). Furthermore, adults with ADHD have

been shown to have significantly greater amounts of striatal dopamine transporters

(Dougherty et al., 1999; Krause et al., 2000), which are predicted to result in reductions

of extracellular dopamine available for individuals with this disorder. Separate research

has identified abnormally high levels of the enzyme dopa decarboxylase in the right

midbrain of children with ADHD, indicative of a dopaminergic dysfunction (Ernst,

Zametkin, Matochik , et al., 1999). If extracellular dopamine and its conversion into

storage are critical for the efficient operation of the frontal-striatal pathway, these

findings could explain why children with ADHD were poorer to selectively inhibit than community controls. Lastly, MPH has been shown to increase levels of extracellular dopamine in the brain (Volkow et al., 2001), with therapeutic doses of MPH inducing 50% blockade of dopamine transporters (Volkow et al., 1998a). It has been suggested that the amplification of dopamine by MPH in children with ADHD could lead to either enhancement in task-related neuronal cell firing (improving attention and decreasing distractibility) or alternatively could enhance the salience of a given task, improving performance (Volkow et al., 2001). Either one of these mechanisms could account for the MPH-induced improvements in selective inhibition demonstrated in children with ADHD (Chapter 3).

The poor selective inhibition evidenced in the very young and very old, as well as in children with ADHD, could also be associated with inefficient working memory. In order to successfully selectively inhibit one response over another, the ability to remember and match a stop-signal stimulus to its appropriate response (or absence of a response) must be re-engaged with each presentation of a stop-signal. Working memory performance has been demonstrated to increase steadily throughout childhood and adolescence and then gradually decline after the age of 20 (Chiappe et al., 2000). Furthermore, this dynamic development of working memory throughout childhood, and its gradual decline associated with aging may result from growing inefficiencies in inhibition (Chiappe et al., 2000). Perhaps the poor selective inhibition observed in the very young and old in the developmental study are indicative of parallel difficulties in working memory. Furthermore, children with ADHD have been shown to have deficits in both verbal and spatial working memory (Karatekin, and Asarnow, 1998), which may

have affected their ability to remember which stop-signal tone required inhibition and which tone did not. In addition, rather than MPH impacting selective inhibition per se, it may be that MPH improved working memory which enabled improvements in selective inhibition. Children with ADHD have shown improvements in both verbal (Tannock et al., 1995b) and spatial (Kempton et al., 1999) working memory with stimulants.

Findings from this thesis would be complimented by a better understanding of what cognitive processes in addition to inhibition influence performance on the selective stop-signal task. This could be achieved by correlating performance on the selective stop-signal task with various psychoeducational measures of achievement such as intellectual capabilities or overall neurological functioning, or with performance on other neuropsychological tasks that measure cognitive processes including working memory, decision making, set shifting or nonselective inhibition.

It has been suggested that cognitive deficits observed in children with psychopathological disorders such as ADHD are due to developmental delays in the development of their frontal lobes (Weinberger, 1987) and that their cognitive abilities may be reflective of those normal comparison children younger in age. However, since performance on the selective stop-signal task was not measured in pre-school aged children in Chapter 2, a comparison of the selective inhibition of the children with ADHD collected in Chapter 3 could not be compared to developmentally younger individuals. Future studies could test this developmental delay theory by either comparing the selective inhibition of school-aged children with ADHD to normal comparison children of pre-school age or by comparing the selective inhibition of normal control school-aged children to the selective inhibition of adolescents and adults with

ADHD. In addition, it would be interesting to collect longitudinal data on the development of selective inhibition in normal control children and in children with ADHD to see if the development of selective inhibition in ADHD is unique to that of normal development.

Theoretical Implications

The underlying theoretical model for the stop-signal task states that the response execution and response inhibition processes are independent of each other and race with the presentation of each stop-signal to finish first (i.e., winning the race) (Logan, 1994). Through the added complication making the response inhibition task a choice reaction time task, the stop-signal task model and its underlying assumption of independence of response execution and inhibition processes was challenged. Results from the lifespan study clearly indicate that despite this added complication, response execution and response inhibition tasks remained independent of one another throughout normal development. This is an important step in establishing the robustness of this paradigm across the lifespan, as it allowed for the subsequent examination of these processes in psychopathologies such as ADHD.

This marked separability of response execution and response inhibition processes is not as clear for the children with ADHD. Evidence for the independence of response execution and inhibition processes is apparent in that the children with ADHD have similar response execution speeds but significantly slower response inhibition speeds than matched community controls. Thus, even though children with ADHD have difficulty with selectively inhibiting a response, their difficulty with this process does not

impact on their execution of a response. However, the observed similar response inhibition and execution speeds for the children with ADHD both off and on stimulant medication is an intriguing finding that may challenge the independence of these two processes in this childhood disorder.

Clinical Implications

Although children with ADHD clearly had poorer performance on the selective stop-signal task than did community controls, the results provided in this thesis do not substantiate the application of this stop-signal task manipulation as a diagnostic tool for ADHD. In the second study, 59 children with a rigorous clinical diagnosis of DSM-IV ADHD performed the selective-stop-signal task: of those 59 children, only 21 (36%) were identified as having impaired selective inhibition in comparison to community controls. Hence, the selective stop-signal task had poor sensitivity in identifying children with ADHD based on impaired selective inhibition.

ADHD is a highly heterogeneous and complicated disease, and consequently diagnosis should not be attempted using any single neurospsychological test measuring a specific cognitive function. This is not to say, however, that the stop-signal task is not a useful research tool. Overall, the selective stop-signal task is a challenging cognitive task for children with ADHD compared to normal controls and MPH improves performance on this test. The selective stop-signal task can and should be used in conjunction with other tests to confirm and describe the extent of an underlying deficit in inhibition, or to determine the presence or absence of additional deficits including poor response accuracy, working memory or discrimination between stop-signal stimuli that may

exacerbate an inhibition deficit. However, from a clinical perspective, performance on the selective stop-signal task would not help parents or teachers in the management of children with ADHD.

Future Directions

This thesis examined the cognitive construct of selective inhibition in children with ADHD by examining their performance on a computer-based stop-signal task manipulated to measure selective inhibition. In doing so, deficits in task performance for children with ADHD were evidenced. A future direction in further understanding the selective inhibition deficit in children with ADHD, as well as the development of selective inhibition, would be to examine activity in the brain during selective stop-signal task performance using neuroimaging techniques. Such techniques include ERPs or magneto encephalography (MEG) that have extremely high temporal resolution (msec level) and have the potential to identify the timing, order of activation, and dynamic coordination of brain regions during the unfolding of the stop-signal task (Pliszka et al.. 2000). In addition, neuroimaging techniques such as fMRI or positron emission tomography (PET) could be used to examine the specific spatial locations of brain regions activated during selective stop-signal task performance.

Previous studies examining anatomical brain differences in children with ADHD versus normal controls during nonselective stop-signal task performance have found results in agreement with both the brain systems (frontal and striatal) thougnt to be involved in inhibition and those established as abnormal in children with ADHD (Pliszka et a.. 2000; Rubia et al., 2001). In addition, children with ADHD demonstrate difficulties

with the orienting and preparatory processing on the stop-signal task, as determined by ERP evidence (Brandeis et al., 1998). Thus, a variety of neuroimaging techniques have been successfully applied to the study of inhibition in children with ADHD.

Neuroimaging techniques have also been applied to examining MPH effects in the brain during performance of a cognitive task. Sunohara, Malone, Rovet, et al. (1999), reported differential MPH dosage effects and a dissociation between dose levels and aspects of processing for children with ADHD using ERPs. They found that MPH altered both early (represented by N200 waves) and later (represented by P300 waves) stages of attentional processing. Specifically, lower doses of MPH were found to decrease P300 latencies and higher doses additionally increased P200 and N200 latencies. Generally, the amplitude of the P300 wave during task performance has been used to assess the amount of processing capacity allocated to a task (Berman, Douglas and Barr, 1999). MPH has been demonstrated to increase the amplitude of P300 during performance on several complex cognitive tests, including the Sternberg task (Klorman et al. 1994) and the Continuous Performance Test (CPT) (Klorman, 1991). A future study using ERPs to examine MPH effects during selective stop-signal task performance in children with ADHD would provide information on various information processing steps of the brain during the response preparation, response execution and selective inhibition stages of selective stop-signal task performance. In addition, the only fMRI study examining MPH effects in children with ADHD has found that MPH increased activation in both pre-frontal cortex and striatum (areas involved in response inhibition) during a go/no-go task (Vaidya et al., 1998). Future research investigating the functional impact of MPH on brain regions used during selective-stop signal task performance is recommended.

Neuroimaging could also be used to investigate the similarities and differences between selective and nonselective inhibition. For example, Rubia et al. (2001) recently used fMRI to investigate brain regions commonly activated in subjects performing different versions of go/no-go and stop tasks, differing in probability of inhibitory stop-signals and contrast conditions. Using this technique, they discovered shared inhibitory neurocognitive networks used during both type of tasks (mesial, medial and inferior frontal and parietal regions), as well as brain activations unique to each inhibitory task (stop task – predominantly right hemispheric regions and go/no-go – bilateral but predominantly left hemispheric activation, thought to reflect specialization for response selection). A similar study design using fMRI to examine both common and distinct brain regions involved in selective and nonselective inhibition would provide crucial information on these different types of inhibition impaired in ADHD.

However, results from neuroimaging work on selective inhibition would need to be interpreted with caution. For instance, spatial location tasks such as fMRI attend to specific brain regions. Hence, one needs to have an *a priori* idea of what brain regions should be monitored during task performance. In pre-selecting specific areas of study, other potential brain regions utilized during selective inhibition may be overlooked. With a cognitively challenging task such as selective inhibition, it is likely that many brain regions and cortical connections are involved in the discrimination, execution and inhibition components used during task performance. Selective inhibition is not as straightforward as nonselective inhibition and most likely requires a greater number of inputs and outputs extended throughout the brain. Knowing what regions to focus on prior to data collection and experimental design would be challenging.

Despite this cautionary notes, the application of neuroimaging tools to the study of selective inhibition is an important and informative future step in furthering our understanding of this cognitive process.

References

Anderson, N. D., Craik, F. I. M., and Naveh-Benjamin, M. (1998). The attention demands of encoding and retrieval in younger and older adults: I. Evidence from divided attention costs. Psychology and Aging, 13(3), 405-423.

American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). Washington, DC: American Psychiatric Association.

Band, G. H. (1996). Preparation, adjustment, and inhibition of responses. Unpublished doctoral dissertation. University of Amsterdam, Faculty of Psychology.

Band, G. P. H., and van Boxtel, G. J. M. (1999). Inhibitory motor control in stop paradigms: review and reinterpretation of neural mechanisms. Acta Psychologica, 101, 179-211.

Barkley, R. A. (1991). The ecological validity of laboratory and analogue assessment methods of ADHD symptoms. Journal of Abnormal Child Psychology, 19(2), 149-78.

Barkley, R. A. (1997). Behavioural inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. Psychological Bulletin, 121(1), 65-94.

Bedard, A.-C., Nichols, S., Barbosa, J., Schachar, R., Logan, G. D., and Tannock, R. (submitted). Development of selective inhibition across the lifespan.

Berman, T., Douglas, V. I., and Barr, R. G. (1999). Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder. Journal of Abnormal Psychology, 108(1), 90-105.

Biederman, J., Newcorn, J., and Sprich, S. (1991). Comorbidity of attention deficit hyperactivity disorder with conduct, depressive, anxiety and other disorders. American Journal of Psychiatry, 148, 564-577.

Bjorkland, D. F., and Harnishfegger, K. K. (1990). The resources construct in cognitive development: Diverse sources of evidence and a theory of inefficient inhibition. Developmental Review, 10, 48-71.

Boyle, M. H., Offord, D. R., Hoffman, H. G., Catlin, G. P., Byles, J. A., Crawford, J. W., Links, P. S., Rae-Grant, N. I., and Szatmari, P. (1987). Ontario Child Health Study: I. Methodology. Archives of General Psychiatry, 44, 826-831.

Boyle, M. H., Offord, D. R., Racine, Y., Fleming, J. E., Szatmari, P., and Sanford, M. (1993). Evaluation of the revised Ontario Child Health Study scales. Journal of Child Psychology and Psychiatry, 34, 189-213.

Brandeis, D., van Leeuwen, T. H., Rubia, K., Vitaco, D., Steger, J., Pascual-Marqui, R. D., and Steinhausen, H. Ch. (1998). Neuroelectirc mapping reveals precursor of stop failures in children with attention deficits. Behavioural Brain Research, 94, 111-125.

Casey, B. J., Castellanos, F. X., Giedd, J. N., Marsh, W. L., Hamburger, S. D., Schubert, A. B., Vauss, Y. C., Vaituzis, A. C., Dickstein, D. P., Sarfatti, S. E., and Rapoport, J. L. (1997). Implication of right frontostriatal ciruictry in response inhibition and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry, 36(3), 374-83.

Cerella, J. (1990). Aging and information processing rate. In J. Birren and K. W. Schaie (Eds.), Handbook of Psychology and Aging. (3rd ed. pages 201-221). New York: Academic Press.

Cerella, J., and Hale, S. (1994). The rise and fall in information processing rates over the lifespan. Acta Psychologica, 86, 109-197.

Chiappe, P., Hasher, L., and Siegel, L. S. (2000). Working memory, inhibition, and reading disability. Memory and Cognition, 28(1), 8-17.

Conners, K. (1995). Conners' Continuous Performance Test Computer Program 3.0: Users Manual. Canada: Multi-Health Systems, Inc.

Conners, C. K. (1997). Conners' Rating Scales – Revised: Technical Manual. New York: Multi-Health Systems, Inc.

Crosbie, J., and Schachar, R. J. (in press). Inhibition as a marker for familial ADHD. The American Journal of Psychiatry.

Dagenbach, D., and Carr, T. H. (1994). Inhibitory processes in attention, memory and learning. San Diego: Academic Press.

Dougherty, D. D., Bonab, A. A., Spencer, T. J., Rauch, S. L., Madras, B. K., and Fischman, A. J. (1999). Dopamine transporter density in patients with attention deficit hyperactivity disorder. Lancet, 354, 2132-2133.

De Jong, R., Coles, M. G., Logan, G. D., and Gratton, G. (1990). In search of the point of no return: the control of response processes. Journal of Experimental Psychology: Human Perception and Performance, 16(1), 164-82.

De Jong, R., Coles, M. G., and Logan, G. D. (1995). Strategies and mechanisms in nonselective and selective inhibitory motor control. Journal of Experimental Psychology: Human Perception and Performance, 21(3), 498-511.

Douglas, V. I. (1999). Cognitive control processes in attention deficit hyperactivity disorder. In Quay, H. C., and Hogan, A. E. (Eds.), Handbook of Disruptive Behavior Disorders (pp 105-138). Plenum Publishing Co.

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

Eslinger, P. J. (1996). Conceptualizing, describing, and measuring components of executive function. In G. R. Lyon and N. A. Krasnegor (Eds). Attention, Memory, and Executive Function. Baltimore, USA: Paul H. Brookes Publishing Co. pp – 367-397.

Faraone, S.V., Biederman, J., Webber, W., and Russell, R., (1998). Psychiatric, neuropsychological, and psychosocial features of DSM-IV subtypes of attention-deficit/hyperactivity disorder: results from a clinically referred sample. Journal of the American Academy of Child and Adolescent Psychiatry, 37, 185-193.

Faraone, S.V., Biederman, J.,and Friedman, D. (2000). Validity of DSM-IV subtypes of Attention-Deficit/Hyperactivity Disorder: A family study perspective. Journal of the American Academy of Child and Adolescent Psychiatry, 39(3), 300-307.

Filipovic, S. R., Jahanshah, M., and Rothwell, J. C. (1999). Cortical potential related to decision-making: Comparison of two types of go/no-go decision. Neuroreports, 10, 3583-3587.

Garavan, H., Ross, T. J., and Stein, E. A. (1999). Right hemispheric dominance of inhibition: An event-related functional MRI study. Proceedings of the National Academy of Science, 96, 8301-8306.

Goldman-Rakic, P. S. (1987). Development of cortical circuitry and cognitive function. Child Development, 58, 601-622.

Gray, J. A. (1982). The Neuropsychology of Anxiety: An Enquiry into Functions of the Septo-Hippocampal System. Oxford: Oxford UP.

Gray, J. A. (1987). The Psychology of Fear and Stress (2nd ed.). Cambridge, England: Cambridge University Press.

Greene, R. W., Biederman, J., Faraone, S. V., Sienna, M., and Garcia-Jetton, J. (1997). Adolescent outcome of boys with attention-deficit/hyperactivity disorder and

social disability: results from a 4-year longitudinal follow-up study. Journal of Consulting and Clinical Psychology,

Hale, S. (1990). A global developmental trend in cognitive processing speed. Child Development. 61, 653-663.

Hasher, L. T., and Zacks, R. T. (1988). Working memory, comprehension, and aging: A review and a new view. In G. H. Bower (Ed.), The Psychology of Learning and Motivation (Vol. 22). Orlando, FL: Academic Press.

Hechtman. L., and Weiss. G. (1983). Long-term outcome of hyperactive children. American Journal of Orthopsychiatry. 53(3), 532-541.

Himmelstein. J.. Schulz, K. P.. Newcorn. J. F., and Halperin. J. M. (2000). The neurobiology of attention-deficit/hyperactivity disorder. Frontiers in Bioscience. 5, 461-478.

Jennings. J. R.. Van der Molen. M. W.. Pelham. W.. Debski. K. B.. and Hoza. B. (1997). Inhibition in boys with attention deficit hyperactivity disorder as indexed by heart rate change. Developmental Psychology. 33(2). 308-318.

Kail. R. (1991). Developmental change in speed of processing during childhood and adolescence. Psychological Bulletin. 109(3). 490-501.

Kail. R. (1993). The role of a global mechanism in developmental change in speed of processing. In M. L. Howe and R. Pasnak (Eds.). Emerging themes in cognitive development Vol.: Foundations. New York: Springer Verlag.

Kane. M. J.. Hasher. L.. Stoltzfus. E. R.. Zacks. R. T.. and Connelly. S. L. (1994). Inhibitory attentional mechanisms and aging. Psychology and Aging. 9(1). 103-112.

Karatekin, C., and Asarnow, R. F. (1998). Working memory in childhood-onset schizophrenia and attention-deficit/hyperactivity disorder. Psychiatry Research. 80(2). 165-176.

Kaufman, J.. et al. (1997). Schedule for affective disorders and schizophrenia for school-age children – present and lifetime version (K-SADS-PL): initial reliability and validity data. Journal of the American Academy of Child and Adolescent Psychiatry. 36. 980-988.

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

Kimko, H. C., Cross. J. T., and Abernathy. D. R. (1999). Pharmacokinetics and clinical effectiveness of methylphenidate. Clinical Pharmacokinetics. 37(6). 457-470.

Kovacs, M. (1992). Children's Depression Inventory (CDI). Toronto: Multi-Health.

Klorman, R. (1991). Cognitive event-related potentials in attention deficit disorder. Journal of Learning Disabilities, 24, 130-140.

Klorman, R. Brumaghim, J. T., Fitzpatrick, P. A., Borgstredt, A. D., and Strauss. J. (1994). Clinical and cognitive effects of methylphenidate on children with attention deficit disorder as a function of aggression/oppositionality. Journal of Abnormal Psychology, 103, 206-221.

Kramer, A. F., Humphrey, D. G., Larish, J. F., and Logan, G. F. (1994). Aging and inhibition: Beyond a unitary view of inhibitory processing in attention. Psychology and Aging, 9, 491-512.

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

Lahey, B.B., Applegate, B., Burnett, K., Biederman, J., Greenhill. L., Hynd, G.W., Barkely, R., Newcom, J., Jensen, P., Richters, J., et al. (1994). DSM-IV field trials for attention-deficit/hyperactivity disorder in children and adolescents. American Journal of Psychiatry, 151 1673-1685.

Lappin, J. S., and Eriksen. C. W. (1996). Use of a delayed signal to stop a visual reaction time response. Journal of Experimental Psychology, 72, 805-811.

Leibson, C. L., Katusic, S. K., Barbaresi, W. J., Ransom. J., and O'Brien. P. C. (2001). Use and costs of medical care for children and adolescents with and without attention-deficit/hyperactivity disorder. Journal of the American Medical Association, 285(1), 60-66.

Leth-Steensen, C., Elbaz, Z. K., and Douglas, V. I. (2000). Mean response times. variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychologica, 104, 167-190.

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

Logan, G. D. (1985). On the ability to inhibit simple thoughts and actions: 2. Stop-signal studies of repetition priming. Journal of Experimental Psychology: Learning. Memory and Cognition, 11, 675-691.

Logan, G. D., and Burkell, J. (1986). Dependence and independence of responding to double stimulation: A comparison of stop, change, and dual-task paradigms. Journal of Experimental Psychology: Human Perception and Performance, 12(4), 549-563.

Logan, G. D., and Cowan, W. B. (1984). On the ability to inhibit thought and action: A theory of an act of control. Psychological Review, 91, 295-327.

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

Logan, G. D., Kantowitz, B. H., and Riegler, G. L. (1986). On the ability to stop selectively: Mechanisms of response interdiction in choice reaction time. Unpublished manuscript, Purdue University.

Logan, G. D., Schachar, R. J., and Tannock, R. (1997). Impulsivity and inhibition. Psychological Science, 8(1), 60-64.

May, C. P., and Hasher, L. (1998). Synchrony effects in inhibition over thought and action. Journal of Experimental Psychology, 24(2), 363-379.

McGee, R. A., Clark, S. E., and Symons, D. K. (2000). Does the Conners' continuous performance test aid in ADHD diagnosis? Journal of Abnormal Child Psychology, 28(5), 415-424.

National Institutes of Health Concensus Development Conference Statement: Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD). (2000). Journal of the Annals of the Academy of Child and Adolescent Psychiatry, 39(2), 182-193.

Nichols, S. L., and Waschbusch, D. A. (submitted). Ecological validity of laboratory cognitive tasks in the assessment of ADHD: What have we learned in the last decade?
Nigg, J. T. (1999). The ADHD response-inhibition deficit as measured by the stop-signal task: replication with DSM-IV Combined type, extension, and qualification. Journal of Abnormal Child Psychology, 27, 393-402.

Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychological Bulletin, 126(2).

Ollman, R. T. (1973). Simple reactions with random countermanding of the "go" signal. In S. Kornblum (Ed)., Attention and Performance IV (pp 571-581). New York: Academic Press.

Oosterlaan, J., Logan, G. D., and Sergeant, J. A. (1998). Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop-signal task. Journal of Child Psychology and Psychiatry, 39(3), 411-25.

Oosterlaan, J., and Sergeant, J. A. (1996). Inhibition in ADHD, anxious and aggressive children: A biologically based model of child psychology. Journal of Abnormal Child Psychology, 24, 19-36.

Oosterlaan, J., and Sergeant, J. A. (1997). Response inhibition and response re-engagement: A developmental investigation in children 8-12 years old. Manuscript submitted for publication.

Oosterlaan, J., and Sergeant, J. A. (1998a). Response inhibition and response re-engagement in attention-deficit/hyperactivity disorder, disruptive, anxious and normal children. Behavioral Brain Research, 94, 33-43.

Oosterlaan, J., and Sergeant, J. A. (1998b). Effects of reward and response cost on response inhibition in AD/HD, disruptive, anxious, and normal children. Journal of Abnormal Child Psychology, 26(3), 161-74.

Osman, A., Kornblum, S., and Meyer, D. E. (1990). Does response programming necessitate response execution? Journal of Experimental Psychology: Human Perception and Performance, 16, 183-198.

Overtoom, C. C., Verbaten, M. N., Kemner, C., Kenemans, J. L., van Endeland, H., Buitelaar, J. K., Comfferman, G., and Koelega, H. S. (1998). Associations between event-related potentials and measures of attention and inhibition in the Continuous Performance Task in children with ADHD and normal controls. Journal of the American Academy of Child and Adolescent Psychiatry, 37(9), 977-85.

Patterson, C. M., and Newman, J. P. (1993). Reflectivity and learning from aversive events: Toward a psychological mechanism

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

Quay, H. C. (1997). Inhibition and attention deficit hyperactivity disorder. Journal of Abnormal Child Psychology, 25(1), 7-13.

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

Purvis, K. L., and Tannock, R. (2000). Phonological processing, not inhibition, differentiates ADHD and reading disability. Journal of the American Academy of Child and Adolescent Psychiatry, 39(4), 485-494.

Rapport, M. D., Denney, C., DuPaul, G. J., and Gardner, M. J. (1994). Attention deficit disorder and methylphenidate: Normalization rates, clinical effectiveness, and response predication in 76 children. Journal of the American Academy of Child and Adolescent Psychiatry, 33(6), 882-893.

Reynolds, C. R., and Richmond, B. O. (1985). Revised Children's Manifest Anxiety Scale (RCMAS) Manual. Los Angeles: Western Psychological Services.

Ridderinkof, K. R., Band, G. P. H., and Logan, G. D. (1999). A study of adaptive behaviour: effects of age and irrelevant information on the ability to inhibit one's actions. Acta Psychologica, 101, 315-337.

Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S. C. R., Simmons, A., and Bullmore, E. T. (1999). Hypofronatilty in attention deficit hyperactivity disorder during higher-order motor control: A study with functional MRI. The American Journal of Psychiatry, 156(6), 891-896.

Rubia, K., Russell, T., Overmeyer, S., Brammer, M. J., Bullmore, E. T., Sharma, T., Simmons, A., Williams, S. C. R., Giampietro, V., Andrew, C. M., and Taylor, E. (2001). Mapping motor inhibition: Conjunctive brain activations across different versions of go/no-go and stop-signal tasks. Neuroimage, 13, 250-261.

Schachar, R., Ickowicz, A., and Wachsmuth, R. (1994). Parent Interview for Child Symptoms - IV (DSM-IV). Unpublished manuscript. The Hospital for Sick Children, Toronto, Canada.

Schachar, R., and Logan, G. D. (1990). Impulsivity and inhibition in normal development and childhood psychopathology. Developmental Psychology, 26(5), 710-720.

Schachar, R., Mota, V. L., Logan, G. D., Tannock, R., and Klim, P. (2000). Confirmation of an inhibition deficit in Attention-Deficit/Hyperactivity Disorder. Journal of Abnormal Child Psychology, 28, 227-235.

Schachar, R., Tannock, R., and Cunningham, C. (1996). Treatment of hyperactive disorders. In S. Sandberg (Ed.). Hyperactive Disorders. Cambridge Monographs in Child and Adolescent Psychopathology.

Schachar, R., Tannock, R., and Logan, G. D. (1993). Inhibition, impulsiveness, and Attention Deficit Hyperactivity Disorder. Clinical Psychology Review, 13, 721-739.

Schachar, R., Tannock, R., Marriott, M., and Logan, G. (1995). Deficient inhibition in Attention Deficit Hyperactivity Disorder. Journal of Abnormal Child Psychology, 23, 411-437.

Shallice, T. (1982). Specific impairments in planning. In D. E. Broadbent and L. Weiskrantz (Eds.). The Neuropsychology of Cognitive Function (pp. 109-209). London: The Royal Society.

Solanto, M. V. (1998). Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behavioural Brain Research, 94, 127-152.

Solanto, M. V. (2000a). Dose-response effects of ritaline on cognitive self-regulation, learning, memory and academic performance. In L. L. Greenhill, and B. B. Osman (Eds.). Ritalin: Theory and Practice 2nd Edition. (pp. 219-235). Larchmont, NY: Mary Ann Liebert, Inc.

Solanto, M. V. (2000b). Dopamine dysregulation in AD/HD: Integrating clinical and basic science research. In Testing the dopamine hypothesis of Attention-Deficit Hyperactivity Disorder (ADHD): hypo or hyper?. Symposium at INABIS 2000: 6th Internet World Congress for Biomedical Sciences.

Sonuga-Barke, E. J., Saxton, T., and Hall, M. (1998). The role of interval underestimation in hyperactive children's failure to suppress responses over time. Behavioural Brain Research, 94(1), 45-50.

Sprague, R. L., and Sleator, E. K. (1977). Methylphenidate in hyperkinetic children: differences in dose effects in learning and social behavior. Science, 198(4323), 1274-1276.

Sunohara, G. A., Malone, M. A., Rovet, J., Humphries, T., Roberts, W., and Taylor, M. J. (1999). Effect of methylphenidate on attention in children with attention deficit hyperactivity disorder (ADHD): ERP Evidence. Neuropsychopharmacology, 21, 218-228.

Szatmari, P., Offord, D. R., and Boyle, M. H. (1989). Ontario Child Health Study: prevalence of attention deficit disorder with hyperactivity. Journal of Child Psychology and Psychiatry, 30(2), 219-30.

Tannock, R. (1998). Attention deficit hyperactivity disorder: Advances in cognitive, neurobiological, and genetic research. Journal of Child Psychology and Psychiatry, 39(1), 65-99.

Tannock, R., Ickowicz, A., and Schachar, R. (1995b). Differential effects of methylphenidate on working memory in ADHD children with and without comorbid

anxiety. Journal of the American Academy of Child and Adolescent Psychiatry, 34(7), 886-96.

Tannock, R., and Schachar, R. (1994). Teacher Telephone Interview for Disruptive Behaviour Disorders (DSM-IV). Unpublished manuscript. The Hospital for Sick Children, Toronto, Canada.

Tannock, R., Schachar, R. J., Carr, R. P., Chajczyk, D., and Logan, G. D. (1989). Effects of methylphenidate on inhibition in hyperactive children. Journal of Abnormal Child Psychology, 17(5), 473-491.

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

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

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

Van der Veen, F. M., Van der Molen, M. W., and Jennings, J. R. (2000). Selective inhibition is indexed by heart rate slowing. Psychophysiology, 37(5), 607-13.

Van Leeuwen, T. H., Steinhausen, H. C., Overtoom, C. C., Pascual-Marqui, R. D., van't Klooster, B., Rothenverger, A., Sergeant, J. A., and Brandeis, D. (1998). The continuous performance test revisited with neuroelectric mapping: impaired orienting in children with attention deficits. Behavioral Brain Research, 94(1), 97-110.

Vince, M. A. (1948). The intermittency of control movements and the psychological refractory period. British Journal of Psychology, 38, 149-157.

Volkow, N. D., Gur, R. C., Wang, G.-J., Fowler, J. S., Moberg, P. J., Ding, Y.-S., Hitzemann, R., Smith, G., and Logan, J. (1998b). Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. American Journal of Psychiatry, 155, 344-349.

Volkow, N. D., Logan, J., Fowler, J. S., Wang, G.-J., Gur, R. C., Wong, C., Felder, C., Gatley, J., Ding, Y.-S., Hitzemann, R., and Pappas, N. (2000). Association between age-related decline in brain dopamine activity and impairment in frontal and cingulated metabolism. American Journal of Psychiatry, 157(1), 75-80.

Volkow, N. D.. Wang, G.-J., Fowler, J. S., Gatley, S. J.. Logan. J.. Ding. Y.-S.. Hitzemann, R., and Pappas, N. (1998a). Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. American Journal of Psychiatry, 155(10), 1325-1331.

Volkow, N. D.. Wang, G-J, Fowler, J. S., Logan, J., Gerasimov. M.. Maynard. L.. Ding, Y-S., Gatley, S. J.. Gifford, A., and Franceschi, D. (2001). Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. The Journal of Neuroscience. 21. RC121 1-5.

Warner-Rogers, J.. Taylor, A.. Taylor, E.. and Sandberg. S. (2000). Inattentive behaviour in childhood: Epidemiology and implications for development. Journal of Learning Disabilities. 33(6). 520-536,

Wechsler, D. (1991). Wechsler Intelligence Scale for Children – Third Edition. New York: Psychological Corporation.

Weinberger, D. K. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry, 44. 660-9.

Welsh. M. C.. and Pennington, B. F. (1988). Assessing frontal lobe functioning in children; views from developmental psychology. Developmental Neuropsychology, 4, 199-230.

Wilkinson, G. S. (1993). The Wide Range Achievement Test – Third Edition (WRAT3). San Antonio. TX: The Psychological Corporation

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

Wolraich. M.. Hannah. J., Pinnock. T.. Baumgartel. A.. and Brown. J. (1996). Comparison of diagnostic criteria for attention-deficit/hyperactivity disorder in a county wide sample. Journal of the American Academy of Child and Adolescent Psychiatry, 35, 319-324.

Woodcock, R. W. (1987). Woodcock Reading Mastery Test-Revised (WRMT-R). Circle Pines, MN: American Guidance Service. Inc.