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Examining Inter- And Intra-Individual Differences In The Neurobiological Mechanisms Associated With Inhibitory Control

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EXAMINING INTER- AND INTRA-INDIVIDUAL DIFFERENCES IN THE NEUROBIOLOGICAL MECHANISMS ASSOCIATED WITH INHIBITORY CONTROL

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ABSTRACT

Adolescence is an ideal time to measure the development of the neural mechanisms associated with inhibitory control because this age period is marked by impulsive and risk taking behaviors. Maturational brain changes in the prefrontal cortex that are associated with the emergence of inhibitory control are thought to occur during this age. With knowledge of how this system develops, it may be possible to identify the development of disorders that arise from poor inhibitory control such as attention deficit hyperactivity disorder (ADHD) and substance use. The goal of the current dissertation is to examine the neurobiological correlates associated with individual differences in inhibitory ability, and examine the age-related changes in neurobiological mechanisms of inhibitory control. This report will be the first of its size (n = 538) to examine within-subject changes longitudinally over five years of adolescent development (age 14 to 19). Furthermore, we supplement the longitudinal data with findings from a split-brain patient on the lateralization of inhibitory control, and we explore a subtle nuance that may have large implications on how to best measure inhibition-related brain activity.

In the second chapter of the dissertation, we examine the lateralization of inhibitory control by measuring hemispheric differences in the ability to inhibit a motor response in a split-brain patient. Here, we found patient J.W.'s right hemisphere performed better than his left hemisphere on three different inhibitory control tasks. Interestingly, although inferior to the performance of the right hemisphere, the left hemisphere still performed relatively well on the three tasks, suggesting the left hemisphere can perform response inhibition independently.

The third chapter examines both the functional correlates of Stop Signal Task performance, and the age-related differences in the functional mechanisms of response inhibition. At age 14 and age 19, similar patterns of activation were associated with performance, however relatively little overall activity exhibited performance-related effects. Superior performance was associated with greater right inferior frontal gyrus (rIFG) activation, as well as greater activation in a set of regions potentially involved with a stimulus-detection and attention-orienting system. However, at age 14 performance was also negatively associated with default mode network activity, and at age 19 performance was also positively associated with left amygdala activity. In the absence of within-subject differences in performance between ages 14 to 19, there were significant decreases in functional activation associated with successful inhibition. The potential mechanisms by which activity decreases over time while performance remains stable are discussed.

The fourth chapter of the dissertation examines the effect of objective task difficulty on the magnitude of activation associated with successful inhibition. The Stop Signal Task employs an adaptive algorithm that alters task difficulty to meet participants' abilities. Typically, when capturing functional activation associated with response inhibition, activation is extracted from all successful trials. Here, we find that individual differences in activation are expanded when using the activation from the extreme, rather than average, aspects of task performance variables. Individual differences in performance may best be captured by examining the maximum difficultly at which a participant is able to inhibit a response, rather than the average of all successful inhibitions. These results also lend support to the minimal activity associated with performance in Chapter 3, and we discuss how improving the measure of stop-related activity may help explain both inter- and intra-individual differences in inhibitory control.

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CHAPTER ONE – Literature Review Introduction

Part 1 of Introduction – Response Inhibition

1.1 Behavioral Inhibition and Executive Functioning

Seminal work in the field of cognitive neuroscience has argued that the cornerstone of executive functioning is inhibitory control (Barkley, 1997; Nigg, 2000; Quay, 1997). In goal-directed behavior, the ability to refrain from responding immediately to a given environment is crucial. As the environment changes, the appropriate response for accomplishing the intended goal must also change to fit the new environmental demands. Because the original response is no longer appropriate, it must initially be inhibited before the behavioral update can occur. Furthermore, inhibiting an immediate response allows other executive functions to occur and the individual to evaluate the environment and generate the new, appropriate response.

Early reports on self-regulation and behavioral inhibition were developed in the context of human language. In 1967, Bronowski created a theory on the uniqueness of human language, in which he proposed the main components of language processing and generation are associated with the human prefrontal cortex (Barkley, 1997). In Bronowski's model, the capacity to delay an immediate verbal response was critical because it allowed for four main prefrontal functions to occur. The four functions were: 1) Prolongation, which is defined as the ability to refer to past events to convey information about the future, 2) Separation of affect, which is the ability to regulate emotional reactivity from the response, 3) Internalization of Language, which can be viewed as the internal rehearsal of a response, and 4) Reconstitution, which is the generation of a novel, complex structure about the future. Thus, inhibiting an immediate response allows for the analysis

of the environment, as well as the generation and testing of novel responses to respond appropriately. Bronowski attributes the four functions, along with the capacity to inhibit, as key defining functions of the human prefrontal cortex.

In 1988, Fuster generated a similar theory of prefrontal functioning (Fuster, 1988). Here, Fuster claims the main function of the prefrontal cortex is to connect mental structures that are temporally separate, but that share a common behavioral goal, to generate appropriate goal-directed behaviors in novel environments. In this model, there are two major elements of prefrontal functioning. First, the individual must have a retrospective function, in which they are able to recall information about past events in a specific sequence, and understand how the specific sequence of these events led to a given outcome. Second, the individual must have a prospective function in which they generate novel goal-directed responses. Essentially, the individual must use information about how specific sequences of events in the past led to a previous outcome to generate a novel sequence of events with the goal of reaching a desired future outcome. Like Bronowski, Fuster also claimed that an immediate response must be inhibited for these prefrontal functions to occur.

Born out of these early reports on the role of the human prefrontal cortex is Barkley's unifying theory of ADHD and executive functioning (Barkley, 1997). Constructed as a hybrid of the works of both Bronowski and Fuster, Barkley's model of executive functioning extends beyond language. The model is proposed as an executive system that may influence what Barkley refers to as non-executive systems to accomplish goal-directed behaviors. That is, the executive system may be functionally dependent on the prefrontal cortex but can be used to influence modalities such as language, memory,

and emotion, which may not be solely attributable to the prefrontal regions. Barkley's model works in a systematic manner, with effective performance of the four main executive functions resulting in motor fluency, motor syntax, and motor control. The four executive functions that Barkley describes in his model are working memory, self-regulation of arousal and motivation, internalization of speech, and reconstitution. These four functions work much like the functions put forth by Fuster and Bronowski. Barkley's executive functions use past experiences in goal directed behavior to organize information about the current environment and generate a novel behavioral construct to achieve the goal.

The core of Barkley's model of executive functioning is behavioral inhibition. Barkley claims that in goal-directed behavior, the first executive act should be an inhibition of a behavioral response. The inhibition of immediate response causes a delay, creating the time during which the four main executive functions can occur. Importantly, inhibiting an immediate response does not directly lead to the performance of the four executive functions. Inhibition of an immediate response only allows the time necessary for these functions to occur. Therefore, if an immediate response is inhibited it will not automatically result in the correct behavioral outcome because it does not automatically cause proper executive functioning. However, if an immediate response is not inhibited then it is likely that the appropriate response is not accomplished because the executive functions were not allowed the time required to be carried out effectively.

Based on the assertion that behavioral inhibition is required to set the occasion for executive functioning to occur, Barkley and others have generated a working hypothesis that the central deficit in ADHD is an impairment in behavioral inhibition (Barkley, 1997; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Quay, 1997). Due to a lack of

behavioral inhibition, individuals with ADHD are less capable of carrying out executive functions during goal-directed behavior and consequently display behaviors that are guided primarily by immediate environmental cues rather than future goals. If the primary impairment in individuals with ADHD is poor inhibition, then secondary impairments should exist in the four executive functions put forth by Barkley. Notably, individuals with ADHD also show impairments in working memory, self-regulation of arousal and motivation, internalization of speech, and reconstitution (Barkley, 1997; Quay, 1997), which subsequently result in poor motor control, motor fluency, and motor syntax.

At this point it is important to note that the present report will not be an examination of ADHD or psychopathology associated with poor behavioral inhibition. Rather, the previously mentioned theories and models articulate how behavioral inhibition fits into the broader context of executive functioning. Being a cornerstone of proper executive functioning, impairments in the domain of behavioral inhibition could contribute to various psychopathologies and conditions of executive dysfunction, such as what has been demonstrated with the example of ADHD. Using ADHD as a vehicle for impairment in this domain, the previous reports have argued for the importance of response inhibition to goal directed behavior and everyday function.

1.2 Response Inhibition in the Laboratory

According to Barkley's model of executive functioning, there are three related processes that compose behavioral inhibition. There is the ability to inhibit a prepotent response, there is the ability to stop an ongoing response, and there is the ability to inhibit interfering information from disrupting the current mental state. More completely,

inhibiting a prepotent response and stopping an ongoing response create a delay, and interference control protects this delay against interference from irrelevant information (Barkley, 1997).

Interference control is measured in the laboratory by tasks such as the Stroop Task and Flanker Tasks (Fan, Flombaum, McCandliss, Thomas, & Posner, 2003; MacLeod, 1991). In these tasks, participants must attend to task-relevant cues and inhibit interference from task-irrelevant cues. For example, in the most common form of the Stroop Task a list of names of colors is presented in various font colors. The participant is asked to read the names of the colors, and then the color of the font in which the names are written. If the names of the colors and the font are the same, there is no competing information and the participant may complete the task reasonably well. However, if the names of the colors and the font color are not the same, the incongruent information competes and it is difficult for the participant to complete the task.

The inhibition of a prepotent response is most commonly measured in the laboratory by the Go/No-Go Task (Casey, Trainor, et al., 1997). Here, participants are presented with a series of stimuli indicating whether to press a response button or to refrain from responding altogether. On "go" trials, participants are presented with a stimulus instructing a button press response (or one of multiple choice response buttons) as quickly and as accurately as possible. On "no-go" trials, participants are presented with a different stimulus instructing them to refrain from pressing any response button. The inhibitory component of this task is generated by the ratio of go trials to no-go trials. The go trials are the predominant trials in the task, often composing about 70-85% of the overall trials. Because the majority of trials are go trials that require a response from the participant, the

participant builds a "prepotent" tendency to respond upon presentation of a stimulus. Thus, when the no-go stimulus is presented on the infrequent no-go trials, the participant must inhibit the prepotent tendency to press a response button.

The ability to inhibit an ongoing response is measured in the laboratory by the Stop Signal Task. Highlighting the importance of inhibition in both motor and cognitive control, Logan and colleagues (Logan, Cowan, & Davis, 1984) created a task in which individuals are required to inhibit an already initiated response. Like the Go/No-Go task, the Stop Signal Task is composed of go and stop trials. On go trials, the participant must respond rapidly via a button press to a "go signal." However, on a minority of trials (stop trials; typically 25%), the go signal will be quickly followed by a "stop signal," indicating that the individual should attempt to inhibit the response. Logan and colleagues built the task on the premise that a measureable behavioral motor response (either pressing the response button or not) is governed by a cognitive control process (Logan et al., 1984). According to the researchers, the cognitive control process dictates the appropriate goal in each environment and generates a command for a motor process to perform. In the context of the Stop Signal Task, the cognitive control process determines if the goal of the task is to "go" upon presentation of the go signal, or "stop" on presentation of the stop signal. Thus, one can observe which cognitive control process was apparent by observing the motor behavior that the participant carried out.

Logan and colleagues designed the Stop Signal Task around what is known as the horse-race model (Logan et al., 1984). The horse-race model states that there is a "go" process that responds to the go signal and a "stop" process that inhibits responses after presentation of the stop signal, and these processes are independent of one another. In the

race model, the behavioral outcome is dictated by which of the two processes is completed, or finishes the race, first. If the go process finishes first then the behavioral response will be a button press, and if the stop process finishes first then the behavioral response will be no button press.

On stop trials, the duration between the onset of the go signal and the onset of the stop signal is referred to as the stop signal delay (SSD), and this duration will dictate the probability of stopping. If the SSD is short, the stop signal appears quickly after the onset of the go signal and the response is easily countermanded. If the SSD is long, the stop signal appears later after the onset of the go signal and the response is more difficult to countermand. According to the race model, when the SSD is short, the go process has only just started the "race" and initiating the stop process this early will likely result in the stop process winning the race. When the SSD is long, the go process has proceeded further and initiating the stop process relatively late will likely result in the go process winning the race.

Under the assumption that the go and stop process are independent of one another, it is possible to calculate the duration of each. To calculate the duration of the go process, one can measure the average response times to all go trials in the task. Calculating the duration of the stop process is slightly more complicated. When calculating the duration of the stop process, the goal is to find the SSD that results in a 50% probability of successfully inhibiting the motor response. To reach the 50% successful SSD, an adaptive algorithm is employed where participants' performance dictate the duration of each subsequent SSD. If a participant successfully inhibits at a given SSD, the next stop trial will employ a SSD that is, typically, 50ms longer, making it more difficult to inhibit. If a

participant is unable to inhibit at a given SSD, the following stop trial will employ a SSD that is 50ms shorter, making is easier to inhibit. When the SSD is reached that elicits 50% probability of stopping, the race between the go and the stop trial is considered a tie (50% of the time the go process wins and 50% of the time the stop process wins). If the duration of the go process is measured (the average reaction time on go trials), and it is presumed that the race between the go process and the stop process is a tie, then the duration of the stop process can be calculated as the difference between the duration of the go process and the length of the SSD that elicits 50% stopping probability. The duration of the stop process is known as the Stop Signal Reaction Time (SSRT). Longer SSRT values indicate the participant requires more time to process a stop signal and inhibit the already initiated motor response, and is considered a marker of poorer response inhibition. Shorter SSRT values indicate the participant requires less time to process the stop signal and inhibit the already initiated motor response, and is considered a marker of superior response inhibition.

1.3 Individual Differences in Stop Signal Reaction Time

Research using the Stop Signal Task has demonstrated that individuals with longer SSRT, that is those demonstrating poorer response inhibition, are characterized by a more impulsive phenotype (Dalley, Everitt, & Robbins, 2011; Logan, Schachar, & Tannock, 1997; Schachar & Logan, 1990). Impulsivity can be defined in a number of ways, but generally impulsivity is a tendency to act quickly and rashly without the intentions of acting in a goal-directed manner (Dalley et al., 2011; Whelan et al., 2012; Whiteside & Lynam, 2001). When considered in the context of the Barkley model, impulsive responses can be

viewed as those that are performed in the absence of the inhibition of an initial response, and are therefore likely not derived from executive functioning (Barkley, 1997). If an immediate response is not inhibited, then there is no window for working memory, self-regulation, internalization of speech, or reconstitution to occur, and the immediate, impulsive response lacks flexibility.

Impulsivity, and corresponding poor response inhibition, is a defining characteristic of various forms of psychopathology. ADHD has been extensively studied using the Stop Signal Task. Multiple reports have indicated that individuals with ADHD display significantly longer SSRT compared to non-clinical controls (Alderson, Rapport, & Kofler, 2007; Casey, Castellanos, et al., 1997; Lijffijt et al., 2005; Oosterlaan, Logan, & Sergeant, 1998; Senderecka, Grabowska, Szewczyk, Gerc, & Chmylak, 2012). The inhibitory deficits observed in ADHD are dissociable from attentional problems (Verbruggen & Logan, 2008), indicating that response inhibition is distinct and uniquely impaired. In the task, individuals with ADHD perform similarly to controls on go trials, further supporting the hypothesis that the deficit is primarily with inhibitory control. Importantly, these reports of poor Stop Signal Task performance in individuals with ADHD agree with the arguments put forth by early models suggesting that the core deficit in ADHD is the inability to inhibit immediate responses (Barkley, 1997; Nigg, 2000; Quay, 1997).

Poor response inhibition has also been linked to various forms of substance abuse and misuse. Fillmore and Rush found that individuals who were dependent on cocaine had significantly longer SSRTs but similar go reaction times compared to non-dependent controls (Fillmore & Rush, 2002). Longer SSRTs have been used to characterize current (Whelan et al., 2014) and predict future alcohol misusers (Nigg et al., 2006), and

pathological gamblers have also displayed poor response inhibition as measured by the Stop Signal Task (Goudriaan, Oosterlaan, de Beurs, & van den Brink, 2006). These findings suggest that ADHD, substance abuse and misuse, and pathological gambling, among others, are related to a central deficit in the ability to inhibit immediate and impulsive responses that are incongruent with goal-oriented behavior.

1.4 Summary of Part 1

Inhibitory control can be viewed as the ability to inhibit an immediate response in the face of a changing environment. If the inhibition of an immediate response is successful, this creates a window of opportunity for executive functions to evaluate the changing environment and construct an adapted, more appropriate behavioral response. One form of response inhibition, the ability to inhibit an already initiated response, has been studied extensively in the laboratory using the Stop Signal Task. Using this task, researchers have the advantage of being able to capture an indirect measure of the duration of the cognitive process that is believed to sub serve the motor control component of the task. The Stop Signal Task has also identified major impairments in inhibitory control in a variety of psychopathologies, and has provided support for early reports that a key feature of ADHD is poor inhibitory control. Furthermore, the task can be used to test the hypotheses set forth by early researchers that response inhibition is one of the many functions that can be attributed to the performance and proper functioning of the prefrontal cortex.

Part 2 of Introduction – Neural correlates of Response Inhibition

2.1 Activation Associated with Successful Response Inhibition

Using different neuroimaging techniques, there is a vast literature detailing the areas of the brain that show activation during successful inhibition of a motor response. In functional magnetic resonance imaging (fMRI), an indirect measure of brain activation can be obtained using an event related task design, such as the Stop Signal Task. Brain activation is calculated as the change in blood oxygenation level dependency (BOLD) during a trial of interest (Ogawa, Lee, Kay, & Tank, 1990). The change in magnetic properties of blood as it transitions from the oxygenated to the deoxygenated state is measurable in fMRI sequencing, and this contrast is thought to result from physiological needs of neural tissue as that region of the brain becomes engaged in the processes required of the task. Thus, by creating a cognitive task and measuring the BOLD changes throughout the brain, one can indirectly measure which areas of the brain are presumably active during completion of the cognitive task. For example, during the Stop Signal Task, the change in BOLD signal can be measured immediately following a stop trial that was successfully inhibited by the participant, providing an index for the brain activation associated with response inhibition.

Many researchers will measure the BOLD signal during successful stopping in relation to a different type of trial to separate the signal that is uniquely associated to successful stopping. For example, because all stop trials begin with the presentation of a go signal, it is assumed that all stop trials will contain some brain activation that can be attributed to the go response. Therefore, researchers will subtract the average BOLD signal from all go trials from the average signal from all successful stop trials to identify the activity that is specifically pertinent to stopping (Aron & Poldrack, 2006; Chevrier,

Noseworthy, & Schachar, 2007; Pliszka, Liotti, & Woldorff, 2000). Alternatively, some researchers have subtracted the BOLD signal from unsuccessful stop trials from successful stop trials, thus providing an index for the activity specifically associated with successful response inhibition (Li, Huang, Constable, & Sinha, 2006; Rubia, Smith, Brammer, & Taylor, 2003). However, it is likely the case that subtracting the unsuccessful stopping signal from the successful stopping signal is too conservative because previous reports have suggested that the major difference between these two types of trials is the timing of these processes and not the patterns of activation (Ray Li, Yan, Sinha, & Lee, 2008).

Neuroimaging research examining response inhibition has identified a set of regions that reliably display stop-related activation across multiple studies. The most commonly reported region found to be associated with response inhibition is the right inferior frontal gyrus (rIFG). Multiple reports using the Stop Signal Task have exhibited increased activation in the rIFG during successful stop trials (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Chevrier et al., 2007; Garavan, Ross, & Stein, 1999; Rubia et al., 2003). Furthermore, lesion studies in both humans and rodents suggest damage to the rIFG results in severe loss of inhibitory function (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Floden & Stuss, 2006), and inhibition is temporarily impaired in individuals who were exposed to Transcranial Magnetic Stimulation (TMS) directed at the rIFG (Chambers et al., 2006, 2007; Siebner & Rothwell, 2003).

Multiple other regions have been implicated in successful response inhibition as well. Notably, cortical areas such as the presupplemtary motor area (preSMA; Aron et al., 2007; Floden & Stuss, 2006; Rae et al., 2016) and parietal lobules (Garavan, Ross, Murphy, K., Roche, R.A.P., & Stein, 2002; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003) all

show increased activity during successful response inhibition. Subcortically, the role of the right subthalamic nucleus (STN) has been extensively researched in inhibitory control. Studies have found increased activation in the STN during successful inhibition (Aron & Poldrack, 2006; Eagle et al., 2008), and surgical lesions of the STN in rodents result in a significant loss of inhibitory abilities (Eagle & Robbins, 2003). Interestingly, stimulation of the STN in patients with Parkinson's disease improves inhibitory control deficits, which are characteristic of the disease (van den Wildenberg et al., 2006). Other subcortical regions, particularly in the basal ganglia, have also been implicated in stopping. Both the caudate nucleus (Chevrier et al., 2007) and the striatum (Vink et al., 2005) have been suggested to play a role during successful inhibition of a motor response.

Although some have argued for the right hemisphere's dominant role in response inhibition (Garavan et al., 1999), others have demonstrated the role of both hemispheres. These reports indicate that during successful inhibition, regions of the left hemisphere, often the left inferior frontal gyrus (lIFG), show a similar increase in activation that is observed in the rIFG (Hirose et al., 2012; McNab et al., 2008; Ray Li, 2006; Rushworth, Krams, & Passingham, 2001). It is possible that the role of the left hemisphere is to supplement the right hemisphere during response inhibition as the difficulty of inhibition increases (Hirose et al., 2012), however this has not been directly tested in the laboratory. Some researchers have found that activation in the left hemisphere during successful response inhibition (Cabeza et al., 1997; Dolcos, Rice, & Cabeza, 2002; Nielson, Langenecker, & Garavan, 2002), as well as other cognitive modalities (Adcock, Wise, Oxbury, Oxbury, & Matthews, 2003; Reuter-Lorenz et al., 2000) increases with age. These researchers have hypothesized that a decrease in right-lateralization during inhibition may

represent either a compensatory mechanism with age or a maturational mechanism with age (Cabeza et al., 1997; Dolcos et al., 2002). Furthermore, individuals with lesions in the lIFG perform worse on a Go/No-Go task compared to controls, suggesting that the left hemisphere plays a central role in response inhibition (Swick, Ashley, & Turken, 2008). Although the left hemisphere appears to be involved in response inhibition, the exact nature of the left hemisphere in these tasks and how the left and right hemispheres work in conjunction to accomplish response inhibition remains unclear.

2.2 Neural Correlates of Response Inhibition Performance

The research described above adds to the understanding of the neural mechanisms involved when successfully inhibiting a motor response. However, these works typically do not address individual differences in the ability to inhibit a motor response, as indexed by the SSRT. Much of the work examining individual differences in the neural correlates of stopping that are associated with individual differences in SSRT have been in the context of comparing a clinical group, such as ADHD, to a healthy control group.

Research examining ADHD Stop Signal Task performance and brain activation compared to controls suggests that performance impairments in the task are accompanied by weaker activation of the key regions implicated in response inhibition. fMRI studies revealed that during successful stop trials, individuals with ADHD display less activity in the rIFG (Casey, Castellanos, et al., 1997; Rubia et al., 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005), the preSMA (Dickstein, Bannon, Xavier Castellanos, & Milham, 2006; Hart et al., 2014; Passarotti, Sweeney, & Pavuluri, 2010), and basal ganglia structures (Casey, Castellanos, et al., 1997; Dickstein et al., 2006; Rubia et al., 2005).

Complementing the fMRI work, event-related potential (ERP) research found decreased N2 and P3 component amplitudes in individuals with ADHD during successful stop trials (Liotti, Pliszka, Perez, Kothmann, & Woldorff, 2005; Pliszka et al., 2000; Senderecka et al., 2012), suggesting a weaker neural activation during response inhibition. These results showing hypoactivation of key inhibitory regions were suggested to be specifically associated with inhibition abnormalities (Cubillo et al., 2010; Dickstein et al., 2006; Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013) and not general attention problems observed in ADHD (Morein-Zamir et al., 2014).

Individual differences in structure and function within these key inhibitory control regions are also associated with subclinical individual differences in inhibitory ability. Numerous reports have found greater activity in the right IFG, the preSMA, and basal ganglia structures to correlate with faster SSRT, indicating better inhibitory control (Chao, Luo, Chang, & Li, 2009; Chikazoe et al., 2009; Congdon et al., 2010; Duann, Ide, Luo, & Li, 2009; Ray Li, 2006; Ray Li et al., 2008; Whelan et al., 2012). Faster SSRT has also been correlated with greater surface area (Curley et al., 2018) and thinner cortex (Batty et al., 2010; Newman et al., 2016) in the right IFG. These results suggest that more mature cortical morphology in the right IFG results in better inhibitory control performance. In ADHD and Trichotillomania (pulling out one's hair, which is also associated with inhibitory control impairments), greater grey matter volume, in various regions involved in successful stopping, was related to poor performance on the Stop Signal Task (McAlonan et al., 2009; Odlaug, Chamberlain, Derbyshire, Leppink, & Grant, 2014).

Structural connectivity analysis revealed that superior inhibitors exhibited greater white matter integrity in the areas surrounding the anterior aspect of the rIFG compared to

poor inhibitors (Forstmann et al., 2008) and greater fractional anisotropy in both the rIFG and right preSMA is associated with faster inhibition (Madsen et al., 2010). Functional connectivity analysis revealed that superior inhibitors displayed greater stop-related connectivity between the rIFG and the right caudate compared to poor inhibitors (Jahfari et al., 2011), and that functional connectivity among the stopping network is disrupted in Parkinson's Disease (Rae et al., 2016).

2.3 Summary of Part 2

The neural mechanisms of response inhibition and the neural correlates of individual differences in inhibitory ability complement one another. Regions such as the rIFG, the preSMA, and the right basal ganglia show enhanced activity during successful inhibition of a motor response, and the magnitude of this activation is correlated with inhibitory ability as measured by the SSRT. The degree to which these regions are structurally and functionally connected during response inhibition has also been related to the level of inhibitory ability. At a clinical level, impairments in inhibitory control, such as in ADHD and Parkinson's disease, have been associated with lower levels of activation in these regions, and potentially disrupted patterns of functional connectivity.

Part 3 of Introduction – Brain Development through Adolescence

3.1 Structural Brain Development

Human postnatal brain development occurs in a nonlinear manner. The brain undergoes a great deal of change early in life, and becomes more stable through adulthood. Brain maturation begins with an overproduction of cells and synapses, which is followed by selective removal of excess tissue. Neurons that are able to form appropriate and meaningful synapses survive, while those that do not contribute to functional or structural integrity are eliminated through programmed cell death (Bourgeois, Goldman-Rakic, & Rakic, 1994; Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Mauch et al., 2001). The process of competitive elimination, known as "pruning," occurs actively during the first two decades of life, and then slows during adulthood (Huttenlocher & Dabholkar, 1997). The remaining synapses are strengthened over time by thickening of myelin along the axon, an increase in the size of the neuron, and an increase in the number of synaptic connections between cells and their targets (Bourgeois et al., 1994; Gogtay et al., 2004). Myelination will occur throughout development and continue through new experiences, new environments, and the development of new functions (Craik & Bialystok, 2006). These cellular changes improve conduction velocity and communication between neurons. Such improvements in cell-to-cell communication are believed to contribute to the formation of neural circuits and pathways.

The developmental trajectories of cortical grey matter and white matter may reflect the underlying processes occurring at the cellular level. Grey matter development portrays an inverted U-shape, with an increase in volume during the first decade of life followed by a steady decrease in volume (Giedd et al., 1999; Gogtay et al., 2004). It is likely this curve represents the overproduction of cells in early stages of development followed by the pruning of excess tissue. By the age of six, the brain has reached approximately 90% of

the adult volume (Giedd, 2004; Gogtay et al., 2004), which corresponds to the peak of the inverted U curve for grey matter. Some researchers hypothesize the steady decline in grey matter volume represents the elimination of redundant neurons and synapses (Craik & Bialystok, 2006). This decrease in cortical grey matter with age is referred to as "normative age-related cortical thinning," and is associated with normal cortical maturation during development (Fjell et al., 2009; Sowell et al., 2004).

In contrast, white matter development portrays a linear increase in volume with age (Giedd et al., 1999). One possible explanation for the linear increase is that it reflects increased myelination of surviving neurons and increased density of their synapses. The brain is constantly adapting to the environment, and the increase in white matter therefore occurs throughout adulthood. For example, in the auditory system, auditory circuits will become more heavily myelinated as an individual is exposed to a wider range of sounds and auditory stimuli (Bick & Nelson, 2016). The exposure to auditory stimuli increases the activity along auditory pathways, which is correlated with thicker myelin surrounding the axons in the pathway. Researchers hypothesize that increased activity along a pathway demands more efficient processing from the fibers involved in the pathway (Craik & Bialystok, 2006; Giedd et al., 1999). Thicker myelin along the axons improves conduction velocity and communication, thus addressing the demand for efficiency.

In theory, normal developmental changes in brain morphology represent pruning and myelination occurring at the cellular level. Research has indicated that changes in brain morphology do not occur uniformly across the whole brain at once. In the past few decades, there has been a surge of research examining the normal developmental trajectory of the human brain. Research using Magnetic Resonance Imaging (MRI) has suggested

that brain regions involved with primary, low-order functions develop first, and regions involved with more complex, high-order functions develop later (Bick & Nelson, 2016; Casey, Jones, & Hare, 2008; Giedd et al., 1999). This research suggests that basic neural circuits must subserve the formation of complex neural circuits.

The pruning process parallels the emergence of function for a given anatomical region (Luna et al., 2001), and the hierarchical nature of brain development is reflected in the increasing sophistication of cognitive, emotional, and behavioral abilities with increasing age. Subcortical regions are the first to mature, followed by primary function cortical regions, and moving later into complex cortical regions involved with cognition and executive functioning (Bick & Nelson, 2016). Within cortical grey matter, the spatial pattern of development is illustrated by the "Posterior to Anterior Shift in Aging" model (PASA). This model suggests that the cortex first matures in occipital regions, working into temporal, parietal, and finishing in the frontal and prefrontal areas (Ansado, Monchi, Ennabil, Faure, & Joanette, 2012; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). Thus, the prefrontal cortex is the last region of the brain to develop.

The prefrontal cortex (PFC) is involved with a variety of functions including, but not limited to, cognition, emotional control, and goal-directed behavior (Bourgeois et al., 1994; Miller & Cohen, 2001; Stevens, Kiehl, Pearlson, & Calhoun, 2007). As indicated above, one function of the PFC is inhibitory control. The PFC has numerous projections stemming from areas such as the dorsolateral prefrontal cortex (DLPFC), the orbitofrontal cortex (OFC), and the inferior frontal gyrus (IFG) that project onto posterior and subcortical areas of the brain, exerting cognitive control during psychological processes. These synapses organize thoughts, emotions, and behaviors (Blakemore & Choudhury, 2006; Casey et al.,

2008; Galvan et al., 2006; Luna et al., 2001; Stevens et al., 2007). The prefrontal cortex, as a whole, has been considered as the center for executive control in the brain (Miller & Cohen, 2001), which agrees with early reports on the role of the prefrontal cortex (Barkley, 1997).

Due to the delayed maturation of the prefrontal cortex compared to subcortical structures, there becomes a period of imbalance during development. During this period of imbalance, subcortical structures and more primitive regions of the brain are more mature and reactive than prefrontal regions, and thus the prefrontal regions are less able to exert inhibitory control over these more mature areas. The lack of mature connections and the inability of the PFC to exert adult-like inhibitory influences throughout the brain results in behaviors that are disproportionately influenced by limbic reactivity (Casey et al., 2008; Casey, Tottenham, Liston, & Durston, 2005; Galvan et al., 2006). This period of development has been given the title "adolescence" and is characterized by impulsive and risk-taking behaviors, poor decision making, and heightened emotional reactivity (Casey et al., 2008). Adolescents are at an increased risk for contracting STDs, unexpected pregnancy, motor vehicle accidents, and using illegal substances (Steinberg, 2008). These behaviors have been suggested to result from the lack of inhibitory control that is caused by the imbalances in architecture and function of the brain during this time (Casey et al., 2008). Researchers believe these behaviors are not evident at such a high level in children or in adults because: A) children do not have mature limbic architecture to guide behaviors based on emotional reactivity, and B) adults have mature inhibitory connections from the PFC to suppress emotionally driven and inappropriate responses (Blakemore & Choudhury, 2006; Casey et al., 2008; Steinberg, 2008).

One common neuroimaging finding supporting this hypothesis of adolescent brain development is that during adolescence there is a higher ratio of limbic to PFC activity during reward tasks (Casey et al., 2008; Galvan et al., 2006; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010). A functional MRI study examined the activation of the nucleus accumbens (NAcc), which is considered a reward center of the brain, and the orbitofrontal cortex during a rewarded decision making task (Galvan et al., 2006). For each trial, participants were asked to indicate which side of the screen, left or right, a stimulus was presented on as quickly and as accurately as possible. Each trial varied between small, medium, and large rewards for a correct response. As the reward for correct responses increased, adolescents showed a greater increase in NAcc relative to OFC activity compared to children and adults. The adolescents had stronger NAcc activity but similar OFC activity compared to children, and had similar NAcc but weaker OFC activity compared to adults. This pattern of results would be consistent with adolescents having more mature and reactive NAcc but relatively immature and less reactive OFC. Other studies have also found a heightened limbic response to reward that is not coupled with an increased PFC activation (Blakemore & Choudhury, 2006), supporting the hypothesis that adolescent behaviors are guided by immediate reactivity with reduced response inhibition. When regarded in the Barkley view of inhibitory control, greater limbic to prefrontal drive suggests that immediate, limbic guided responses are less likely to be inhibited, and thus are not aimed toward future goals and outcomes.

3.2 Development of Inhibitory Control

If adolescence is marked by impulsive behaviors that result from poor inhibitory control, then emergence from adolescence should be marked by the development of inhibitory control enabling goal-directed behavior. Additionally, given the maturation of the prefrontal cortex during adolescence and the role of the prefrontal cortex in inhibitory control, improvements in response inhibition should be observed during this developmental period (Dempster, 1992; Nelson & Bloom, 1997). Using the Stop Signal Task, Williams and colleagues mapped the SSRT of 275 participants aged 6 to 81 years old (Williams, Ponesse, Schachar, Logan, & Tannock, 1999). The researchers found that performance on the task significantly improved throughout childhood and adolescence, peaking in young adulthood (ages 18-29). Further research into the development of response inhibition also found age-related improvements throughout childhood and into early adulthood (Bedard et al., 2002; Huizinga, Dolan, & van der Molen, 2006; Ridderinkhof, Band, & Logan, 1999), and researchers hypothesized these improvements to be related to the maturation of prefrontal systems.

Most research examining the development of the neural correlates of inhibitory control in adolescence compare performance and neural activity between children, adolescents, and adults. A major theory regarding the brain activation associated with development of inhibitory control is that as age increases, less activation in the cortex is required during inhibitory control (Durston et al., 2006; Shaw et al., 2006; Urry et al., 2006; Velanova, Wheeler, & Luna, 2008). Velanova and colleagues found that adolescents showed a smaller area of activation in the DLPFC than children but a larger area of activation than adults on an anti-saccade inhibitory task (Velanova et al., 2008). The age groups performed similarly on the task, suggesting that neural activation required for

inhibitory control becomes more efficient and transitions from diffuse to focal throughout adolescence. One potential explanation for this trend is that adolescents require greater "effort" than adults during these tasks because the neural architecture responsible for inhibitory control has not yet matured (Bokura, Yamaguchi, & Kobayashi, 2001; Jonkman, 2006). That is, in adolescents, the neural architecture involved with inhibitory control is less mature and therefore requires a greater area of activation, whereas in adults, the neural architecture is more mature and efficient, and requires a smaller area of activation.

Supporting the efficiency model of development, Sarah Durston and colleagues examined if increasing task difficulty on an inhibitory control task affects children differently than adults (Durston et al., 2002). Here, participants were presented with easy, medium, and difficult inhibitory motor tasks. In adults, the increasing difficulty of the task was matched by an increase in activation in ventrolateral prefrontal regions. In children, the amount of activity in this region peaked on the easy trials, and exhibited lower activity on the medium and difficult trials. Furthermore, children's performance on the medium and hard trials was poor, whereas the adults performed well on all levels of the task. These results suggest that in a more mature inhibitory system, adults can increase activation of inhibitory regions to meet the increasing demands of the task. However in a relatively immature inhibitory system, children show maximal activity with easy demands, subsequently cannot activate the inhibitory regions more, and are unable to successfully inhibit in more difficult conditions (Durston et al., 2002, 2006).

One possible explanation for the age-related decrease in cortical activation is that synaptic pruning and myelination are occurring in top-down and/or inhibitory networks. If pruning and myelination are occurring in these networks, then it is possible the amount of

tissue required for successful response inhibition decreases because excess tissue has been pruned in that cortical area. The neurons that survive the pruning process are likely those that have formed appropriate synapses to other areas of the brain. Recent research suggests that adults exhibit stronger activation within frontal-striatal-thalamic pathways and frontal-parietal pathways during inhibitory tasks (Arnsten & Rubia, 2012; Hwang, Velanova, & Luna, 2010; Rubia, 2013; Stevens et al., 2007). The stronger signal within these presumable cognitive control networks could indicate that adults display stronger structural and functional connectivity among regions involved in the task. If true, this would suggest the formation and strengthening of inhibitory networks occurs during the transition from adolescence into adulthood. In addition to a stronger signal within these networks, there was a decrease in the area of the ventral lateral prefrontal cortex (VLPFC) activation during the task (Stevens et al., 2007). Again, these data support the hypothesis that as top-down pathways form, less cortical tissue is required to activate the pathways.

A number of both animal and human studies suggest top down pathways stemming from the PFC strengthen significantly throughout adolescence. Human MRI studies have consistently found an age-related increase in the signal from prefrontal-subcortical projection fibers during inhibitory tasks (Cunningham, Bhattacharyya, & Benes, 2002; Munakata et al., 2011; Stevens et al., 2007). Diffusion weighted imaging (DWI) studies in humans have found fibers stemming from the PFC and projecting to subcortical, parietal, and posterior areas of the brain exhibit an age-related increase in structural integrity throughout the adolescent years (Sturman & Moghaddam, 2011). Animal research has indicated similar increases in white matter connectivity stemming from the prefrontal cortex. In a study examining the connectivity of fibers from the medial prefrontal cortex

(MPFC) and the basolateral amygdala in rats, researchers found that the adolescent age range was associated with significant increases in the axo-dendritic and axo-axonic synapses between these two areas (Cunningham et al., 2002). In addition to an increase in synaptic density, there was also an increase in the size of the fiber itself. These data support the hypothesis that top-down networks form during adolescence.

3.3 Summary of Part 3

The human brain develops in a hierarchical manner. Because of this pattern, there is a period of development, known as "adolescence," when subcortical structures are more mature compared to the prefrontal cortex. This imbalance results in behaviors guided primarily by immediate limbic and emotional reactivity. The formation of top-down, cognitive control pathways from the prefrontal cortex to subcortical areas is crucial to developing inhibitory control and appropriately guiding behaviors. Both human and animal research indicate that the formation of these networks occur throughout the adolescent stage of development. Given the cellular mechanisms responsible for brain development, it is possible that cortical thinning and top-down pathway formation represent cellular pruning and axonal myelination, respectively.

Part 4 of Introduction – The Current Report.

The focus of the current report is to examine inter- and intra-individual differences in response inhibition. The research described above details previous theories and research findings regarding the central role response inhibition plays in executive functioning, the neural correlates of response inhibition, and the development of response inhibition in

adolescence. Despite the abundance of research in this field, important aspects of inhibitory control remain unclear. First, the debate over the lateralization of inhibitory control has not been settled by previous research. Second, research on the development of the neural mechanisms of inhibitory control focused within the adolescent age range is limited. In addition to examining both questions, the report will also explore the way individual differences in functional activation associated with response inhibition are currently measured.

While the bulk of work in response inhibition has indicated the process to be right-hemisphere dominant, others have suggested that the left hemisphere also plays a key role. The current report will address this question in two ways. First, using data from a split-brain patient, hemispheric differences in the ability to inhibit a prepotent response as well as the ability to inhibit a response that has already been initiated will be tested. This will provide novel insight into the question of lateralization of inhibitory control because each hemisphere will be targeted in isolation to complete the tasks. Second, the current report will also briefly discuss the hemispheric differences in how stop-related activity changes from 14 to 19 years old. Though laterality will not be discussed, examining within-subject changes in activation associated with response inhibition provides interesting insights into differences in hemispheric development of inhibitory control.

The second area that will be addressed by the current report is the development of inhibitory control during the adolescent age range. As indicated above, the adolescent period of development is considered the time during which inhibitory and cognitive control processes emerge, and therefore this age range is ideal for examining within-subject changes in the neural components of response inhibition. The current report will explore

the age-related changes in the ability to stop an already initiated response, as well as the functional activation associated with successful stopping, in a longitudinal sample of adolescents from age 14 to 19. Furthermore, the current report will examine how the functional activation associated with individual differences in inhibitory ability changes from 14 to 19, which has yet to be explored in the literature.

Importantly, the current report will only focus on stop-related BOLD activation. The literature on the development of inhibitory control indicates potentially interesting relationships between the development of this ability and the development of neural structure, activation, and connectivity. However, it is imperative to gain an understanding of the functional underpinnings of laterality and development of response inhibition before pursuing other brain imaging modalities. From these preliminary reports, subsequent research examining the structural, structural connectivity, and functional connectivity correlates of response inhibition will follow.

Lastly, the current report will explore and discuss the way that stop-related functional activity is currently captured. Given the variability in task demands of the Stop Signal Task, important variance associated with individual differences in stop-related activity may be attenuated in the current method. The current report examines how objective task difficulty influences the magnitude of activation during successful inhibition of a motor response. The Stop Signal Task is a popular paradigm in inhibitory control research, and the best way to capture activation associated with successful stopping has not been addressed thus far in the literature.

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CHAPTER TWO

A split-brain case study on the hemispheric lateralization of inhibitory control

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Abstract
Understanding the neurobiological mechanisms underlying inhibitory control is crucial given its role in various disease states and substance abuse/misuse. Neuroimaging research examining inhibitory control has yielded conflicting results on the relative importance of the left and right hemisphere during successful inhibition of a motor response. In the current study, a split-brain patient was examined in order to assess the independent inhibitory capabilities of each hemisphere. The patient's right hemisphere exhibited superior inhibitory ability compared to his left hemisphere on three inhibitory control tasks. Although inferior to the right, the left hemisphere inhibited motor responses on inhibitory trials in all three tasks. The results from this study support the dominance of the right hemisphere in inhibitory control.

Keywords: Response Inhibition; Stop Signal; Go/No-Go

1. Introduction

The ability to inhibit inappropriate thoughts, emotions, and behaviors is a critical component of executive functioning and cognitive control. Humans must continuously adapt to changing environments and circumstances, filter out irrelevant information, and evade danger and harm, all of which require inhibitory control. Deficits in inhibitory control contribute to clinical conditions including Parkinson's disease (Gauggel et al., 2004), attention deficit hyperactivity disorder (ADHD; Casey et al., 1997; Slaats-Willemse et al., 2003), and obsessive-compulsive disorder (OCD; Bannon et al., 2002; Penades et al., 2007). Additionally, sub-clinical impairments in inhibitory control are associated with impulsivity and risk-taking behaviors evident in substance misuse (Helfinstein & Poldrack, 2012; Nigg et al., 2006; Whelan et al., 2012).

Two task paradigms commonly used to assess inhibitory control are the Go/No-Go task and the Stop Signal Task (SST). Both tasks require rapid behavioral responding to a go signal on a majority of trials, and a withholding of the response on a subset of "no-go" and "stop" trials. In the Go/No-Go paradigm, an individual must inhibit the prepotent go response when presented with an infrequent stimulus, the no-go signal (Bokura et al., 2001; Eimer, 1993; Menon et al., 2001). In the SST, an individual must inhibit an already initiated response when presentation of a go signal is followed by the presentation of a stop signal, which occurs on a minority of trials (Logan, 1994; Logan & Cowan, 1984).

Neuroimaging studies that use the SST and the Go/No-Go task have found conflicting results as to the lateralization of inhibitory control. A large body of research has identified

the right inferior frontal gyrus (rIFG) as a key area for successful response inhibition. Functional neuroimaging studies have found increased activation in the rIFG during successful inhibition of a motor response in both the Go/No-Go and the SST (Aron et al., 2004; Garavan et al., 1999; Hampshire et al., 2010; Rubia et al., 2003). Further, patients with damage to the rIFG show decreased performance in the SST compared to healthy controls (Aron et al., 2003) and inhibition is temporarily impaired in individuals who were exposed to Transcranial Magnetic Stimulation (TMS) that was directed at the rIFG (Chambers et al., 2007; Siebner & Rothwell, 2003).

However, there is also compelling research suggesting a role of the left inferior frontal gyrus (lIFG) in response inhibition. Much of this research describes the activation of the lIFG in conjunction with rIFG activation during successful inhibition in Go/No-Go and SST (Hirose et al., 2012; Li et al., 2006; McNab et al., 2008; Rubia et al., 2001; Rushworth et al., 2001). Results from these studies suggest that as the difficulty of inhibition increases, the lIFG is recruited to supplement the rIFG (Hirose et al., 2012). However, Swick and colleagues (2008) found that individuals with lesions in the lIFG performed worse on a Go/No-Go task compared to healthy controls, suggesting that the lIFG plays a critical, rather than a supplemental role, in response inhibition. Taken together, previous research highlights the importance of both the left and right hemispheres in response inhibition, and therein the lateralization of the neural mechanisms underlying inhibitory control remains unclear.

In addition to left and right prefrontal systems, subcortical structures, namely the basal ganglia and the subthalamic nucleus (STN), have been implicated in response inhibition as well. Research examining the role of the STN in response inhibition has found increased activation in the STN during successful inhibition (Aron & Poldrack, 2006), and surgical lesions of the STN in rodents result in a significant loss of inhibitory abilities (Eagle & Robbins, 2003). Interestingly, van Wildenberg and colleagues (2006) found that stimulation of the STN in patients with Parkinson's Disease improved inhibitory control deficits that are a primary characteristic of the disease. Thus, researchers have proposed a neural circuit involving both the prefrontal cortex and the basal ganglia for response selection and response inhibition (Nambu et al., 2002).

Examining an individual who has undergone a corpus callosotomy provides a unique approach to address the hemispheric lateralization of response inhibition. Complete resection of the corpus callosum results in near total loss of communication between the right and left hemispheres at the cortical level, which includes the transfer of perceptual, sensory, cognitive, and motor information (Gazzaniga, 2005). Split-brain patients have been studied extensively to expose the independent functions of each hemisphere (Gazzaniga, 2000; Gazzaniga, 2005; Springer & Deutsch, 1998). Due to the neural architecture of the visual system, a stimulus can be presented laterally in the visual field such that the visual information is only processed in one hemisphere (Brindley, 1960). Split-brain patients lack commissural fibers for inter-hemispheric communication, and therefore the hemisphere that processes a visual stimulus must complete the task indicated

by the stimulus. Thus, presenting a task in the lateral visual field of a split-brain patient can isolate the function of a single hemisphere.

The goal of the present study is to explore the lateralization of inhibitory control using a corpus callosotomy patient. We test the patient using both Go/No-Go and Stop Signal tasks in which only one hemisphere is probed at a time for each stimulus. We hypothesize that the right hemisphere will possess superior inhibitory abilities compared to the left hemisphere during both Go/No-Go and Stop Signal tasks.

2. Materials and Methods

2.1 Participant

The participant in the current study was patient J.W., a 48-year-old, right-handed male of average intelligence. Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). At the age of 25, J.W. received a two-stage surgical resection of his corpus callosum as treatment for medically intractable epilepsy. Post-surgical MRI confirmed complete resection of the corpus callosum with no additional brain damage. Patient J.W.'s medical details and cognitive profile have been previously described (Gazzaniga et al., 1984).

2.2 Divided Visual Field

The current study examines previously collected data from a one day visit in which J.W. participated in an assessment of response inhibition. These data were not a part of a larger test battery. J.W. completed three motor inhibition tasks: one Go/No-Go task, a single choice Stop Signal Task, and a forced choice Stop Signal Task, in this order. Breaks were

provided as needed. For all three tasks, the divided visual field technique was employed on all stimuli presented. The technique is designed to target only one hemisphere per stimulus. The visual system is organized such that the medial hemiretina of the eye projects to the contralateral hemisphere and the lateral hemiretina projects to the ipsilateral hemisphere. Thus, a stimulus presented lateral to midline will be perceived by the contralateral hemisphere. For example, if the image is presented left of midline, the left medial retina and the right lateral retina will detect the image, and both will project to the right hemisphere.

2.3 Experimental Design

J.W. was seated 57cm from the computer screen and was instructed to fixate on a midline fixation cross. Stimuli were presented for 150ms. 150ms stimulus presentation has been used in previous work using the divided visual field design with split brain patients (Corballis et al., 2002; Colvin et al., 2005), and a report by Funnel et al. (2007), which used eye-tracking software, reported this stimulus length to not produce saccadic movements. The medial edges of the stimuli were at least 3cm lateral to midline, which fall outside the field of nasotemporal overlap. These parameters ensure that only the hemisphere contralateral to the visual field of stimulus presentation perceives the stimuli.

Responses to stimuli were made via key press on a standard Macintosh keyboard with the hand ipsilateral to the visual field of presentation. Therefore, the hemisphere receiving the visual stimuli was the same hemisphere generating the motor response. Four keys, two for left hand responses (A and Z) and two for right hand responses (“ and /), were marked with

stickers to indicate the correct response keys. On the Go/No-Go and single choice Stop Signal Task, one key for each hand was used for a response to the go signal. On the forced choice Stop Signal Task, there were two possible key responses for each hand corresponding to the two possible go signals.

2.4 Go/No-Go Task

A series of the letters X and Y were presented in a ratio of 15:1, pseudorandomly. The letters were presented equally often in both the left visual field and the right visual field. J.W. was instructed to make a key press as quickly as possible with his left hand when the letter X appeared on the left side of the screen, a key press with his right hand as quickly as possible when the letter X appeared on the right side of the screen, and to make no response when the letter Y appeared on either side of the screen. There were 256 trials in each session, with 128 stimuli presented in each visual field. Trials were presented randomly in each visual field and J.W. was asked to maintain fixation on the center of the screen. J.W. completed 5 sessions, each session lasted approximately four and a half minutes.

2.5 Single Choice Stop Signal Task

The first Stop Signal Task was a single-choice task (Figure 2). J.W. was presented with a series of X's (go signal) and instructed to respond via key press, as quickly as possible with the hand ipsilateral to the side of the screen the X was presented. Following 25% of the X's, a stop signal flashed on the screen, signaling to J.W. to no longer respond to the X. The onset of the stop signal presentation varied from 50-250ms delay at 50ms intervals.

Each stop signal delay (SSD) was presented equally often. There were 96 total trials in each session, with 48 stimuli presented in each visual field. Trials were presented randomly in each visual field and J.W. was asked to maintain fixation on the center of the screen. J.W. completed 16 sessions of the task, each session lasted just under three minutes.

2.6 Forced Choice Stop Signal Task

The second stop signal task required J.W. to choose between two possible response keys on the go signal. In this task, J.W. was presented with either an X or an O as the go signals (Figure 2). J.W. responded as quickly as possible with the appropriate key on all go trials with the hand ipsilateral to the stimuli presentation. There were four possible keys for go responses: one key for the O stimuli in the left visual field, a key for the O stimuli in the right visual field, a key for the X stimuli in the left visual field, and a key for the X stimuli in the right visual field. Both go signals appeared equally often and both signals appeared in each visual field equally often. As in the first stop signal task, J.W. was presented with a stop signal after 25% of the go signals, signaling to J.W. to inhibit responding to the go signal. There were 96 total trials in each session, with 48 stimuli presented in each visual field. Trials were presented randomly in each visual field and J.W. was asked to maintain fixation on the center of the screen. J.W. completed 10 sessions of this task (due to time restraints, J.W. was unable to complete 16 sessions), each session lasted just under 3 minutes.

2.7 Stop Signal Reaction Time

Stop Signal Reaction Time (SSRT) was calculated for the single choice and the forced choice Stop Signal Tasks to compare the performance of the two hemispheres. The SSRT is a calculation designed to measure the time required to process a stop signal and successfully inhibit an already initiated motor response (Logan et al., 1984; Logan et al., 1997). In this regard, the SSRT calculation is a measure of inhibitory control that adjusts for individual differences in response times. Here, SSRT was calculated as described in (Logan, 1994). The average duration of the SSD on all successful stop trials was subtracted from the nth response time in the distribution of go trial responses (where n refers to the accuracy level on stop trials). For example, if J.W. inhibited on 65% on stop trials, the average successful SSD was subtracted from the response time at the 65th percentile of the response time distribution on go trials.

3. Results

3.1 Statistical Analyses

The experiments involve analysis of single-subject data in which each hemisphere serves as a control for the other, and therefore accuracy data were analyzed using chi-squared analyses. For each comparison, the total number of successful inhibitory trials was compared between the hemispheres. Because the split-brain design assumes independent functioning of the two hemispheres, response time analysis to compare hemisphere performance was conducted using independent samples t-test.

3.2 Go/No-Go Task

Accuracy and response time data for the Go/No-Go task can be found in Table 1. Chi-squared analysis of accuracy data revealed that J.W.'s right hemisphere inhibited responses on no-go trials significantly more frequently than his left hemisphere (X^2 (1, N = 80) = 7.22, $p < 0.05$; Figure 1). There was no significant difference in the response frequency to go signals between the two hemispheres ($p = 0.18$). However, the left hemisphere exhibited significantly faster response times than the right hemisphere ($t(1196) = 9.04$, $p < 0.01$; Figure 3).

3.3 Single Choice Stop Signal Task

Accuracy and response time data for the single choice Stop Signal Task can be found in Table 1. First, the right and left hemispheres were compared on total accuracy for all stop trials. J.W.'s right hemisphere was able to inhibit significantly more motor responses than his left hemisphere (X^2 (1, N = 384) = 8.71, $p < 0.01$), across all stop signal delays. Next, the right and left hemispheres were compared using accuracy data at each SSD individually (Figure 2; Table 2). At the level of individual SSD, J.W.'s right hemisphere inhibited on significantly more stop trials than his left hemisphere at SSD length of 50ms (X^2 (1, N = 64) = 10.54, $p < 0.01$). The left hemisphere exhibited significantly faster response times than the right hemisphere ($t(1127) = 3.90$, $p < 0.01$; Figure 3) on correct go trials.

3.4 Forced Choice Stop Signal Task

Accuracy and response time data for the forced choice Stop Signal Task can be found in Table 1. Right and left hemispheres were first compared using total accuracy across all stop trials. Chi-squared analysis revealed that J.W.'s right hemisphere inhibited a motor

response significantly more frequently than his left hemisphere (X^2 (1, N =240) = 29.63, p < 0.01) across all SSDs. Right and left hemispheres were then compared using accuracy data at each SSD individually (Figure 2; Table 2). J.W.'s right hemisphere inhibited significantly more than the left hemisphere at SSDs of 100ms and longer (100ms: X^2 (1, N = 40) = 5.63, p < 0.05; 150ms: X^2 (1, N = 40) = 10.99, p < 0.01; 200ms: X^2 (1, N = 40) = 5.58, p < 0.05; 250ms: X^2 (1, N = 40) = 6.47, p < 0.05). The right hemisphere had significantly slower response times than the left hemisphere (t(693) = 9.88, p < 0.01; Figure 3) on correct go trials.

3.5 Stop Signal Reaction Time

SSRT was calculated for each hemisphere for single and forced choice Stop Signal Tasks as a measure of inhibitory ability. In the single choice Stop Signal Task, the left hemisphere SSRT was 329ms and the right hemisphere SSRT was 284ms. In the forced choice Stop Signal Task, the left hemisphere SSRT was 360ms and the right hemisphere SSRT was 291ms. Although we cannot test for statistically significant differences from one data point, the data suggest the right hemisphere exhibits shorter SSRT in both Stop Signal Tasks compared to the left hemisphere.

4. Discussion

In the current study, inhibitory performance was measured in a split-brain patient using a Go/No-Go task, a single choice Stop Signal Task, and a forced choice Stop Signal Task. A divided visual field design was used to probe the right and left hemispheres independently. On all three tasks, the right hemisphere inhibited on a significantly greater

number of inhibitory trials than the left hemisphere. Furthermore, the right hemisphere inhibited on significantly more inhibitory trials in the forced choice Stop Signal Task for stop trials with longer than 100ms SSD. Although the right hemisphere exhibited significantly longer response times on all three tasks, the right hemisphere exhibited shorter SSRTs than the left hemisphere.

The results from the current study indicate that the right hemisphere is superior to the left hemisphere when inhibiting a motor response. Patient J.W.'s right hemisphere exhibited greater inhibitory accuracy than the left hemisphere on the go/no-go, the single choice SST, and the forced choice SST. The superior performance of the right hemisphere on all three inhibitory tasks supports a dominant role for the right hemisphere in inhibitory control and complements the neuroimaging, lesion and TMS findings described earlier that implicate the right inferior frontal gyrus as a key source of inhibitory control in the brain (Aron et al., 2003; Aron et al., 2004; Garavan et al., 1999; Rubia et al., 2003).

However, the extent to which these data support the primary role of the rIFG, specifically, in response inhibition is limited. Because neuroimaging was not conducted in the present experiment and J.W. has intact subcortical architecture, the results from the current study do not indicate cortical compared to subcortical involvement in response inhibition. It is possible that the superior performance of the right hemisphere is driven by predominance of the right STN and other basal ganglia circuitry during response inhibition rather than differences at the cortical level. Regardless of the extent of cortical and subcortical

importance in response inhibition, here we show that the right hemisphere exhibits superior performance on three inhibitory control tasks.

The right hemisphere displayed slower response times on go trials, which may indicate a more conservative response bias leading to greater inhibitory accuracy (i.e., a speed-accuracy trade-off). Furthermore, J.W. is right handed, which may explain faster reaction times attributed to the left hemisphere on all three tasks. To address these concerns, we calculated the SSRT for the left and right hemispheres on the two variants of the stop signal task. The SSRT calculation accounts for differences in go response time by calculating the time to inhibit an already-initiated response, thereby adjusting for individual differences in response time (Logan, 1994). In the current study, calculating SSRT adjusted for the difference in response times between the two hemispheres. On both stop signal tasks, J.W.'s right hemisphere had faster SSRT values than his left hemisphere (45ms advantage on the single choice task and 69ms advantage on the forced choice task), further supporting the superior inhibitory abilities of the right hemisphere.

Interestingly, patient J.W.'s left hemisphere was capable of inhibiting responses on stop and no-go trials, demonstrating that motor inhibitory control is not solely attributable to the right hemisphere. In the Go/No-Go task, the left hemisphere responded on 100% of go trials and 62.5% of no-go trials. In the singe choice Stop Signal Task the left hemisphere responded on 98.1% of go trials and 44.8% of stop trials. In the forced choice Stop Signal Task the left hemisphere responded on 98.8% of go trials and 44.2% of stop trials. The

decrease in responding rate for no-go and stop trials compared to go trials on all three tasks demonstrates the left hemisphere's ability to countermand a motor response.

As noted earlier, previous neuroimaging and lesion studies have demonstrated a role for the left hemisphere in response inhibition (Hirose et al., 2012; Swick et al., 2008) including a role for the left supramarginal gyrus in motor attentional control (Rushworth et al., 2001). In comparing these results with the large neuroimaging literature that has stressed the right hemisphere's role in inhibitory control, it is worthwhile noting that the mass univariate thresholding commonly employed in imaging studies could miss sub-threshold activity. Further, neuroimaging studies that have stressed lateralized activation patterns (e.g., Garavan et al., 1999) rarely test if the above-threshold activation in one region is larger than the sub-threshold activation in its homologue in the other hemisphere.

One limitation of the current study is the lack of a control subject. While participant J.W. provides a unique opportunity to examine independent functions of the left and right hemispheres, we acknowledge that his overall performance may be impaired due to his neurological condition. However, even if so, we nonetheless believe that even in the presence of an overall impairment in performance, the different abilities of his two hemispheres is insightful – and, indeed, is the rationale underlying the body of research that investigates split-brain patients.

5. Conclusion

The present results indicate that both the right and left hemispheres are capable of response inhibition with the right hemisphere successfully inhibiting more frequently and with shorter SSRTs. Examining the callosotomy patient J.W. provided a unique opportunity to measure the left and right hemispheres independently of one another and offered a novel approach to addressing the lateralization of this core executive function.

Task	Accuracy	Mean Response Time
Go/No-Go		
Right Hemisphere	68%	304ms
Left Hemisphere	38%	261ms
Single Choice SST		
Right Hemisphere	70%	481ms
Left Hemisphere	55%	445ms
Forced Choice SST		
Right Hemisphere	88%	577ms
Left Hemisphere	56%	472ms

Table 1. General descriptive statistics collapsed across all trials on the Go/No-Go, single choice Stop Signal Task, and forced choice Stop Signal Task. Accuracy and Mean Response Time are provided separately for the right and left hemispheres. Accuracy is listed as the percentage of successful inhibitory trials (no-go trials in the Go/No-Go task and stop trials in the two Stop Signal Tasks). Mean Response Time is the average response time, in milliseconds, on all successful go trials. In the Go/No-Go task there were 40 total no-go trials for each hemisphere, in the Single Choice SST there were 192 total stop trials for each hemisphere, and in the Forced Choice SST there were 120 stop trials for each hemisphere. In all three tasks, the right hemisphere inhibited on significantly more inhibitory trials compared to the left hemisphere, and in all three tasks the left hemisphere exhibited significantly faster response times.

Task	SSD	Right Hemisphere	Left Hemisphere
Single Choice SST	0ms	84%	75%
	50ms*	94%	59%
	100ms	81%	69%
	150ms	69%	63%
	200ms	53%	34%
	250ms	38%	31%
Forced Choice SST	0ms	100%	85%
	50ms	90%	70%
	100ms*	95%	65%
	150ms*	90%	40%
	200ms*	85%	50%
	250ms*	65%	35%

Table 2. Accuracy data from the single choice Stop Signal Task and the forced choice Stop Signal Task for each Stop Signal Delay (SSD). Accuracy is listed as the percentage of successful inhibitory trials. In the Single Choice SST, there were 32 stop trials presented at each stop signal delay for each hemisphere. In the Forced Choice SST, there were 20 stop trials presented at each stop signal delay for each hemisphere. The '*' after the SSD indicates a significant difference in accuracy between the two hemispheres at the given SSD.

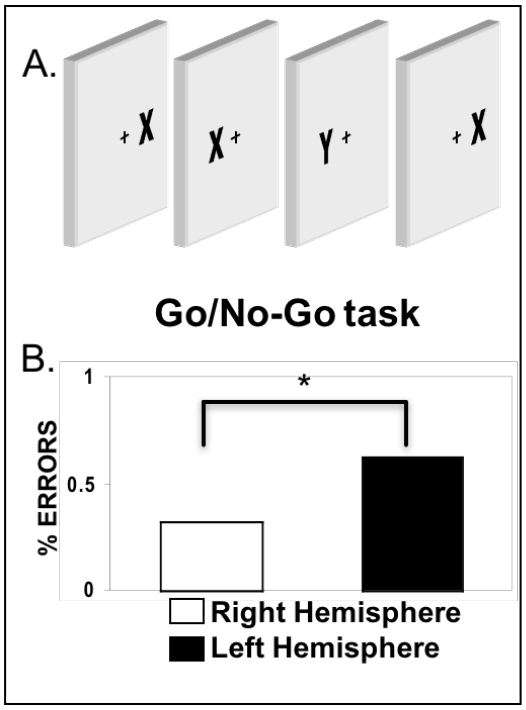

Figure 1. Task design and performance accuracy on no-go trials for the Go/No-go task. A. Task design. X's (go signal) were presented equally often in both left and right visual fields. Presentation of the Y indicated a no-go trial, and the Y's were presented equally often in both left and right visual fields. B. Accuracy data for no-go trials. Right hemisphere (left visual field) performance is plotted as the white bar and left hemisphere (right visual field) performance is plotted as the black bar. The right hemisphere had significantly fewer errors on no-go trials compared to the left hemisphere, as indicated by the *.

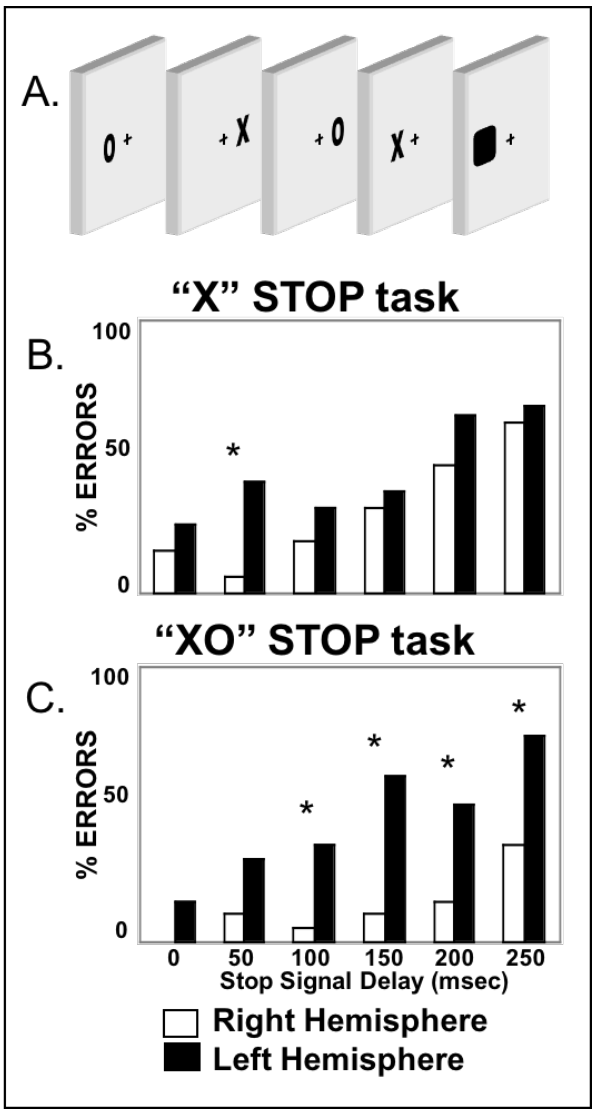

Figure 2. Performance on the two variants of the stop signal task. A. Experimental design of the forced choice stop signal task. Note that the design for the single choice task was identical, except all go stimuli were the letter X. B. Percent error performance on stop trials across the six SSDs for the single choice task. The right hemisphere exhibited significantly fewer errors than the left hemisphere only at SSD length of 50ms, as indicated by the *. C. Percent error performance on stop trials across the six SSDs for the forced choice task. The right hemisphere exhibited significantly fewer errors than the left hemisphere at SSDs of 100ms and greater, as indicated by the *.

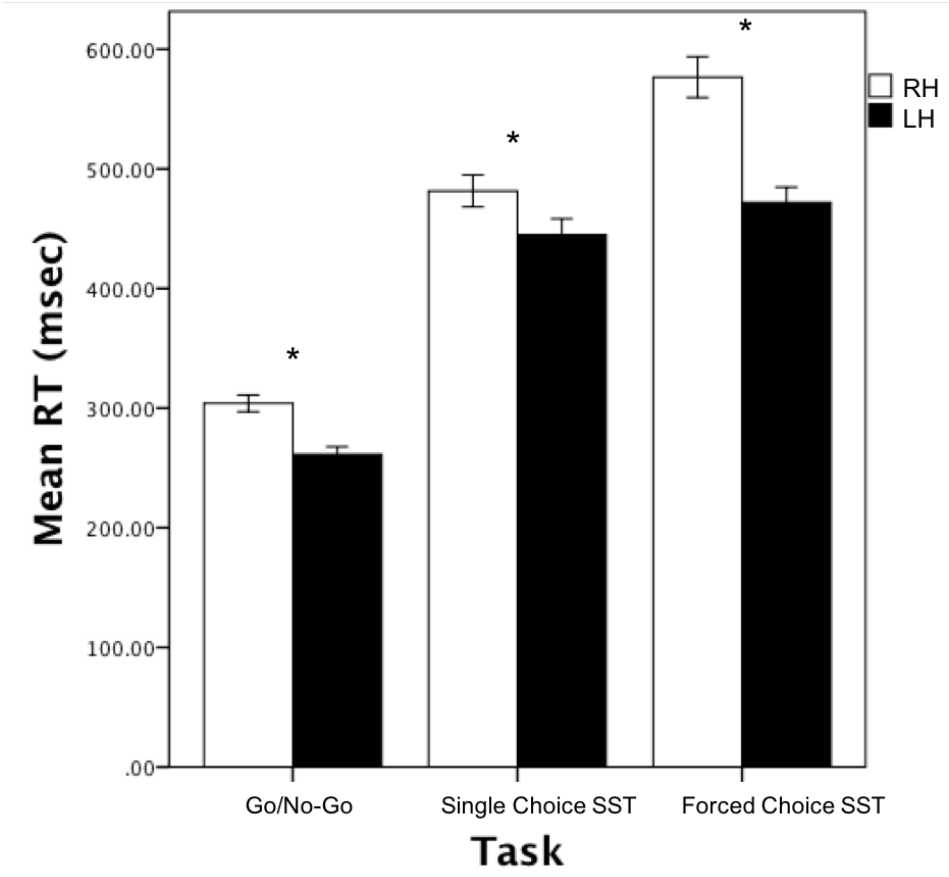

Figure 3. Average response time for all successful "go" trials in the three different tasks are plotted. White bars indicate response times for the right hemisphere ("RH"; stimuli presented in the left visual field) and black bars indicate response times for the left hemisphere ("LH"; stimuli presented in the right visual field). For all three tasks, response times were significantly faster for the left hemisphere, as indicated by the *. Error bars represent +/- 2 standard error.

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CHAPTER THREE

A longitudinal study of inter- and intra-individual differences in stop-related activity

Abstract
Given the maturational patterns of brain development, adolescence is an ideal age to measure the age-related changes in the neural mechanisms of inhibitory control. Here, we examine both the functional correlates of Stop Signal Task performance, and the age-related differences in the functional mechanisms of response inhibition in a large, longitudinal sample. At age 14 and age 19, similar patterns of stop-related activation were associated with task performance. Superior performance was associated with greater right inferior frontal gyrus (rIFG) activation, as well as greater activation in a set of regions potentially involved with a stimulus-detection and attention-orienting system. However, at age 14 stop signal reaction time (SSRT) was also positively associated with default mode network activity, and at age 19 performance was also negatively associated with left amygdala activity. In the absence of within-subject differences in SSRT between ages 14 to 19, there were significant decreases in functional activation associated with successful inhibition. The potential mechanisms by which activity decreases over time while performance remains stable are discussed.
Keywords: Adolescence; Inhibitory Control, Stop Signal Task

INTRODUCTION

Human brain development progresses in a posterior to anterior manner, with the prefrontal cortex being the last area of the brain to mature (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Galvan et al., 2006; Giedd et al., 1999). One of the primary functions of the prefrontal cortex is considered to be inhibitory control (Barkley, 1997; Bick & Nelson, 2016; Bourgeois, Goldman-Rakic, & Rakic, 1994; Miller & Cohen, 2001; Stevens, Kiehl, Pearlson, & Calhoun, 2007). Given this developmental trajectory, there is a period during development when other regions of the brain, such as limbic areas, may be more developed than the prefrontal cortex, and thus behaviors can be guided more from limbic and emotional reactivity with little inhibition. This developmental imbalance typically occurs in the adolescent age, and adolescents can exhibit an increase in impulsive and risk-taking behaviors, poor decision making, and heightened emotional reactivity (Casey, Jones, & Hare, 2008). Improvements in the ability to maintain goal-directed behaviors and inhibit immediate, impulsive responses is considered to reflect prefrontal development and mark the transition out of adolescence (Bedard et al., 2002; Casey et al., 2008; Huizinga, Dolan, & van der Molen, 2006; Ridderinkhof, Band, & Logan, 1999).

Studies examining the development of inhibitory control have found that performance on response inhibition tasks improves through childhood and adolescence, peaking in young adulthood. A common task used to assess inhibitory control is the Stop Signal Task, wherein participants must inhibit an already initiated motor response (Logan & Cowan, 1984; Logan, Cowan, & Davis, 1984). The performance measure of the Stop Signal Task, the stop signal reaction time (SSRT), is an index of the speed by which an individual can

process a stop signal and countermand the preceding motor response. Faster SSRT values indicate a faster stopping process, and reflects superior inhibitory ability. Previous work by Williams and colleagues mapped the performance of 275 participants aged 6 to 81 years on the Stop Signal Task. The researchers found that SSRT decreased until ages 18-29, at which point it plateaued, and then declined later in life (Williams, Ponesse, Schachar, Logan, & Tannock, 1999). Similarly, Huizinga and colleagues found improvements in SSRT through age 15, but performance did not improve after age 21 (Huizinga et al., 2006).

Multiple reports have explored developmental differences in the functional brain activity associated with response inhibition, with many of these studies comparing neural activity between children, adolescents, and adults. A common finding in this literature is that as age increases, less activity in the prefrontal cortex is required to successfully inhibit a motor response (Durston et al., 2006, 2002; Shaw et al., 2006; Urry et al., 2006; Velanova, Wheeler, & Luna, 2008). Children exhibit greater activation than adolescents, and adolescents exhibit greater activation than adults during inhibitory tasks (Velanova et al., 2008). Additionally, Durston and colleagues found widespread decreases in activation from age 9 to 11 in a small-sample longitudinal study of children (Durston et al., 2006). Some researchers hypothesize that the greater activation in younger participants represents the relatively immature architecture of young prefrontal cortex, with greater activation being required to perform the task (Bokura, Yamaguchi, & Kobayashi, 2001; Jonkman, 2006). However, research focused specifically on adolescent age-related changes in functional activation during successful inhibition is relatively sparse.

Research has also explored the neural correlates of response inhibition performance. Notably, studies examining this relationship have found that greater activation in the right inferior frontal gyrus (IFG), the pre-supplementary motor area, and aspects of the basal ganglia are correlated with better inhibitory performance (Chao, Luo, Chang, & Li, 2009; Chikazoe et al., 2009; Congdon et al., 2010; Duann, Ide, Luo, & Li, 2009; Ray Li, 2006; Ray Li, Yan, Sinha, & Lee, 2008; Whelan et al., 2012). Furthermore, in attention deficit hyperactivity disorder (ADHD), in which inhibitory control is significantly impaired, individuals exhibit decreased prefrontal activation relative to nonclinical controls (Casey et al., 1997; Rubia et al., 1999; Rubia, Smith, Brammer, Toone, & Taylor, 2005). However, previous research has failed to examine how the relationship between activation and performance changes over time. It is possible, particularly during adolescence when the prefrontal cortex undergoes substantial developmental change, that the functional correlates of response inhibition performance change as stop-related activity decreases.

The objective of the current study is two-fold. First, the current study will examine inter-individual differences in stop-related activity associated with Stop Signal Task performance. Second, the current study will examine age-related intra-individual changes in the magnitude of stop-related activity, and how these are associated with age-related intra-individual changes in Stop Signal Task performance.

METHODS

Participants

538 participants from the large, longitudinal neuroimaging study, IMAGEN (https://imagen-europe.com) were selected for the current study. Here, data collected at the baseline collection time (target age = 14) and the second follow-up collection time (target age = 19) were examined. Participants were included in the current study if both quality-controlled behavioral and neuroimaging data were available at both time points. The average age of participants at baseline was 14.53 (*SD* = 0.44) years and 19.06 (*SD* = 0.76) at follow-up. The 538 participants were composed of 242 females and 296 males, 472 of whom were right-handed and 66 were left-handed. Participants were equally sampled across the eight different data collection sites of this multi-site European study.

The Stop Signal Task

All participants completed the IMAGEN version of the Stop Signal Task (SST) during functional MRI acquisition at both baseline and follow-up. Standardized hardware for visual stimulus presentation was used at all scanning locations (NordicNeurolabs, www.nordicneurolab.com). On go trials, arrows pointing to the left required a left-hand button response, and arrows pointing to the right required a right-hand button response. For baseline, 80 stop trials were pseudorandomly mixed with 300 go trials, and at follow-up 60 stop trials were pseudorandomly mixed with 300 go trials. Stop trials consisted of an arrow pointing up (stop signal) that quickly followed the go signal. The task used a tracking algorithm wherein the Stop Signal Delay (SSD) was continuously manipulated based on a subject's performance (Logan, Schachar, & Tannock, 1997). The goal of the

tracking algorithm was to arrive at 50% accuracy on stop trials for all participants. The initial stop trial SSD was 150ms, and varied by 50ms based on performance on the previous trial (increasing to make the next stop trial more difficult if the participant successfully inhibited on the previous stop trial and decreasing to make the next stop trial easier if the participant failed to successfully inhibit on the previous stop trial). Stop Signal Reaction Time (SSRT) was computed as described previously (Whelan et al., 2012) and involved subtracting the median SSD of all successful stop trials from the nth percentile go reaction time, where n represents the percentage of successful inhibitions.

Quality control for neuroimaging data at both collection times excluded images that contained excessive motion (i.e., mean framewise displacement > 0.9mm as indicated by Siegel et al., 2014). Stop Signal Task performance quality control was performed on follow-up data in accordance with Congdon et al., 2012 (i.e. >50ms SSRT, percent successful inhibition between 25% and 75%, less than 10% erros on go trials, and fewer than 10 stop trials in which the participant responded before the onset of the go signal). For quality control of task performance at baseline, please refer to (Whelan et al., 2012). Any participants that failed to meet performance or neuroimaging data requirements were excluded from the study.

FMRI Acquisition and Analysis

MRI was performed at the eight IMAGEN assessment sites (London, Nottingham, Dublin, Mannheim, Dresden, Berlin, Hamburg, and Paris) with 3T whole body MRI systems made by four manufacturers (Siemens: 4 sites, Philips: 2 sites, General Electric: 1 site, and

Bruker: 1 site). For structural images, high-resolution anatomical MRIs were acquired with three-dimensional T1 weighted magnetization prepared gradient echo sequence (MPRAGE), with 2300ms TR and slice thickness of 1.1mm. For functional images, blood oxygenation level dependent (BOLD) fMRI images were acquired with a gradient-echo echoplanar image sequence using a relatively short echo-time, with 2200ms TR and slice thickness of 2.4mm. Image acquisition parameters were held constant across all sites to ensure comparison of fMRI data across the different image acquisition facilities. Image acquisition parameters were also held constant from baseline to follow-up. Full a full description of the MRI acquisition, quality control procedures, and multi-site standardization, see Schumann et al., 2010.

Baseline and follow-up images were processed using the same protocol. Functional image processing included realignment, slice-timing correction, movement correction, non-linear warping into MNI space using a custom EPI template, and Gaussian-smoothing at 5mm full width half maximum. The custom EPI template was constructed as an average template of images collected from both baseline and follow-up to ensure warping was equal across both sampling times. Using automatic spike detection, any time points containing artifact were regressed out of each subject's data. All first level analysis contrast images were generated using Statistical Parametric Mapping (SPM) version 8.

Activation contrast images were computed using a general linear model with an auto-regressive noise model. Based on behavioral records relative to each collection time, each participant's design matrix included regressors for the different trials in the task and six motion regressors (3 for translational and 3 for rotational movement) included as nuisance variables. Regressors modeling the experimental conditions were convolved using SPM's

default hemodynamic response function. Task condition regressors included stop success trials, stop failure trials, trials on which the go response was too late and trials on which the go response was wrong (if any). Contrast images were generated for successful stops (stop success) against the implicit baseline of the go success condition while removing variance associated with the other regressors in the design matrix, as this has been the model used previously on the IMAGEN dataset (Whelan et al., 2012). For all contrast images, intensity in each voxel represents the estimated percent BOLD signal change associated with the regressor.

Statistical Analysis

Univariate t-tests were used to measure baseline and follow-up stop-related activity against zero (i.e., the null hypothesis of no task-induced activation). Paired-sample t-test was used to measure the within subject change in stop-related activity from baseline to follow-up. Linear regressions were performed separately at baseline and follow-up to measure the stop-related activity associated with SSRT derived from behavioral data at the respective collection time. Additionally, the relationships between change in stop-related activity from baseline to follow-up and change in SSRT from baseline to follow-up were tested. For these analyses, voxel-wise analysis were performed, restricted to a grey matter mask, using the AFNI software program 3dttest++ (Cox, 1996). Correction for multiple comparisons was employed using the optional 3dttest++ input "clustsim," yielding unique significant cluster thresholds for each analysis (reported in the results). For linear mixed effects, AFNI's 3dLME was used to explore the difference from baseline to follow-up in the correlation between SSRT and stop-related BOLD activation.

RESULTS

Demographic and behavioral data

Within subject age-related changes in SSRT were tested to examine if inhibitory control improved from baseline to follow-up. To test within subject effects, repeated measures analysis of covariance (ANCOVA) was performed with SSRT as the dependent variable, data collection time as a repeated measure, and age at baseline, change in age from baseline to follow-up, sex, site of scan acquisition, and handedness as covariates. SSRT at baseline (M = 216.19, SD = 36.33) was not significantly different than SSRT at follow-up (M = 210.12, SD = 36.42; $f(1, 526) = 0.801$, $p = 0.37$). Thus, any age-related differences in stop-related activity are interpreted in light of an absence of age-related changes in task performance.

Stop-related activity at baseline and at follow-up

Separately for each collection time, all 538 participants' activation were included in a group level t-test against zero, with age, sex, site of scan acquisition, and handedness included as covariates. Displayed in Figure 1, the activation and deactivation patterns for subjects at baseline and follow-up are qualitatively quite similar.

Changes in stop-related activity from baseline to follow up

To examine quantitatively the within-subject change in the magnitude of activation during successful stop trials between baseline and follow-up, a voxel-wise whole-brain paired sampled t-test was performed using AFNI 3dttest++. Age at baseline, change in age from baseline to follow-up, sex, site of scan acquisition, and handedness were included as

covariates in the t-test. At a whole-brain correction for false discovery rate of $\alpha < 0.05$, the "clustsim" option in AFNI 3ddttest deemed clusters of at least 32 contiguous voxels significant if all voxels in the cluster exhibited difference in activation at a level of $\alpha < 0.001$.

Multiple regions displayed a significant decrease in stop-related activity from baseline to follow-up, and one region displayed a significant increase in stop-related activity from baseline to follow-up (Figure 2; Figure 3; Table 1). Significant clusters displaying an age-related decrease in activation were observed in the dorsal aspects of the right and left inferior frontal gyri, the right and left parietal lobules, a midline occipital region including aspects of the primary visual cortex, the pre-supplementary motor area, the right superior frontal gyrus, and a region that included aspects of both the right inferior frontal gyrus and the right anterior insula. An age-related increase in activation was observed in a cluster including regions of both the left inferior frontal gyrus and the left anterior insula.

Baseline BOLD correlates of SSRT

A voxel-wise whole-brain linear regression was performed to identify baseline stop-related activity correlated with baseline SSRT. AFNI 3dttest++ was used including baseline SSRT as the independent variable and baseline age, sex, site of scan acquisition, and handedness as covariates in the model. For this analysis, with a whole-brain correction for false discovery rate at $\alpha < 0.05$, the "clustsim" option yielded a significance cluster threshold of 33 contiguous voxels in which all voxels displayed a correlation level of $\alpha < 0.001$. Three significant clusters emerged from this analysis (Figure 4, Table 1). In a cluster in the right

occipital cortex and a cluster encompassing regions in both the right inferior frontal gyrus and the right anterior insula, there were significant negative correlations between stop-related activity and SSRT. These regions typically exhibit positive activation during successful stopping (See Figure 1), thus greater activity in these regions was associated with faster SSRT. In the ventral medial prefrontal cortex (vmPFC), there was a significant positive correlation between stop-related activity and SSRT. Post-hoc activation extraction revealed the vmPFC typically is deactivated during successful stopping (see Supplemental Figure 1). The positive correlation with SSRT indicates faster SSRT is associated with greater deactivation in this region, whereas slower SSRT is associated with less deactivation in this region.

Follow-Up BOLD correlates of SSRT

A separate linear regression was performed to examine follow-up stop-related activity associated with follow-up SSRT. A voxel-wise whole-brain linear regression was performed using AFNI 3dttest++, including follow-up SSRT as the independent variable, and follow-up age, sex, site, and handedness as covariates in the model. With a whole-brain correction for false discovery rate at $\alpha < 0.05$, the "clustsim" threshold for significant clusters was 31 contiguous voxels in which all voxels displayed a correlation with SSRT at a level of $\alpha < 0.001$. Five significant clusters emerged from this analysis, all exhibiting a negative correlation with SSRT (Figure 5, Table 1). The significant clusters include: large, bilateral clusters encompassing the occipital cortex and aspects of the anterior lobe of the cerebellum, a cluster in the midline thalamus, a left subcortical cluster including the amygdala and surrounding tissue, and a cluster including aspects of the right inferior frontal

gyrus and the anterior insula. The negative correlation between activation in all clusters and SSRT indicates greater activation in these regions was associated with faster SSRT.

Sub-threshold overlap between Baseline and Follow-up Correlates of SSRT

Some regions that display a significant relationship between SSRT and stop-related BOLD activation at baseline also demonstrate a similar relationship at follow-up, while other regions appear to be unique to their respective collection time. For example, both baseline and follow-up analyses reveal correlations in the right inferior frontal gyrus and anterior insula, as well as areas of the right occipital cortex. However, some correlates appear to be unique, such as the vmPFC is only correlated with SSRT at baseline, and the left occipital, left subcortical, and thalamus only exhibit a correlation at follow-up. To probe the degree to which these relationships are unique to each time-point, the correlation thresholds at each collection time were reduced to $\alpha < 0.005$, and cluster threshold size was kept at 33 voxels for baseline and 31 voxels for follow-up (thus these are uncorrected for whole-brain comparisons). At this lower threshold, baseline correlates of SSRT also include bilateral occipital regions and the thalamus, but not the left subcortical region (Figure 6). For follow-up, the lower threshold correlates of SSRT do not yield effects in the vmPFC. Thus, it is possible that only the vmPFC is a unique baseline correlate of SSRT and only the left subcortical region is a unique follow-up correlate of SSRT, whereas the other regions are correlated, albeit subthreshold, with SSRT at both collection times.

Whole-Brain Linear Mixed Effects

Next, an analysis was performed to examine regions in the brain where the correlation between stop-related BOLD activity and SSRT changed significantly from baseline to follow-up. For this analysis, a linear mixed effects model was computed voxel-wise across the whole brain using AFNI 3dLME. This model explores regions that exhibit an interaction between SSRT and Collection Time (baseline and follow-up) on stop-related BOLD activity. With a whole-brain correction for false discovery rate at $\alpha < 0.05$ the AFNI command "3dClustSim," computed interaction effects significant if at least 121 contiguous voxels exhibited an effect of at least $\alpha < 0.001$. There were no significant clusters showing an interaction effect between Collection Time and SSRT, suggesting there were not significant within-subject changes in the correlation between stop-related BOLD activity and SSRT from baseline to follow-up.

Changes in stop-related BOLD activity correlation with changes in SSRT

A secondary analysis was performed measuring the relationship between the change in stop-related activity from baseline to follow-up and the change in SSRT from baseline to follow-up. Using AFNI 3dttest++, the effect of change in SSRT from baseline to follow-up was examined on the difference in stop-related activity from baseline to follow-up. Baseline SSRT, age at baseline, change in age from baseline to follow-up, sex, site of scan acquisition site, and handedness were also included in the model as covariates. The "clustsim" option in AFNI 3dttest++, with a false discovery rate correction at $\alpha < 0.05$, yielded significant clusters of 31 contiguous voxels, in which each voxel exhibited the examined relationship at a level of $\alpha < 0.001$.

Three clusters exhibited a significant relationship, all demonstrating a negative correlation between change in stop-related BOLD activation and change in SSRT. Clusters were found in the right and left occipital cortex, and one cluster was found in a left subcortical region including aspects of the parahippocampal gyrus, amygdala, and ventral striatum (Figure 7). This data suggests that a decrease in SSRT from baseline to follow-up is associated with an increase in activity in these regions, while an increase in SSRT from baseline to follow-up is associated with a decrease in activity in these regions (See supplemental figure 3). Thus, individuals that showed improvements in SSRT from baseline to follow-up (decrease in SSRT) also showed increases in stop-related activity in these regions.

DISCUSSION

The goal of the current study was to examine the age-related changes in the neurobiological mechanisms of response inhibition using a longitudinal sample of adolescents. Given the literature regarding the development of inhibitory control, and what is currently understood about the maturational patterns of brain development, adolescence is a particularly interesting age to examine age-related changes in this domain. Here, Stop Signal Task performance and functional activation from successful stop trials in 538 adolescents were examined at age 14 and again at age 19.

Although there were no significant within-subject changes in performance, participants exhibited widespread age-related decreases in the magnitude of activation required to inhibit an already initiated motor response, and one region demonstrated an age-related increase in activation over time. The functional correlates of performance at baseline remained qualitatively similar at follow-up, with the exceptions that activation in the vmPFC was only significantly correlated with performance at baseline and activation in a left subcortical region was only significantly correlated with performance at follow-up. However, a whole-brain linear mixed effects exhibited no interaction between collection time and SSRT, suggesting that collection time did not significantly moderate the relationship between performance and activation. Lastly, three regions exhibited a significant relationship between the change in activation and change in performance from baseline to follow-up, suggesting an increase in activity in these specific regions was associated with slight improvements in task performance.

With the lack of within-subject, age-related differences in SSRT, the results should be interpreted in the context of no observable change in inhibitory control across the sample. Interestingly, although there is no age-related improvement in task performance, there is an age-related decrease in the magnitude of activation during successfully inhibited stop trials in bilateral dorsal IFG, bilateral parietal lobules, a midline occipital region, the presupplemtary motor area, the right SFG, and a region including aspects of both the right IFG and right anterior insula. Interestingly, these are regions that demonstrate a positive BOLD signal change during successful stop trials at both time points (see Figure 1 and

Figure 3), indicating they may be meaningfully involved in response inhibition. Therefore, these effects are not likely a decrease of excessive or irrelevant brain activation over time.

The absence of within-subject changes in performance coupled with decreased activation suggests that as individuals age from 14 to 19 years, less activation is required to achieve the same level of inhibitory control, and thus the neural mechanisms of response inhibition may become more efficient over time. These results agree with previous reports by Durston and colleagues demonstrating an age-related decrease in magnitude of activation (Durston et al., 2006, 2002). However, Durston examined children (9-11 years), whereas the current study examined adolescents. It is possible that the age-related decreases in stop-related activity begin before adolescence and continue into young adulthood. The lack of within-subject improvements in task performance is not surprising given that previous reports have also noted a plateau in improvements during this age period (14-19 years) with performance on the Stop Signal Task peaking in young adulthood (Huizinga et al., 2006; Williams et al., 1999). The current study adds to these previous reports in that the results here suggest that despite the plateau in behavioral improvement in inhibitory control, the neural mechanisms associated with response inhibition continue to exhibit age-related changes.

Additionally, an increase in stop-related activity was observed in the left IFG and anterior insula from baseline to follow-up. This was the only region in the brain to exhibit a significant age-related increase in stop-related activity. The left IFG has previously been reported to play an important role in response inhibition (Swick, Ashley, & Turken, 2008).

Some researchers have also found age-related increases in left hemisphere activation during successful response inhibition in adult samples (Cabeza et al., 1997; Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Nielson, Langenecker, & Garavan, 2002). This result could reflect a delayed maturation of the left hemisphere's role in response inhibition. While others have demonstrated an age-related increase in left IFG response inhibition activity in adults, Durston and colleagues found an age-related increase in right IFG response inhibition activity in children (Durston et al., 2006). Additionally, it has been argued that the right hemisphere develops relatively earlier than the left hemisphere (Thatcher, Walker, & Giudice, 1987). Thus, the age-related increase in left IFG and anterior insula stop-related activity found here may reflect similar, but relatively delayed, developmental patterns as previously reported for the right IFG (Durston et al., 2006).

The functional correlates of SSRT at baseline and follow-up are, for the most part, qualitatively similar. At baseline, SSRT was negatively correlated with aspects of the right IFG and anterior insula, and a region in right occipital cortex, and SSRT was positively correlated with a region in the vmPFC. At follow-up, SSRT was negatively correlated with bilateral occipital regions, aspects of the thalamus, the right IFG and anterior insula, and a left subcortical region including aspects of the parahippocampal gyrus and the amygdala. However, at slightly lower thresholds, all but the vmPFC and left subcortical regions exhibit correlations at both time points. Thus, the right IFG and anterior insula, occipital regions, and the thalamus may be developmentally stable correlates of performance. All relationships between SSRT and these regions are negative, and indicate that greater activity in these regions is associated with better performance (faster SSRT). The

combination of occipital, thalamic, and anterior insula regions may represent a functionally interconnected set of regions involved with salience detection in top-down control for goal-directed behavior. These areas have been included in a proposed network of regions that work to direct attention towards goal-relevant stimuli (Corbetta & Shulman, 2002; Uddin, 2014). Thus, these regions may be working to direct attention towards the change in goal behavior represented by the presentation of the stop signal (i.e. a change from responding to not responding).

Because the vmPFC is considered a part of the Default Mode Network (DMN; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001), the positive relationship between SSRT and vmPFC activity at baseline may reflect task-related deactivation of the DMN. The DMN is considered a functionally connected set of regions that are active during the absence of an extraneous task. During task-directed behavior, the activity in the DMN is thought to decrease, allowing the task-relevant areas to execute the required behavior. This notion is supported here, as less deactivation in the vmPFC at baseline was correlated with worse performance on the task, suggesting individuals who were unable to deactivate the vmPFC upon presentation of the stop signal performed poorly. Interestingly this relationship was not apparent at follow-up, suggesting that individuals were more able to deactivate the DMN and activate the task-relevant regions during successful response inhibition.

The left subcortical area that included the amygdala as well as aspects of the parahippocampal gyrus and ventral caudate was negatively correlated with SSRT only at

follow-up. Additionally, a similar region showed a significant relationship between change in activation and change in SSRT, indicating an increase in activity from baseline to follow-up was related to an improvement in performance. The amygdala has been associated with relevance detection, particularly with stimuli or input that is considered fearful (Anderson & Phelps, 2001). However, some reports have argued that the role of the amygdala extends beyond detection of fearful stimuli and can be generalized to detection of goal-relevant novel stimuli (Ousdal et al., 2008; Sander, Grafman, & Zalla, 2003). The combination of findings of age-related increases in activity associated with age-related decreases in SSRT and greater activity associated with faster SSRT at follow-up suggest that better detection of the stop signal through a mechanism involving the amygdala leads to better response inhibition.

Stop-related activity in the right IFG and anterior insula exhibited a negative correlation with SSRT at baseline and at follow-up, but also showed a significant decrease in activity over time. Although the magnitude of stop-related activity decreases with age, this area appears to be a developmentally stable correlate of response inhibition performance. We hypothesize that the decrease in magnitude of functional activation may coincide with an increase in the degree of functional connectivity among the regions involved with this task. Particularly with the right IFG and anterior insula, although there is significantly less activity at follow-up, the activity remains correlated with performance. A stronger functional connection among the right IFG and anterior insula and other regions in the task may compensate for the loss of activity over time while maintaining the correlation with performance. Future studies should explore the development of the functional connections

with the right IFG and anterior insula during successful response inhibition throughout adolescence.

The results from the current report also indicate a potential area of concern. Although there is vast activation associated with successful stop trials (see Figure 1), little of this activity is correlated with task performance at either collection time. It is possible there are multiple factors that contribute to these sparse effects. First, it may be the case that amplitude of activation is not the ideal metric for capturing individual differences in response inhibition. Rather, individual differences in task performance may best be captured by the functional connectivity among a set of regions involved with the task. Also, it is possible that not including the unsuccessful stop trials while examining individual differences neglects meaningful differences in activity. The difference in activation between successful and unsuccessful stop trials may inform how some individuals perform better on this task than others.

Lastly, a better measure of activation, rather than average BOLD signal change for all successful stop trials, may provide a better representation of individual differences. In the Stop Signal Task, an algorithm adapts the difficulty of the trials to meet the participants' abilities. Superior inhibitors can inhibit trials with longer stop signal delays, while poor inhibitors are only able to inhibit trials with shorter stop signal delays. The maximum successful stop signal delay from a superior inhibitor will be longer than that of a poor inhibitor. However, when stop-related BOLD activity is captured, this variance is somewhat neglected as only the average activity from all successfully inhibited stop trials

is included. It is possible that the important variance that explains individual differences in performance is associated with the maximum performance a participant can achieve, and this variance is attenuated by only extracting the average activation. Or it is possible that another metric, such as the increase in activation based on stop signal delay length, would capture these subtle individual differences as well. Regardless, we believe a better measure of stop-related activity would better capture individual differences in response inhibition.

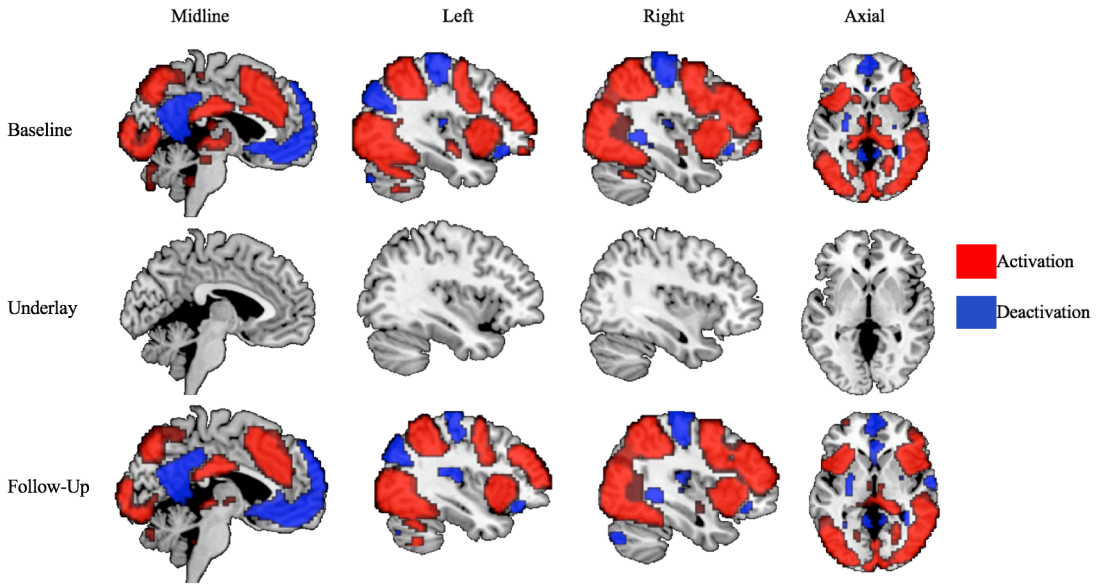


Figure 1. Whole-brain activation and deactivation patterns for successful stop trials at baseline and follow-up. Positive changes in percent BOLD signal change are depicted in red ("activation"), and negative changes are depicted in blue ("deactivation"). A mid-sagittal, left sagittal, right sagittal, and axial at the level of the basal ganglia underlays are used for anatomical reference.

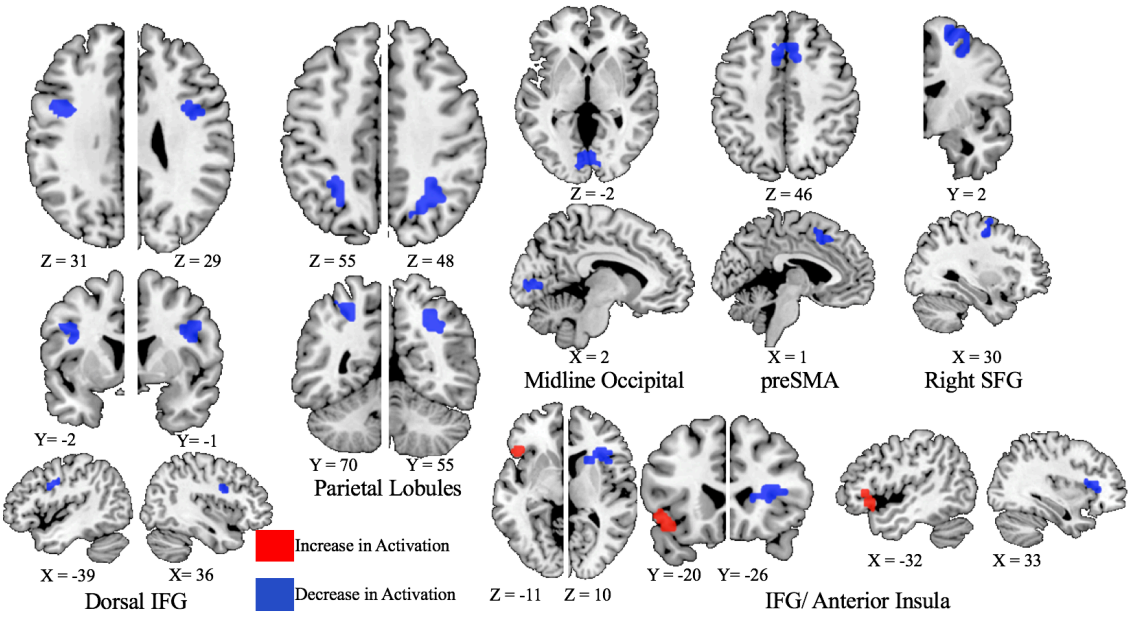


Figure 2. Results from the paired-sample t-test comparing stop-related activity at baseline and follow-up. The clusters depicted are those that survived whole-brain FDR correction using the "clustsim" option in AFNI 3dttest++ at a level of $\alpha < 0.05$. All voxels within these significant clusters exhibit a difference in activity ($t = 3.296$, $p < 0.001$). Regions that exhibit a significant decrease in stop-related activity from baseline to follow-up are presented in blue, and regions that exhibit a significant increase in stop-related activity from baseline to follow-up are presented in red. Please refer to Table 1 for size, in voxels, of these clusters along with the MNI coordinates of local maxima. See Figure 3 for graphical representation of age-related changes in BOLD activity in these regions.

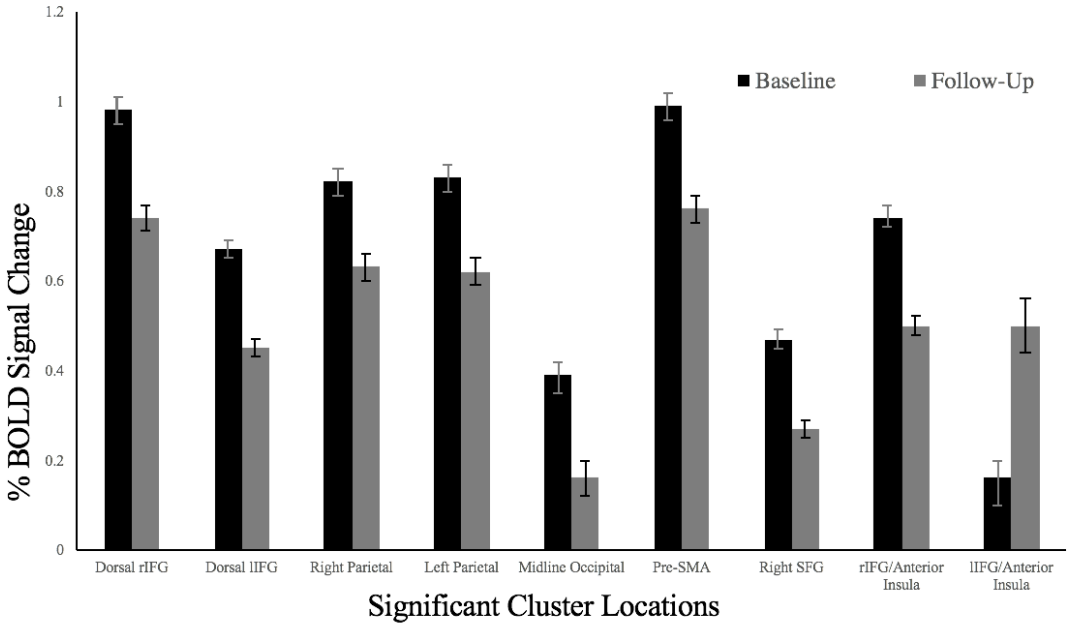


Figure 3. Significant clusters exhibiting an age-related change in stop-related BOLD activity. For each region, average activation across all 538 participants was extracted at baseline and follow-up. Error bars represent +/- one standard error. In all regions except for the lIFG/Anterior Insula, there was a significant decrease in activation from baseline to follow-up, and in the lIFG/Anterior Insula there was a significant increase in activation from baseline to follow-up. Please refer to Figure 2 in the main text for visual representation of these regions.

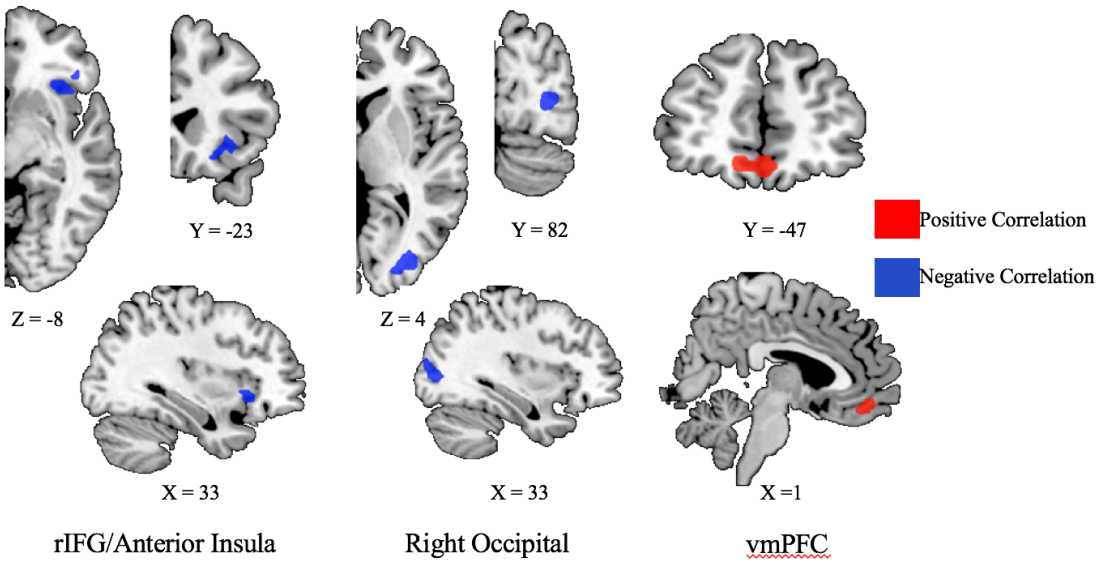


Figure 4. Stop-related BOLD activity correlated with SSRT at baseline. All three significant clusters survived whole-brain FDR correction using the "clustsim" option in AFNI 3dttest++ at a rate of $\alpha < 0.05$. Each voxel exhibited a significant correlation with SSRT at least at a level of $t = 3.277$, $p < 0.001$. Regions in blue depict areas that are negatively correlated with SSRT, thus greater activity in these regions is associated with shorter, faster SSRT. The vmPFC is positively correlated with SSRT, and greater deactivation is associated with faster SSRT. For cluster size and MNI coordinates of local maxima, refer to Table 1.

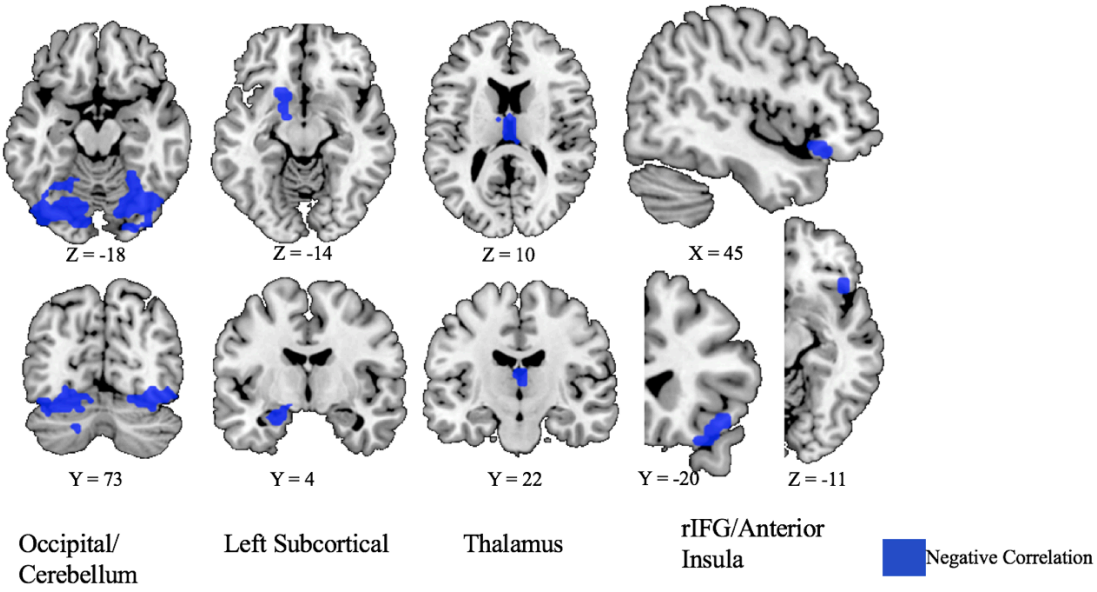


Figure 5. Stop-related BOLD activity correlated with SSRT at follow-up. All significant clusters survived whole-brain FDR correction using the "clustsim" option in AFNI 3dttest++ at a rate of $\alpha < 0.05$. Each voxel exhibited a significant correlation with SSRT at least at a level of $t = 3.277$, $p < 0.001$. All regions are presented in blue as they are areas that are negatively correlated with SSRT, thus greater activity in these regions is associated with shorter, faster SSRT. For cluster size and MNI coordinates of local maxima, refer to Table 1.

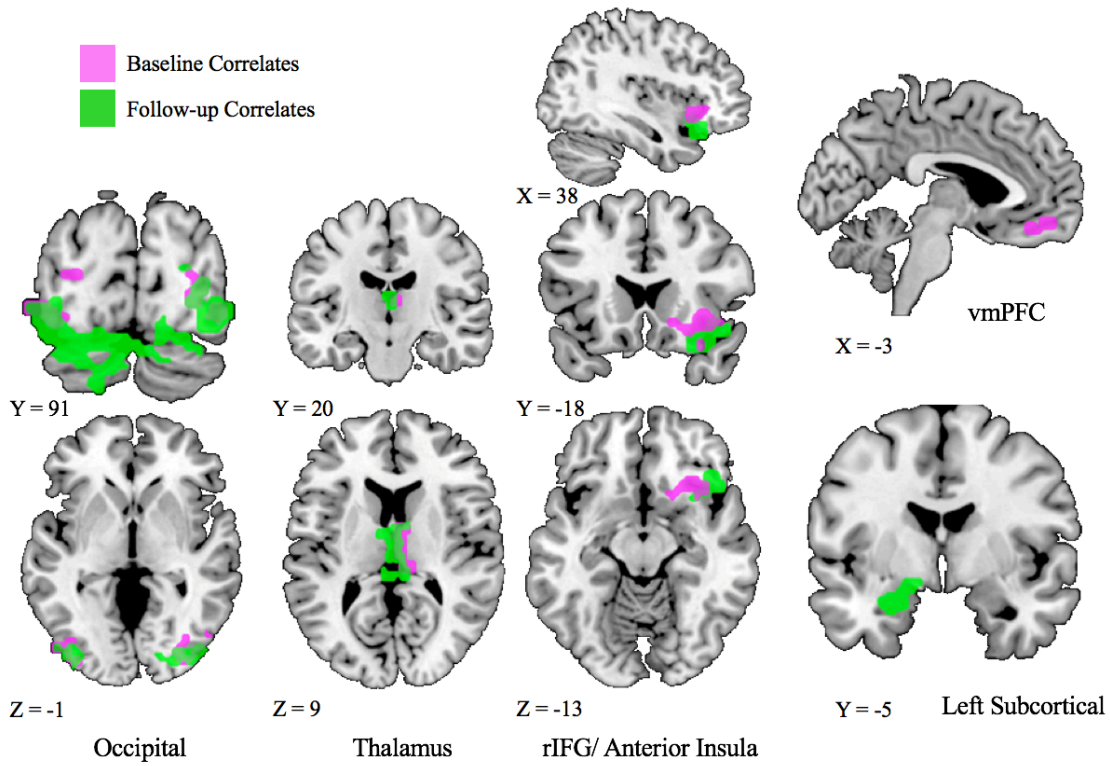


Figure 6. Subthreshold correlates of SSRT at baseline (purple) and follow-up (green). When reducing the effect of SSRT correlation on stop-related activity from $\alpha < 0.001$ to $\alpha < 0.005$, the similar correlates of performance are found at baseline and follow-up. All regions, except for the vmPFC, exhibit a negative correlation with SSRT. At the lower threshold, SSRT is correlated with baseline and follow-up activity in bilateral occipital regions, midline thalamus, and right inferior frontal gyrus and anterior insula, with considerable overlap between the baseline and follow-up correlates. Activity is only correlated with SSRT in the vmPFC at baseline and in the left subcortical region at follow-up.

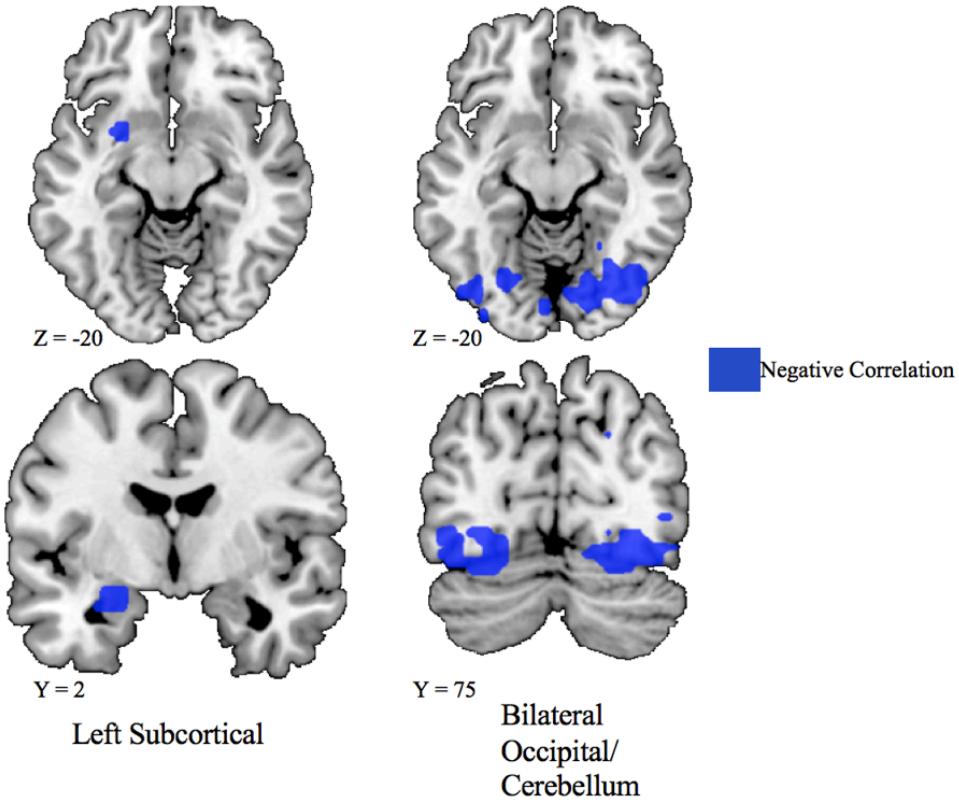
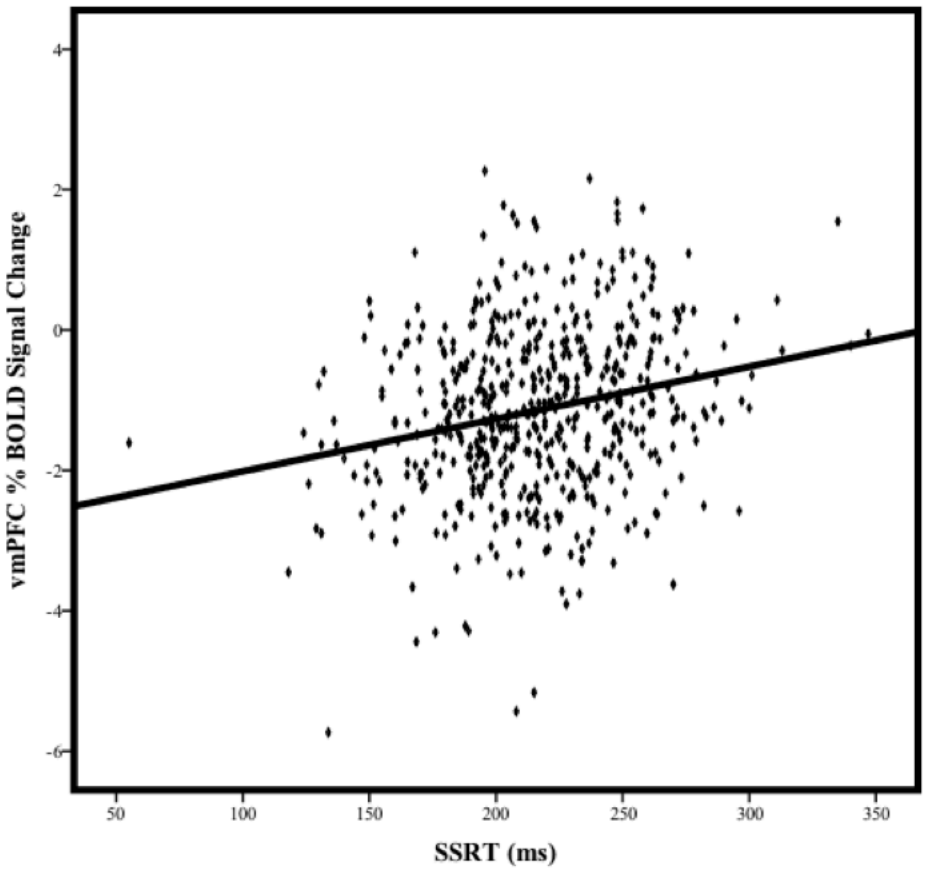


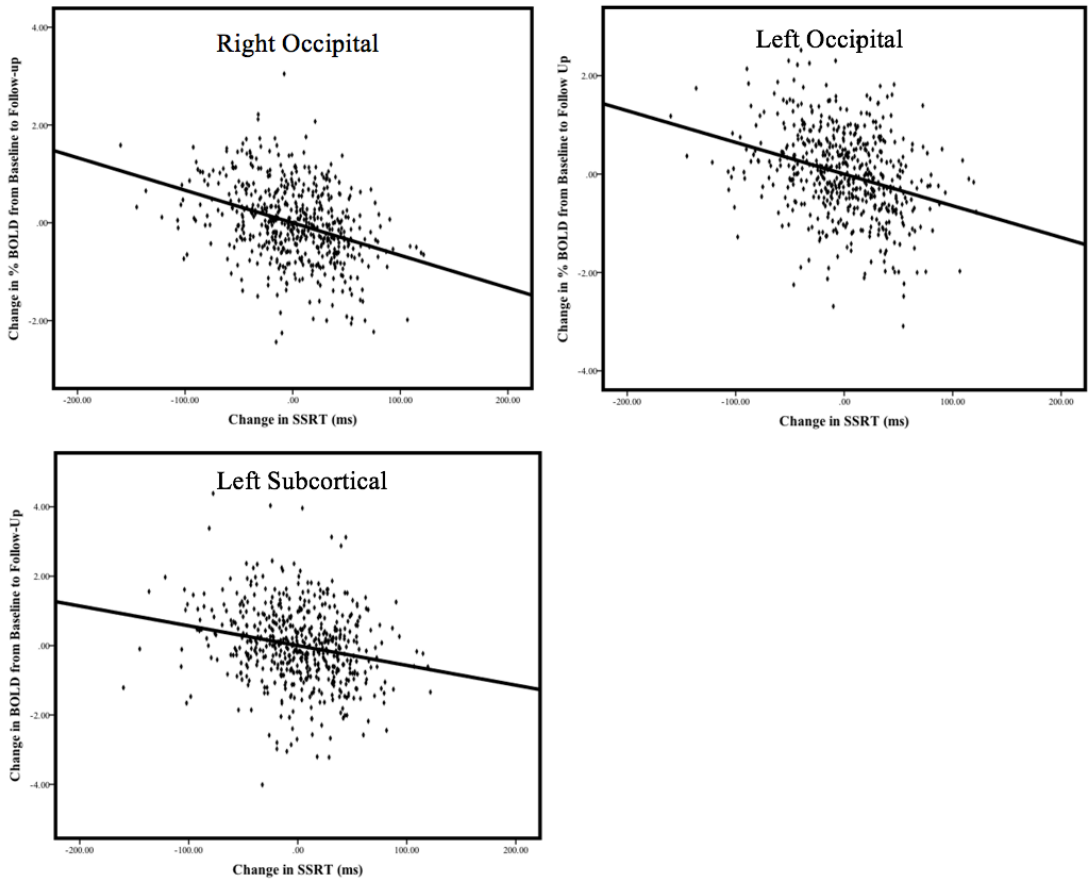
Figure 7. Correlation between the change in SSRT from baseline to follow-up and the change in stop-related BOLD activity from baseline to follow up. All significant clusters survived whole-brain FDR correction using the "clustsim" option in AFNI 3dttest++ at a rate of $\alpha < 0.05$. Each voxel exhibited a significant correlation with SSRT at least at a level of $t = 3.296$, $p < 0.001$. Age-related change in activation in the three regions is negatively correlated with age-related change in SSRT. Refer to supplemental figures 3 for a graphical representation of these relationships.

Analysis	Cluster Anatomical Region	Peak Coordinates (MNI - X, Y, Z)	Cluster Size # of Voxels
Age-Related Changes	dorsal left inferior frontal gyrus	-39, -2, 31	163
	midline occipital	0, 79, -2	77
	right superior frontal gyrus	30, 4, 67	71
	pre-supplementary motor area	0, -26, 46	68
	left parietal lobule	-30, 70, 55	66
	right parietal lobule	30, 55, 40	65
	right inferior frontal gyrus / ant. insula	33, -26, 10	62
	right dorsal inferior frontal gyrus	36, -8, 31	45
	left inferior frontal gyrus / ant. insula	-32, -20, -11	32
Baseline Correlates of SSRT	right inferior frontal gyrus / ant. insula	33, -23, -8	51
	right occipital cortex	33, 82, 4	48
	ventral medial prefrontal cortex	0, -47, -14	34
Follow-Up Correlates of SSRT	right occipital / cerebellum	30, 73, -17	528
	left occipital / cerebellum	-30, 73, -20	506
	midline thalamus	0, 22, 10	96
	left parahippocampal / amygdala / striatum	-15, 4, -14	54
	right inferior frontal gyrus / ant. insula	45, -20, -11	39
ΔBOLD Correlates of ΔSSRT	right occipital	24, 76, -17	853
	left occipital	-30, 73. -20	211
	left subcortical	-27, 1, -20	31

Table 1. List of significant clusters from 1) Within subject change in stop-related activity from baseline to follow-up, 2) functional correlates of SSRT at baseline, 3) functional correlates of SSRT at follow-up, and 4) the correlates between the age-related changes in BOLD stop-related activity and SSRT. MNI coordinates of local maxima within the cluster and size in number of voxels is also listed for each cluster. These details for each cluster correspond to the clusters expressed in Figures 2, 3, 4, and 5, respectively.



Supplemental Figure 1. Activation of the vmPFC at baseline regressed against baseline SSRT. The depicted values represent the adjusted relationship after accounting for age, sex, site of scan acquisition, and handedness as covariates. Faster SSRT are correlated with greater deactivation of the vmPFC during successful stop trials.



Supplemental Figure 2. Correlation between change in SSRT and change in stop-related BOLD activation in three significant clusters. Both calculations were performed as Change = Follow-up – Baseline, thus negative values indicate an age-related decrease in the measurement. The depicted values represent the adjusted relationship after accounting for baseline age, change in age from baseline to follow-up, baseline SSRT, sex, site of scan acquisition, and handedness as covariates. In all three regions, a decrease in SSRT was associated with an increase in activation, whereas an increase in SSRT is associated with a decrease in activation.

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CHAPTER FOUR

Individual differences in stop-related activity are inflated by the adaptive algorithm in the Stop Signal Task

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Abstract
Research using the Stop Signal Task employing an adaptive algorithm to accommodate individual differences often report inferior performance on the task in individuals with ADHD, OCD, and substance use disorders compared to non-clinical controls. Furthermore, individuals with deficits in inhibitory control tend to show reduced neural activity in key inhibitory regions during successful stopping. However, the adaptive algorithm systematically introduces performance-related differences in objective task difficulty that may influence the estimation of individual differences in stop-related neural activity. This report examines the effect that these algorithm-related differences have on the measurement of neural activity during the stop signal task. We compared two groups of subjects (n = 210) who differed in inhibitory ability using both a standard fMRI analysis and an analysis that resampled trials to remove the objective task difficulty confound. The results show that objective task difficulty influences the magnitude of between-group differences and that controlling for difficulty attenuates stop-related activity differences between superior and poor inhibitors. Specifically, group differences in the right inferior frontal gyrus, right middle occipital gyrus, and left inferior frontal gyrus are diminished when differences in objective task difficulty are controlled for. Also, when objective task difficulty effects are exaggerated, group differences in stop related activity emerge in other regions of the stopping network. The implications of these effects for how we interpret individual differences in activity levels are discussed.

Keywords: response inhibition; stop signal delay; objective task difficulty

INTRODUCTION

The ability to inhibit unwarranted behaviors and thoughts is considered a major component of executive functioning (Barkley 1997). Inhibitory control is thought to be the central deficit in attention deficit hyperactivity disorder (ADHD; Casey et al. 1997; Quay 1997; Slaats-Willemse et al., 2003), and is also impaired in substance use disorders (Nigg et al., 2006; Whelan et al., 2012) and obsessive compulsive disorder (OCD; Penades et al., 2007). In the laboratory, tasks examining aspects of motor response inhibition have been used to assess inhibitory control and identify impairments in this domain, and therefore it is critical that such tasks accurately describe inter-individual differences so that pathologies associated with impairments can be characterized appropriately.

The Stop Signal Task (SST; Logan & Cowan, 1984) has, to a large extent, been a hallmark assessment for inhibitory control in neuroimaging and neurophysiological research. The SST is composed of go and stop trials. On go trials, the participant must respond rapidly via a button press to a "go signal." However, on a minority of trials (stop trials; typically 20-25% of trials), the go signal will be followed by a "stop signal," indicating that the individual should attempt to countermand the already initiated response. On stop trials, the interval between the onset of the go signal and the onset of the stop signal is known as the stop signal delay (SSD), and this delay will determine the difficulty of successful inhibition. If the SSD is short (i.e. the stop signal appears very soon after the go signal is presented) it is easier to inhibit the motor response, and if the SSD is long it is more difficult to inhibit the motor response (Logan, 1994).

Often the SST employs an adaptive algorithm tracking procedure in which a participant's performance dictates the SSD of the subsequent stop trial to reach an SSD that elicits 50% stopping accuracy. In the tracking procedure, successful stopping results in a longer SSD in the following stop trial, which reduces the probability of successful inhibition, and unsuccessful stopping results in a shorter SSD in the following stop trial, which increases the probability of successful inhibition. By equating accuracy on stop trials across all participants at approximately 50%, it is possible to quantitatively compare inhibitory abilities across participants. The tracking procedure allows for simple calculation of the Stop Signal Reaction Time (SSRT), or the time required to inhibit an already initiated motor response (Logan, Schachar, & Tannock, 1997). The SSRT is an indirect measure of inhibitory ability and commonly used as the main outcome variable of the SST.

Numerous neuroimaging and neurophysiological studies have used the tracking SST to compare stop-related neural activity between groups of participants. The literature suggests that more impulsive responders (those with a longer SSRT) show decreased neural activity in key response inhibition regions of the brain. First, there is a sizeable behavioral literature suggesting individuals with ADHD perform poorly on the SST (for reviews, see Alderson, Rapport, & Kofler, 2007; Lijffijt et al., 2005; Oosterlaan et al., 1998). Supplementing the behavioral studies on the SST and ADHD, fMRI studies have also found that individuals with ADHD performed worse compared to controls, as noted by longer SSRT, and this poor performance was associated with reduced activity in the right mesial frontal cortex, right inferior prefrontal cortex, and left caudate (Rubia et al., 1999; Rubia et al., 2005) as well as the right pre-supplementary motor area, right dorsolateral prefrontal cortex, and

right basal ganglia structures (Dickstein et al., 2006; Hart et al., 2014; Passarotti et al., 2010) during successful inhibition. Event-related potential (ERP) studies have yielded similar results, finding decreased right frontal N2 and P3 amplitudes during successful stopping in individuals with ADHD during the SST (Liotti et al., 2005; Pliszka, Liotti, & Woldorff, 2000; Senderecka et al., 2012). Furthermore, this prefrontal and basal ganglia hypoactivity observed in individuals with ADHD is attributed to response inhibition deficits in ADHD, rather than attentional deficits (Cubillo et al., 2009; Dickstein et al., 2006; Hart et al., 2013, Morien-Zamir et al., 2014). These results indicate that a key feature of ADHD is poor performance on the SST, and, importantly, this is related to decreased activation of regions associated with response inhibition.

In research examining healthy participants, normal variation in SST performance has also been associated with different levels of neural activity. Multiple studies have reported significant negative correlations between SSRT and stop-related activity in key inhibitory control regions (Chikazoe et al., 2009; Chao et al., 2009; Congdon et al., 2010; Duann et al., 2009; Li et al., 2006; Li et al., 2008; Whelan et al., 2012), suggesting that increased inhibitory ability is associated with increased neural activity, consistent with the clinical findings above. Aron & Poldrack (2006) found that stop-related activity in the right inferior frontal cortex correlated negatively with SSRT and, using a median split of SSRT to create two groups of participants, found increased activity in the right inferior frontal cortex in the faster SSRT group. These findings suggest that superior response inhibition performance, and therein superior inhibitory control, is associated with increased neural activity in regions associated with this executive function.

Despite the extensive literature demonstrating individual differences using the adaptive SST, there may be concerns with its suitability for determining inter-individual, and to some degree intra-individual, differences in neural activity. Although the tracking procedure is designed to elicit equal *subjective* task difficulty across participants (meaning all participants inhibit at approximately 50% of stop trials), this results in unequal *objective* task difficulty across participants (meaning different participants reach 50% stopping accuracy at a range of SSDs). That is, individuals who differ on inhibitory abilities will ultimately complete different versions of the SST. When an individual with relatively superior inhibitory abilities completes the task, he/she will be able to successfully inhibit at longer, more difficult SSDs, and, subsequently, the adaptive algorithm will increase the SSDs to ensure 50% inhibition rate for that individual. In contrast, a relatively poor inhibitor will complete shorter, easier SSDs to ensure their 50% accuracy. This is potentially problematic, especially considering that as SSD increases, activation increases in various inhibitory regions. Aron & Poldrack (2006) found that SSD was positively correlated with activity in the right subthalamic nucleus, the right pre-supplementary motor area, and the right globus pallidus. Therefore, the increased activity observed in superior inhibitors may be due to the higher demands of a more objectively difficult version of the SST rather than reflecting an inherent characteristic of the activation levels of superior inhibitors.

Given the results from previous neuroimaging and neurophysiological work on the SST, it is difficult to discern if neural activation differences observed between superior inhibitors

and poor inhibitors reflect differences in inherent inhibitory abilities, or reflect differences in *objective* task difficulty. This is of potential concern when considering the literature suggesting that a major deficit of ADHD is poor response inhibition coupled with hypo-activation and considering the multiple reports finding SSRT scores correlate negatively with neural activity. The goal of the current study is to examine if group differences in stop-related activity are influenced by differences in objective task demands (i.e. the stop signal delay duration of successfully inhibited stop trials). To accomplish this, we compared two groups of individuals that were selected based on differences in SSRT scores while performing the SST during fMRI acquisition. We compared regional activity from the two groups in which *subjective* difficulty was equivalent (both groups perform at a similar successful inhibition rate) and in which *objective* difficulty was equivalent (both groups successfully inhibit an identical set of trials). We hypothesized that group differences in regional activity observed in the subjectively equal condition would be attenuated when groups were compared during the objectively equal condition.

METHODS

Participants

Neuroimaging data used in the current study were collected as part of the large, longitudinal neuroimaging study, IMAGEN (https://imagen-europe.com). A description of participant recruiting procedures, assessment and data collection, and inclusion criteria has been previously described in Schumann et al (2010). In the current study, we examined data

from 210 participants collected during the second neuroimaging time point (Mean age = 18.96, *SD* = 0.72).

The Stop Signal Task

All participants completed the IMAGEN version of the Stop Signal Task (SST) during functional MRI acquisition. Standardized hardware for visual stimulus presentation was used at all scanning locations (NordicNeurolabs, www.nordicneurolab.com). On go trials, arrows pointing to the left required a left-hand button response, and arrows pointing to the right required a right-hand button response. 60 stop trials were pseudorandomly mixed with 300 go trials. Stop trials consisted of an arrow pointing up (stop signal) that quickly followed the go signal. Difficulty of stopping was manipulated by varying the length of the stop signal delay (SSD) on each stop trial using a tracking algorithm based on participants' performance (Logan, Schachar, & Tannock, 1997). The goal of the tracking algorithm is to arrive at a 50% accuracy on stop trials for all participants. The initial stop trial SSD was 150ms, and varied by 50ms based on performance on the previous trial (increasing to make the next stop trial more difficult if the participant successfully inhibited on the previous stop trial and decreasing to make the next stop trial easier if the participant failed to successfully inhibit on the previous stop trial). The main performance measure of the SST, the Stop Signal Reaction Time (SSRT), was computed as described previously (Whelan et al., 2012). SSRT was computed by subtracting the median SSD of all successful stop trials from the nth percentile go reaction time, where n represents the percentage of successful inhibitions.

Superior and Poor Inhibitors

The goal of the present study was to examine how the tracking algorithm influences inter-individual differences in stop-related activity, and therefore two groups of subjects were chosen that would best exhibit group differences. The two groups of participants, superior and poor inhibitors, were defined based on SSRT performance values derived from the SST. 725 participants who had stop task neuroimaging data that passed quality control for excessive motion (i.e. mean framewise displacement < 0.9mm as indicated by Siegel et al., 2014) were ranked based on their SSRT. Superior inhibitors were the top 20% of participants with the fastest SSRT values (mean SSRT = 137ms) and the poor inhibitors were the bottom 20% of participants with the slowest SSRT values (mean SSRT = 250ms), resulting in 125 participants in each group. Further task performance quality control was performed (in accordance with Congdon et al., 2012; i.e. >50ms SSRT, percent successful inhibition between 25% and 75%, less than 10% errors on go trials, and fewer than 10 stop trials in which the participant responded before the onset of the go signal). Finally, after dropping participants from the analysis to ensure equal sample sizes in the two groups, the final sample size contained 210 participants with 105 in each group.

AllSSD, CommonSSD, and UncommonSSD

To examine the effects of objective task difficulty on inter-individual differences in stop-related activity, we compared superior and poor inhibitors on three different subtypes of trials. In the first analysis, the AllSSD condition, activation maps for each participant were generated using all successful stop trials, as is standard in the neuroimaging literature. Here, the two groups are participating at equal subjective task difficulty (all participants

inhibiting on approximately 50% of stop trials), however the two groups were compared on a task that was objectively more difficult for the superior inhibitors (the superior inhibitors successfully inhibited on trials with longer SSDs; see Figure 1).

The goal of the second analysis, the CommonSSD condition, was to examine group differences on a subset of trials that were equal in objective task difficulty (shaded region, Figure 1). The CommonSSD condition contained an equal number of trials at each SSD for the two groups (Table 1). To accomplish this, we randomly selected successful stop trials from each group so that both groups had the same number of successful stop trials at each SSD. Additionally, we matched the number of participants from each group that contributed to the analyses at each SSD (see Table 1). For example, at 250ms SSD, there were 45 poor inhibitors that successfully inhibited on 120 stop trials in total and there were 101 superior inhibitors that successfully inhibited on 599 stop trials in total. To match these groups, we randomly selected 45 of the 101 superior inhibitors, and from the 45 selected participants, we randomly chose 120 successful stop trials. This procedure was conducted for SSDs of 50-500ms. The trials that were not selected for the CommonSSD condition comprised the UncommonSSD condition (unshaded region, Figure 1); these trials maximize the SSD confound between the superior and poor participants. Therefore, the model for this analysis was identical to that of the AllSSD condition, except here all successful stop trials were assigned to either the CommonSSD or UncommonSSD trial types.

AllSSD-subsample

The CommonSSD condition contains approximately half the number of trials used to generate activation contrasts in the AllSSD condition (48% of successful stop trials for the superior inhibitors and 53% of successful stop trials for the poor inhibitors; see Table 1). To control for the potential influence this loss of power may have when comparing results from the AllSSD to the CommonSSD condition, we created a third condition. The AllSSD-subsample condition is composed of 50% of trials randomly selected from the AllSSD condition of each participant. In this manner, the AllSSD-subsample condition preserves the same group differences in the distribution of SSD length on successful stop trials as in the AllSSD condition, while also containing a similar number of trials used to generate activation contrasts as in the CommonSSD condition.

FMRI Acquisition and Analysis

Full a full description of the MRI acquisition, quality control procedures, and multi-site standardization please refer to Schumann et al., 2010. MRI Acquisition Scanning was performed at the eight IMAGEN assessment sites (London, Nottingham, Dublin, Mannheim, Dresden, Berlin, Hamburg, and Paris) with 3T whole body MRI systems made by four manufacturers (Siemens: 4 sites, Philips: 2 sites, General Electric: 1 site, and Bruker: 1 site). Image acquisition parameters were held constant across all sites to ensure comparison of fMRI data across the different image acquisition facilities. For structural images, high-resolution anatomical MRIs were acquired with three-dimensional T1 weighted magnetization prepared gradient echo sequence (MPRAGE), with 2300ms TR and slice thickness of 1.1mm. For functional images, blood oxygenation level dependent

(BOLD) fMRI images were acquired with a gradient-echo echoplanar image sequence using a relatively short echo-time, with 2200ms TR and slice thickness of 2.4mm.

Functional image processing included realignment, slice-timing correction, movement correction, non-linear warping into MNI space using a custom EPI template, and Gaussian-smoothing at 5mm full width half maximum. Statistical Parametric Mapping (SPM) version 12 was used for generation of all first level analysis contrast images. Activation maps were computed using a general linear model with an auto-regressive noise model. Based on behavioral records, each participant's design matrix included regressors for the different trials in the task and six motion regressors (3 for translational and 3 for rotational movement) included as nuisance variables. Regressors modeling the experimental conditions are convolved using SPM's default hemodynamic response function. Task condition regressors include stop success trials (more details below), stop failure trials, trials on which the go response was too late and trials on which the go response was wrong (if any). Contrast images are generated for successful (stop success) responses against the implicit baseline of the go success condition while removing variance associated with the other regressors in the design matrix, as this has been the model used previously on the IMAGEN dataset (Whelan et al., 2012). For all contrast images, intensity in each voxel represents the estimated percent BOLD signal change associated with the regressor.

Three different design matrices were used in the current study to create activation contrasts for successful stop trials. The three design matrices were identical except for how successful stop trials were modeled. For the AllSSD condition, all successful stop trials were included in the “stop success” regressor, generating a contrast image for all available successful stop trials. For the CommonSSD and UncommonSSD condition, the “stop

success" regressor was split into two distinct regressors according to the duration of the SSD as described above, generating contrast images for the CommonSSD trials and for the UncommonSSD trials, separately. For the AllSSD-subsample analysis, all successful stop trials were randomly separated to one of two regressors ensuring that the AllSSD-subsample regressor contained a similar number of trials as were represented in the CommonSSD regressor.

Regions of Interest Generation

Functionally-defined regions of interest (ROI) were created to compare percent signal change associated with successful stop trials between superior and poor inhibitors. To define the ROIs, contrast images were first generated for stop success activity from all successful stop trials from all 210 participants. Regions were then selected by the ten peaks exhibiting the greatest activity for the stop success contrast, and spheres with a radius of 5mm were centered on the ten local maxima. All ten regions were grey matter masked to remove white matter and CSF from the sphere. Marsbar ROI toolbox for SPM was used to extract the average percent signal change for voxels within each of the ten ROIs (marsbar.sourceforge.net). Figure 2 depicts each ROI along with the MNI coordinates and Brodmann area that each ROI lies within. Regions are labeled with a short naming schema used for future descriptions in text, however Figure 2 caption includes more anatomical specificity for each ROI. To verify that the locations of these ten regions were not driven by the activation from the superior or poor inhibitors, we calculated the peaks of activation separately for each group. Importantly, the distance from each groups' activation peaks and the regions used here was equal, suggesting the results are not biased towards activation of either group.

Post Hoc Separation of IFG and Insula.

Although the focus of the current study is to examine the effects of objective task difficulty on stop-related activity, the right IFG/anterior insula and the left IFG/anterior insula include voxels from two anatomically distinct regions. This is potentially problematic considering the inferior frontal gyrus and the anterior insula exhibit unique architectonic characteristics and may be involved in functionally separable networks (Aron, Robbins, & Poldrack, 2004; Menon & Uddin, 2010). To address this concern, a post hoc analyses was performed to address the effects of objective task difficulty on stop-related activity specifically in the right and left inferior frontal gyri and the right and left anterior insula. Four new functionally-defined regions of interest were generated (see Figure 3). Similar to the ten regions used in the main analyses of the current study, the four new regions were defined by the stop success activity from all successful stop trials in the 210 participants. Here, ROIs were defined by the peak of stop-related activity that lay at least 5mm away from the boundary of the IFG and insula. The post-hoc regions of interest are spherical ROIs with a radius of 5mm (same size as the main 10 regions) that reside completely within the inferior frontal gyrus or anterior insula of their respective hemispheres, which was confirmed by applying the Automated Anatomical Labeling atlas (AAL; Tzourio-Mazoyer et al., 2002) to the ROIs.

RESULTS

Demographic and Performance

Group means and standard deviations for demographic variables of the superior and poor inhibitors can be found in Table 2. There were no significant differences in age ($t(208)$ =

0.38, $p = 0.71$), sex ($X^2(1) = 3.49, p = 0.07$), or handedness ($X^2(1) = 1.69, p = 0.19$) between the two groups. Group means and standard deviations for performance variables including SSRT, average successful SSD, average reaction time from go trials (RT), and percent of stop trials successfully inhibited can also be found in Table 2. Compared to poor inhibitors, superior inhibitors, by design, had significantly faster SSRT values ($t(208) = 38.97$, $p < 0.001$) and significantly longer average SSD ($t(208) = 12.68$, $p < 0.001$). Superior inhibitors had a greater percent of stop trials successfully inhibited ($t(208) = 6.05$, $p < 0.01$) compared to poor inhibitors. There was no significant difference between superior and poor inhibitors on average reaction times from successful go trials ($t(208) = 1.03$, $p = 0.3$).

AllSSD fMRI

First, superior and poor inhibitors were compared using activity derived from all successful stop trials across the ten regions of interest. Univariate analysis of covariance (ANCOVA) was used to compare the two groups, and age, sex, handedness, scan acquisition site and percentage of stop trials successfully inhibited were used as covariates in the model (all results held if the percentage of successful stop trials was not included as a covariate). Given that group differences were tested at ten regions functionally defined by the same task contrast and are not completely independent of one another, we employed a modified Bonferroni adjustment accounting for the average correlation of stop success activity across the ten ROIs (r = 0.38) (Bender & Lange, 2001). This resulted in a corrected significance threshold of $p < 0.012$.

Superior inhibitors displayed significantly greater stop success activity compared to poor inhibitors in the right IFG/anterior insula ($F(197) = 12.28$, $p < 0.005$) and right temporal ($F(197) = 11.02$, $p < 0.005$) ROIs (Figure 4). In the right occipital ROI, the results suggest superior inhibitors exhibit greater stop success activity than poor inhibitors, however the difference did not pass the corrected statistical threshold ($p = 0.048$).

CommonSSD and UncommonSSD fMRI

A 2x2 mixed effects analysis of covariance (ANCOVA) was run using trial subset as the within-subject variable (CommonSSD and Uncommon SSD), group as the between-subject variable (superior and poor inhibitors), and age, sex, handedness, scan acquisition site, and percentage stop success as covariates. The mixed effects ANCOVA revealed significant main effects of group in the right IFG/anterior insula ($F(1) = 14.52$, $p < 0.001$), the right occipital ($F(1) = 5.14$, $p < 0.01$), the right temporal ($F(1) = 10.61$, $p <0.01$), and the right DLPFC ($F(1) = 4.79$, $p < 0.05$). Critically, significant interactions between group and trial subset were found in the right IFG ($F(1,197) = 6.31$, $p < 0.05$), the right occipital ($F(1,197) = 7.54$, $p < 0.01$), the left occipital ($F(1,197) = 9.36$, $p <0.01$), the left IPL ($F(1,197) = 5.84$, $p < 0.05$), the right temporal ($F(1,197) = 7.33$, $p < 0.01$), and the left DLPFC ($F(1,197) = 6.87$, $p < 0.01$) regions of interest.

Post-hoc comparisons of superior and poor inhibitors were run using the CommonSSD trial subset and the UncommonSSD subtype separately. Bonferroni-adjusted threshold accounting for average correlation was performed for the CommonSSD and UncommonSSD conditions ($r = 0.43$, $p < 0.014$; $r = 0.49$, $p < 0.016$; respectively). In the

CommonSSD analysis, the superior inhibitors did not display greater activity compared to the poor inhibitors in any region of interest that passed corrected statistical threshold (Figure 5) although there were subthreshold effects in the right IFG/anterior insula and right temporal region. When comparing the groups using the UncommonSSD subgroup of stop success trials, superior inhibitors displayed significantly greater activity compared to the poor inhibitors in the right IFG/anterior insula, the right occipital, and the right temporal regions of interest (Figure 5). For the left occipital, the left IPL, the left DLPFC, the data suggest greater activity in the superior inhibitors compared to the poor inhibitors, however the results do not survive correction for multiple comparisons ($p = 0.042$, $p = 0.021$, and $p = 0.025$, respectively).

AllSSD-subsample fMRI

Comparing superior and poor inhibitors on activation derived from a random half of each participant's stop trials yielded similar results to those from the AllSSD analysis. Similar to the AllSSD analysis, superior and poor inhibitors were compared using univariate analysis of covariance (ANCOVA) with age, sex, handedness, scan acquisition site, and percentage of successful stop trials included as covariates. In the AllSSD-subsample analysis, Bonferroni-adjusted correction for multiple comparisons accounting for average correlation across the ten regions (r=0.39) created a significance threshold of $p < 0.012$. Superior inhibitors displayed significantly greater activity compared to poor inhibitors in the right IFG/anterior insula ($F(197) = 10.18$, $p < 0.005$) and in the right temporal ($F(197) = 8.84$, $p < 0.05$) regions of interest, as was the case in the AllSSD analysis.

Post Hoc Separation of IFG and Insula

To separate effects in the right and left inferior frontal gyri from effects in the right and left anterior insula, superior and poor inhibitors were compared in the AllSSD analysis and Common/UncommonSSD x group interaction in the four regions created post hoc (See figure 3). In both analyses, age, sex, scan acquisition site, handedness, and percentage of successful stop trials were included as covariates. In the AllSSD analysis superior inhibitors displayed significantly greater activity than poor inhibitors in the left IFG ($F(197) = 7.35$, $p < 0.05$) and the right IFG ($F(197) = 4.45$, $p < 0.05$), with no group differences in the right or left insula (Figure 6). In the Common/UncommonSSD x group analysis, there was a significant interaction in the left IFG ($F(1,197) = 8.75$, $p < 0.05$), the right IFG ($F(1,197) = 3.91$, $p < 0.05$), and the right insula ($F(1,197) = 4.84$, $p < 0.05$). Post hoc comparison of superior and poor inhibitors were performed for the CommonSSD and UncommonSSD analyses separately (Figure 7). There were no group differences in any of the four regions for the CommonSSD analysis. In the UncommonSSD analysis, superior inhibitors displayed greater activity compared to poor inhibitors in the left IFG ($F(197) = 17.87$, $p < 0.05$), the right IFG ($F(197) = 9.13$, $p < 0.05$), and the right insula ($F(197) = 6.01$, $p < 0.05$).

DISCUSSION

The current study examined the influence of the adaptive algorithm in the Stop Signal Task when measuring inter-individual differences in stop-related activity. The adaptive SST has particular strengths for inhibitory control research in that it allows for easy calculation of a measure of the speed of inhibitory processes (i.e., the SSRT) and it ensures all participants

are inhibiting at an equal inhibition rate (approximately 50% of stop trials). However, the cause for concern raised in this report is that it achieves the latter by creating an objectively more difficult version of the task for superior inhibitors. Consequently, these differences in task difficulty may contribute to the greater stop-related activity seen in superior inhibitors and in healthy controls when compared to clinical participants.

The present results suggest that comparing superior and poor inhibitors on trials matched for objective difficulty (i.e., trial SSD) yields different results than comparing the groups on trials matched for inhibition rate performance (i.e. subjective task difficulty). In the AllSSD condition (equal subjective difficulty), superior inhibitors displayed greater activity than poor inhibitors in the right IFG/anterior insula and the right temporal regions of interest. In the CommonSSD condition (equal objective difficulty) these effects did not survive correction for multiple comparisons. Furthermore, results from the AllSSD-subsample condition matched those from the AllSSD condition, suggesting the attenuation of group differences observed in the CommonSSD condition is not a result of the reduction in the number of trials (i.e. loss of statistical power) used to generate stop-related activity.

In the right IFG/anterior insula, the right occipital, the left occipital, the left IPL, the right temporal, and the left DLPFC, there were significant interactions between condition (CommonSSD v UncommonSSD) and group. If difficulty to inhibit increases as SSD increases, then the UncommonSSD condition reflects the largest group difference in objective task difficulty, being composed of the shortest SSD trials from the poor inhibitors and the longest SSD trials from the superior inhibitors. As seen in Figure 5, *post hoc*

analyses of these interactions show these regions of interest exhibit larger group differences in the UncommonSSD condition compared to the CommonSSD condition. Combined with the main effects of the AllSSD and CommonSSD analyses, these results support the hypothesis that differences in objective task difficulty inflate group differences in stop-related activity. That said, it should be noted that the subthreshold effects observed in the CommonSSD condition and the pattern of effects in Figure 5 show the influence of task difficulty to be largely quantitative in nature.

Although the focus of the current study was to examine the influence of objective task difficulty on stop-related activity and not the neurobiology of individual differences in inhibitory ability per se, the analyses here may identify dissociable roles for the inferior frontal gyri and insulae. The post-hoc separation of the inferior frontal gyri and the anterior insulae revealed that in the AllSSD analysis superior inhibitors displayed greater activity compared to poor inhibitors in bilateral IFG but not in either left or right insula. This result alone is interesting supporting the distinct roles of the IFG and insula in the stopping network and salience network, respectively (Aron & Poldrack, 2006; Menon & Uddin, 2010). Furthermore, that the effect was observed in both the right and left IFG agrees with previous work arguing the role of both the right and left hemispheres in inhibitory ability (D'Alberto et al., 2017). The interaction of group and trial subset revealed larger group differences in the UncommonSSD analysis compared to the CommonSSD analysis in the left IFG, the right IFG, and the right Insula. These results reiterate the conclusion that objective task difficulty influences stop-related activity, particularly in regions that exhibit group differences in the standard AllSSD analysis. Future studies should further explore

how the effects of objective task difficulty influence the neurobiology associated with individual differences in inhibitory control, particularly in studies with finer spatial resolution such as those employing the Human Connectome Project processing stream (Van Essen et al., 2012).

The findings from the AllSSD analysis replicate previous neuroimaging work on the SST demonstrating that superior performance on the task is associated with increased neural activity (Aron & Poldrack, 2006; Chikazoe et al., 2009; Chao et al., 2009; Congdon et al., 2010; Duann et al., 2009; Li et al., 2006; Li et al., 2008; Whelan et al., 2012). However, these studies have failed to acknowledge the potential influence of SSD length, and therein objective task difficulty. Thus, the current report is, to our knowledge, the first to show that group differences in neural activity are diminished when controlling for objective task difficulty in the Stop Signal Task.

Although the present results suggest that objective task difficulty influences stop-related activity, the AllSSD analysis, which includes all trials and is standard in the literature, should still be considered a valuable probe of individual differences in inhibitory ability. Rather than interpreting the increased activation level of a superior inhibitor as indicating that they necessarily activate more when inhibiting, we suggest instead that it reveals the increased activation "capacity" that the superior inhibitor has. The adaptive SST successfully reveals the superior ability of this participant (faster SSRT and longer successfully inhibited SSD) and the increased levels of activity that they can achieve. The corollary is that it is not the case that the superior inhibitor must activate more in order to

successfully inhibit (once the influence of task difficulty is accommodated). Previous work has found similar effects in tasks of working memory and proactive response inhibition. Specifically, Schneider-Garces and colleagues (2010) found that on a working memory task in which young adults outperform a group of elderly participants, young adults showed an increase in neural activity as task demands increased, whereas elderly participants did not show this increase. Similarly, a study examining the Go/No-Go task found that adults, but not children, were able to increase activation in ventral prefrontal regions as interference increased from additional go trials (Durston et al., 2002). Although the current study cannot interpret results from a developmental framework as the two aforementioned reports do, the results here also suggest superior task ability is associated with an increased capacity for activation as objective task demands increase.

The results from the current study suggest a caveat when interpreting group difference in activation in the presence of performance differences, as is often the case when contrasting a clinical group against controls. If activation differences are related, in part, to the differences in task difficulty that arise from differences in inhibitory ability then the magnitude of those activation differences are will be affected by the SSD effects described here. The degree to which groups differ on stop-related activity will be related to the degree to which those groups differ on the distribution of successful stop signal delays. Thus, the magnitude of group differences in activation will reflect a combination of both inherent difference in the ability to activate *per se* and the task difficulty effect. Arising from this conclusion, the authors propose the following recommendations for future research. First, if researchers wish to account for the influence of objective task difficulty on stop-related

BOLD activity, then the research design might employ the "CommonSSD" analysis approach used here. Second, for research continuing to use the standard "AllSSD" analysis, we offer a nuanced interpretation of individual differences in stop-related BOLD activity. That is, individual differences in inhibitory ability are reflective of a greater capacity for activation as the objective difficulty to inhibit a response increases. Thus, superior inhibitors do not activate the STOP network more than poor inhibitors if the two are compared on trials of similar objective task difficulty (i.e. SSD). However, the superior ability of the former group is demonstrated by their ability to perform more difficult trials yielding greater levels of activation. This interpretation offers insight into the neurobiological mechanisms that characterize individual differences in inhibitory control.

CONCLUSION

While the SST retains very many strengths, we suggest that interpretations of individual or group differences in activation should be cognizant of the effect of the adaptive algorithm. The standard analysis based on all trials yields activation measures that reflect both the inherent inhibitory abilities of the individual plus the activation related to the difficulty level of the task produced by the algorithm.

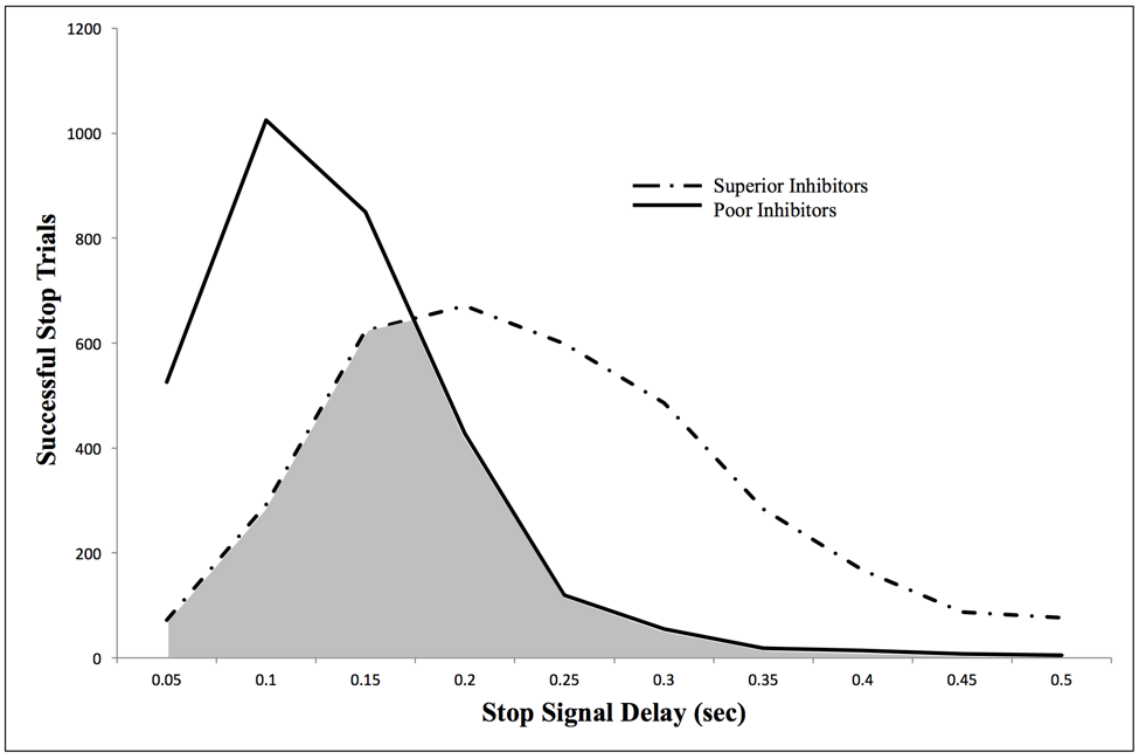

Figure 1. Distribution of stop success trials completed by the superior inhibitors (dotted line) and the poor inhibitors (solid line). For each SSD, the total number of successful stop trials completed at that given SSD length is plotted for each group. Notably, the superior inhibitors' distribution is shifted towards longer SSDs, and the poor inhibitors' distribution is shifted towards shorter SSDs. The shaded region represents the distribution of trials that were inhibited by both superior and poor inhibitors, and thus formed the subset of trials for the CommonSSD analysis. The non-shaded regions represent the trials that were uniquely inhibited by only one group, and thus formed the subsets of trials for the UncommonSSD analysis.

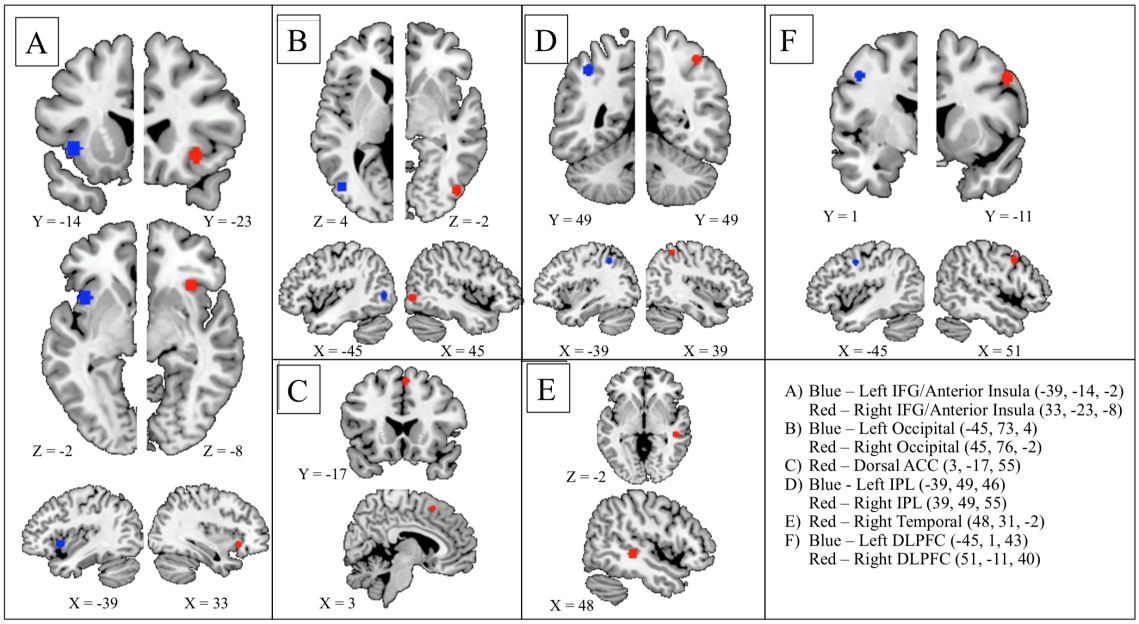

Figure 2. Ten functionally-defined ROIs that were used in the current study for ROI-based analyses, along with their MNI coordinates. All regions within the left hemisphere are marked in blue and all regions within the right hemisphere are marked in red. If applicable (A, B, D, and F), regions are displayed with their contralateral counterpart. In A, B, D, and F, the right and left hemisphere slices do not align, and the slice number is provided to clarify the spatial discrepancies. The legend provided includes the MNI coordinates (R, A, I) with the abbreviated names that are used throughout the text of this paper. The following represents a more anatomically detailed description of the regions including dominant Brodmann areas (BA): A) Blue: anterior aspect of the left insula extending into the left inferior frontal gyrus (BA 13/47). Red: anterior aspect of the right insula extending into the right inferior frontal gyrus (BA 13/47). B) Blue: anterior aspect of the left middle occipital gyrus (BA 19). Red: anterior aspect of the right middle occipital gyrus (BA 19). C) dorsal anterior cingulate gyrus, including bilateral medial superior frontal gyrus (BA 6). D) Blue: left inferior parietal lobule extending into the superior parietal lobule (BA 40). Red: right inferior parietal lobule extending into the superior parietal lobule (BA 40). E) posterior aspect of the right middle temporal gyrus (BA = 21). F) Blue: posterior aspect of the left middle and superior frontal gyrus (BA 9). Red: posterior aspect of the right middle and superior frontal gyrus (BA 9).

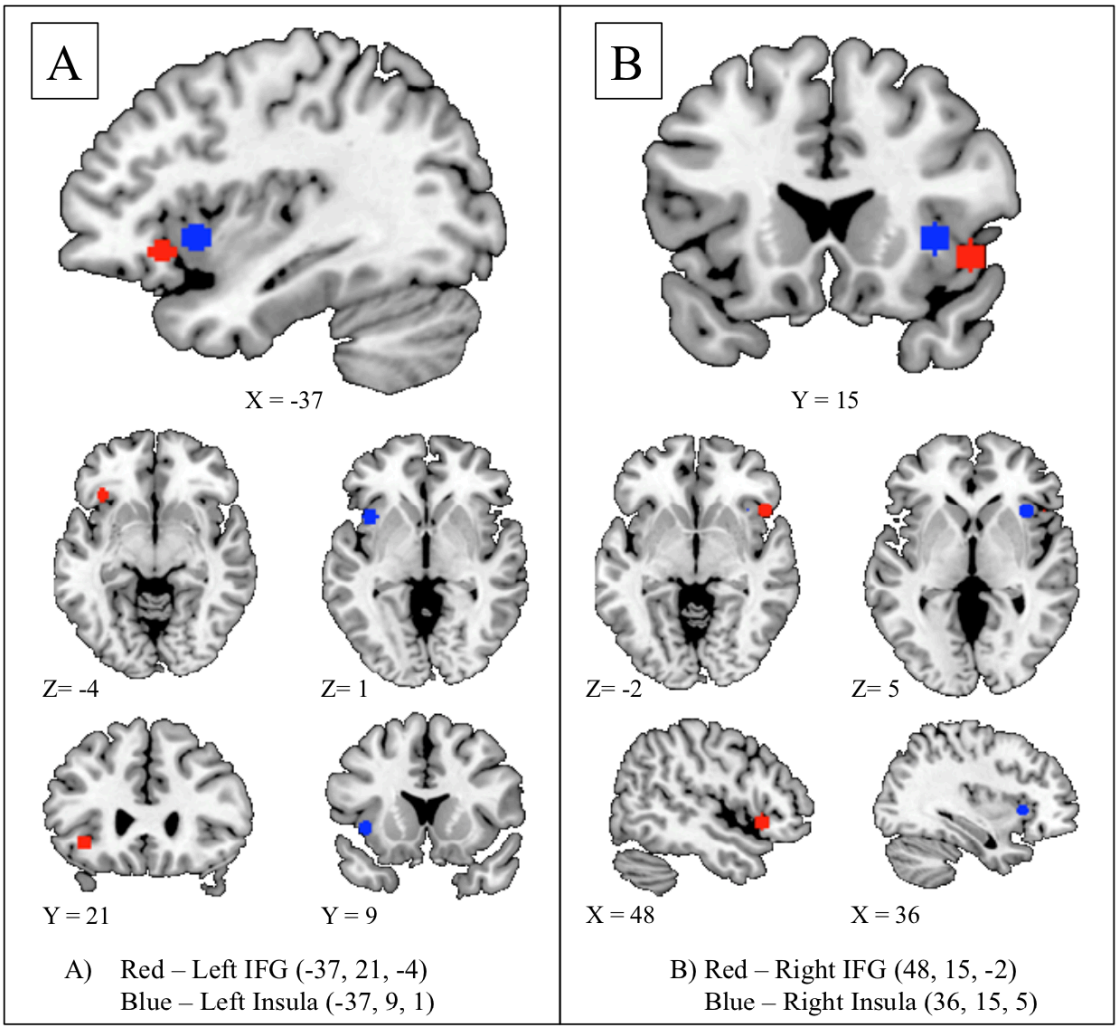

Figure 3. Four new functionally defined ROIs that were generated post hoc to separate inferior frontal gyrus and anterior insula, as these regions were combined in the ROIs used in the earlier analyses. The newly generated ROIs are listed for the right and the left hemisphere, along with their MNI coordinates. A) The left inferior frontal gyrus (red) and left anterior insula (blue) ROIs are displayed together in the sagittal image, as well as separately in the axial and coronal images. B) The right inferior frontal gyrus (red) and right anterior insula (blue) are displayed together in the coronal image, as well as separately in the axial and sagittal images.

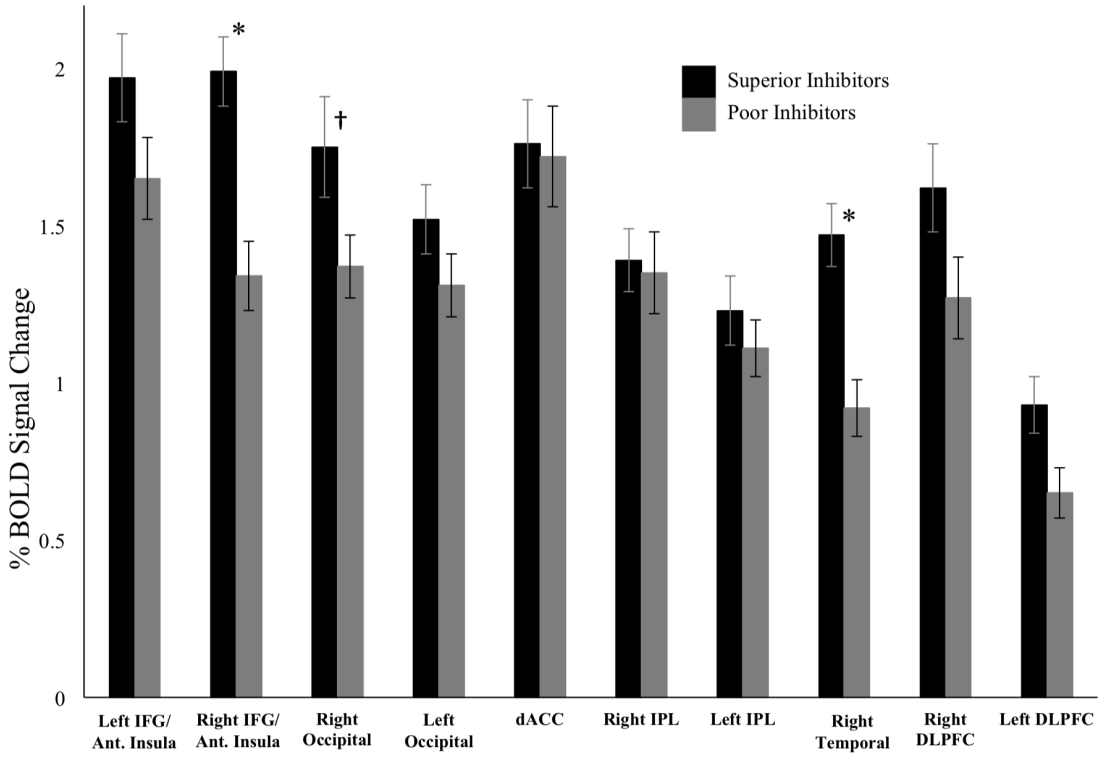

Figure 4. Average percent BOLD signal change for the superior and poor inhibitors in the AllSSD analysis. The ten regions of interest that were analyzed are listed on the x-axis. Error bars are plotted for ± 1 standard error. An * denotes significant differences between the two groups that survived Bonferroni-adjusted threshold for significance ($p < 0.012$). For the right occipital, † is used to indicate a marginal effect in the right occipital region ($p = 0.048$) that did not survive the Bonferroni-adjusted threshold. To demonstrate effect sizes in the regions showing significant effects, partial eta squared was calculated as $\eta_p^2 = 0.059$ and $\eta_p^2 = 0.053$ for the right IFG/ anterior insula and the right temporal regions, respectively.

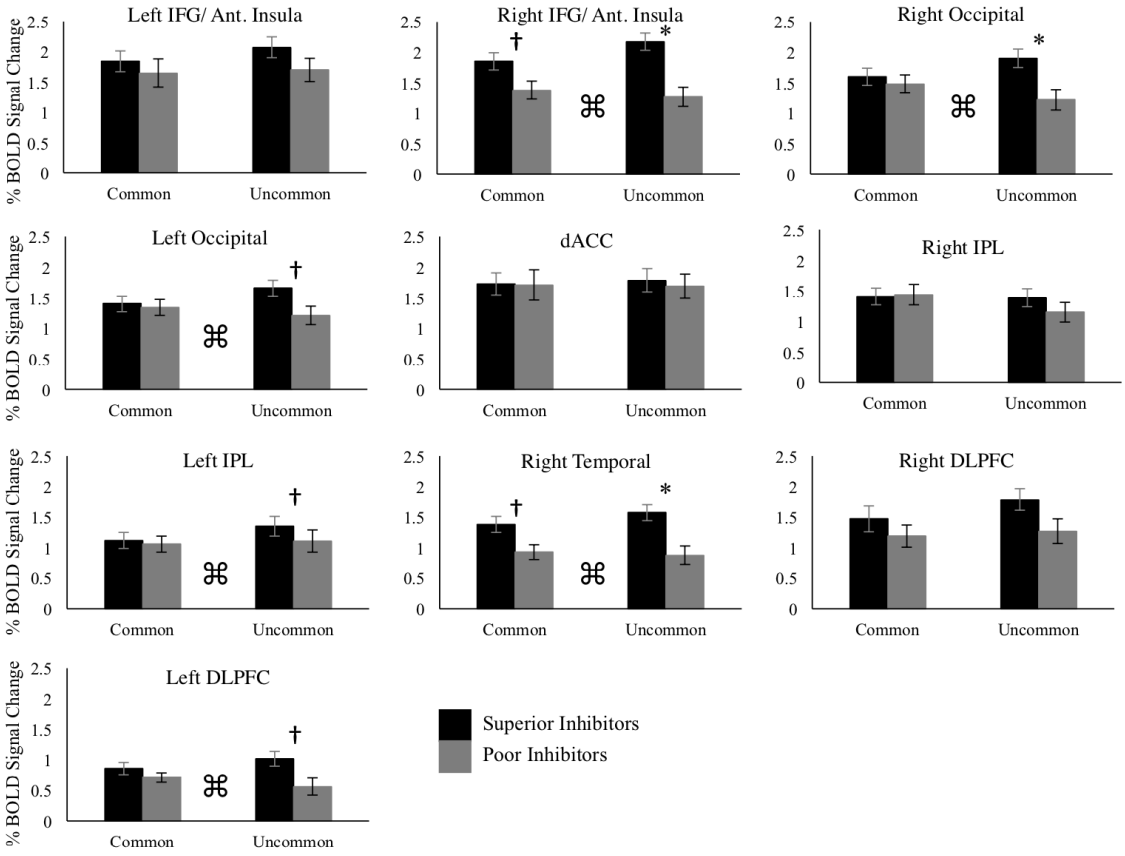

Figure 5. Average percent BOLD signal change for all ten regions of interest in both the CommonSSD and UncommonSSD analyses. Error bars are plotted for ± 1 standard error. Bonferroni adjusted thresholds accounting for average correlation across the ten regions of interest were calculated separately for the CommonSSD ($p < 0.014$) and UncommonSSD ($p < 0.016$) analyses. An * denotes group differences that surpass the Bonferroni-corrected thresholds, and † is used to denote p values that are less than 0.05 but do not pass Bonferroni-corrected thresholds. ⌘ is used to indicate an interaction between group and analysis condition (CommonSSD v. UncommonSSD). In regions showing significant interactions, the following effect sizes were calculated for post hoc group differences in the CommonSSD and UncommonSSD analyses. CommonSSD: right IFG/anterior insula $\eta_p^2 = 0.015$; right occipital $\eta_p^2 = 0.000$; left occipital $\eta_p^2 = 0.000$; left IPL $\eta_p^2 = 0.001$; right temporal $\eta_p^2 = 0.009$; left DLPFC $\eta_p^2 = 0.000$. Uncommon SSD: right IFG/anterior insula $\eta_p^2 = 0.083$; right occipital $\eta_p^2 = 0.046$; left occipital $\eta_p^2 = 0.042$; left IPL $\eta_p^2 = 0.027$; right temporal $\eta_p^2 = 0.077$; left DLPFC $\eta_p^2 = 0.043$.

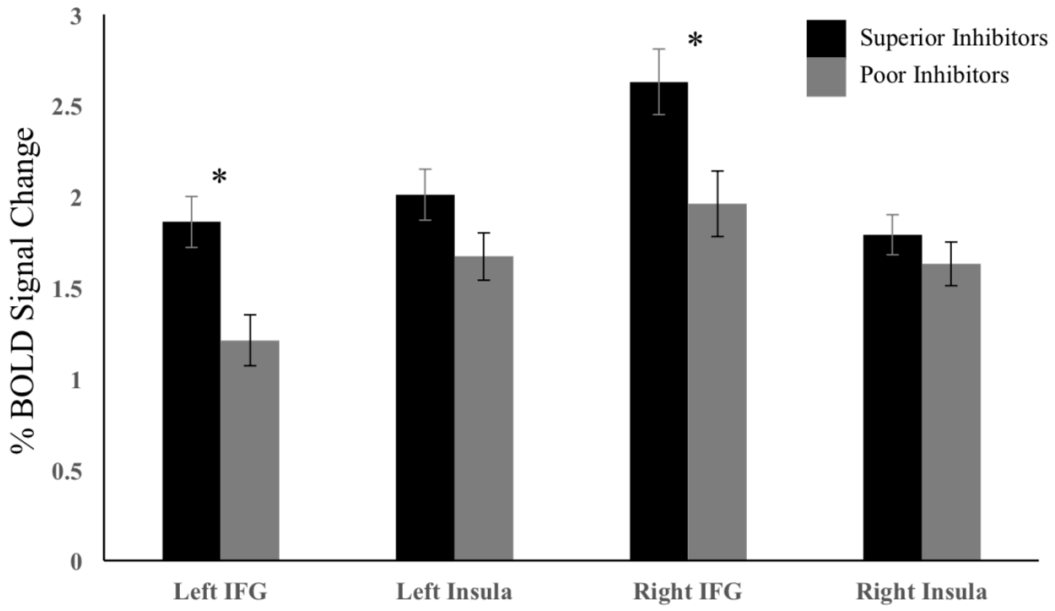

Figure 6. Average percent BOLD signal change for the superior and poor inhibitors in the AllSSD analysis for the four R.O.I.s that were functionally defined post hoc to separate the inferior frontal gyri from the insula. Error bars are plotted for ± 1 standard error. An * denotes significant differences between the two groups at a level of $p < 0.05$. To demonstrate effect sizes in the regions showing significant effects, partial eta squared was calculated as $\eta_p^2 = 0.036$ and $\eta_p^2 = 0.022$ for the left IFG and the right IFG, respectively.

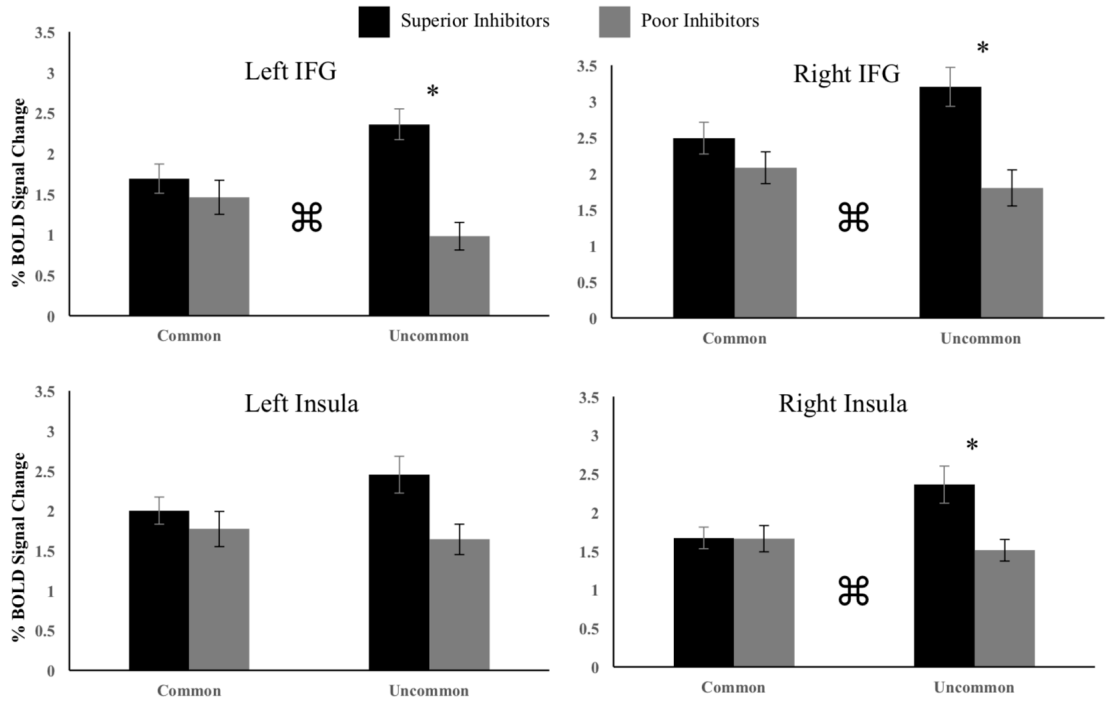

Figure 7. Average percent BOLD signal change for post hoc inferior frontal gyri and insula regions in the CommonSSD and UncommonSSD analyses. Error bars are plotted for ± 1 standard error. An * denotes group differences at a level of $p < 0.05$. ⌘ is used to indicate an interaction between group and analysis condition (CommonSSD v. UncommonSSD). In regions showing significant interactions, the following effect sizes were calculated for post hoc group differences in the CommonSSD and UncommonSSD analyses. CommonSSD: left IFG $\eta_p^2 = 0.003$; right IFG $\eta_p^2 = 0.006$; right insula $\eta_p^2 = 0.002$. Uncommon SSD: left IFG $\eta_p^2 = 0.083$; right IFG $\eta_p^2 = 0.041$; right insula $\eta_p^2 = 0.031$. left IPL $\eta_p^2 = 0.027$; right temporal $\eta_p^2 = 0.077$; left DLPFC $\eta_p^2 = 0.043$.

	Superior		Poor	
SSD	Trials	Participants	Trials	Participants
50ms	**72**	**35**	526	90
100ms	**292**	**83**	1025	103
150ms	**624**	**105**	850	105
200ms	671	105	**428**	**88**
250ms	599	101	**120**	**45**
300ms	486	91	**55**	**19**
350ms	283	67	**18**	**6**
400ms	167	47	**14**	**4**
450ms	87	31	**8**	**2**
500ms	77	19	**5**	**2**

Table I. Distribution of successful stop trials from the superior and poor inhibitors in the CommonSSD and AllSSD analyses. The SSD is listed in milliseconds on the left panel of the table. For each SSD, the total number of successful stop trials for each group is listed from the AllSSD condition (Trials), along with the total number of participants that successfully inhibited at that delay (Participants). The bolded numbers represent the CommonSSD distribution of participants and trials that were taken from both groups for this analysis.

	Superior Inhibitors		Poor Inhibitors		Effect	
					t / X^2	p -value
Age	M = 18.94	SD = 0.76	M = 18.98	SD = 0.68	1.21	0.71
Sex	54M	51F	41M	64F	3.25	0.07
Handedness	90R	15L	96R	9L	1.69	0.19
	M	SD	M	SD	F	p -value
SSRT	137	27	250	12	37.01	< 0.001*
SSD	241	75	131	47	21.92	< 0.001*
RT	418	60	426	48	10.01	0.30
% Success	51.9	2.1	50.4	1.5	6.05	< 0.01*

Table II. Means, standard deviations, and comparison results from demographic and performance data for the superior and poor inhibitors. Age is listed in years, sex denotes the total number of males (M) and females (F) in each group, and handedness denotes the total number of left-handed (L) and right-handed individuals (R) in each group. Stop signal reaction time (SSRT), average successful stop signal delay (SSD), and reaction time on go trials (RT) are listed in milliseconds. Also included are percent of stop trials successfully inhibited (% Success). For the effect, either the t statistic or the Pearson's X^2 is provided (X^2 is for sex and handedness), along with the corresponding p value. An * is used to denote statistical significance of $p < 0.05$.

Disclosures

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CHAPTER FIVE – General Discussion

Part 1 of General Discussion - Objective of the Dissertation

The goal of the current set of experiments was to examine intra- and inter-individual differences in the neurobiological mechanisms associated with inhibitory control. Given the normal maturational patterns of brain development, one of the last areas of the brain to mature is the prefrontal cortex. One of the main functions of the prefrontal cortex is considered to be inhibitory control. The relatively late development of the prefrontal cortex compared to the rest of the brain results in a period of imbalance when it is thought the prefrontal cortex is less able to exert inhibitory control over motivational drives, and this can cause impulsive behaviors and an inability to inhibit immediate responses. This period of development, coinciding, broadly, with adolescence, is thought to be a critical age for the emergence of inhibitory control. Understanding the development of the neurobiological mechanisms associated with inhibitory control through adolescence will greatly improve our understanding of normal brain trajectories during this time. With this knowledge, it may be possible to identify disorders that could be associated with abnormal development of inhibitory control, such as attention deficit hyperactivity disorder (ADHD), substance use and abuse, and more.

The innovation and significance of the current report is that it advances the literature in three main areas. First, the current report addresses the neurobiology of inhibitory control with converging data from a split-brain patient and data from a large neuroimaging database. We integrate behavioral findings from patient J.W. and functional neuroimaging findings from two different time points from the IMAGEN study to address the lateralization of inhibitory control. Second, the current report includes one of the largest

investigations of age-related changes in the neurobiological mechanisms of inhibitory control. Previous work investigating age-related developments in this domain have primarily relied on cross-sectional data comparing children, adolescents, and adults. The few studies that have employed a longitudinal design relied on small sample sizes and were likely under-powered. Third, the current report addresses the development of inhibitory control within the adolescent age range. Given the literature on adolescent brain development, it is a particularly interesting age to examine the age-related changes in the neurobiological mechanisms of response inhibition. Previous reports have examined age-related changes in adults, in children, or even across the entire lifespan. However, to our knowledge this is the first report that focuses specifically on the changes occurring within adolescence.

Part 2 of General Discussion – Review of Major Findings

In the second chapter of the dissertation, we examined the lateralization of inhibitory control with testing on a split-brain patient. The split-brain patient provides an ideal opportunity to address lateralization questions because the performance of each hemisphere can be probed independently of the other. Using the divided visual field technique, we tested patient J.W. on a Go/No-Go Task, a Single-Choice Stop Signal Task, and a Forced-Choice Stop Signal Task. On all three tasks, patient J.W.'s right hemisphere performed better than his left hemisphere. The right hemisphere also exhibited faster reaction times on go trials on all tasks. However, the right hemisphere displayed faster Stop Signal Reaction Times (SSRT) on all three tasks. This suggests that although faster reaction times were apparent for the right hemisphere, faster stopping speed was also

apparent, indicating better inhibitory ability. Interestingly, the left hemisphere still performed all three inhibitory tasks relatively well, indicating the left hemisphere is capable of response inhibition in isolation.

The third chapter had two main components. First, we examined the development of the functional mechanisms associated with successful stop trials in the Stop Signal Task from age 14 to 19 in 538 adolescents from the IMAGEN study. Although we did not find age-related differences in SSRT, we observed significant age-related changes in stop-related activity. Significant decreases in activity were found in the left and right dorsal inferior frontal gyrus, the left and right parietal lobules, an area surrounding the primary visual cortex, the right superior frontal gyrus, and an area including aspects of the right inferior frontal gyrus and anterior insula. Significant increases in activity were found in a region including the left inferior frontal gyrus and anterior insula.

The second component of chapter three examined the functional correlates of individual differences in SSRT in the same group of 538 adolescents at age 14 and age 19. At age 14, SSRT was negatively correlated with activity in a right occipital region and a region including aspects of the right inferior frontal gyrus and anterior insula. SSRT was positively correlated with activity in the ventral medial prefrontal cortex. At 19, SSRT was negatively correlated with activity in a region of bilateral occipital and cerebellum areas, a left subcortical area comprised primarily of the amygdala, midline thalamus, and a region including aspects of the right inferior frontal gyrus and anterior insula. A linear mixed effects model found no significant interaction effects between SSRT and age on stop-related activity. Furthermore, when lowering the thresholds at each collection time, the functional correlates of SSRT at 14 are quite similar to those at 19. At lower thresholds,

only the positive correlation between SSRT and ventral medial prefrontal cortex remained unique to age 14, and only the negative correlation between SSRT and left subcortical activity remained unique to baseline.

In the fourth chapter of the dissertation, we examined the effect of task difficulty on stop-related activity and individual differences in inhibitory control. Here, we selected 105 superior inhibitors and 105 inferior inhibitors, based on SSRT, from the 19-year-old collection time of the IMAGEN project. We compared stop-related activity between the groups in twelve regions of interest under 3 conditions. First, we compared the groups using activity generated from all successful stop trials. Second, we compared the groups only on trials, defined by the Stop Signal Delay, that were successfully inhibited by both groups (Common Trials), thereby ignoring the hardest trials that only the superior inhibitors could inhibit and the easy trials that only the poor inhibitors were exposed to. Third, we compared the groups on the hardest trials that only the superior could inhibit and the easiest trials that only the poor inhibitors were exposed to (Uncommon Trials). We found that group differences in stop-related activity were attenuated in the Common Trials analysis and exaggerated in the Uncommon Trials analysis.

Part 3 of General Discussion – Overall Findings and Future Directions

3.1 Laterality

While a great deal of research has identified the right-lateralization of inhibitory control, others have also found the left hemisphere to play an important role. In the current dissertation, we report multiple findings lending to this discussion. First, our findings provide insight to the discussion on the lateralization of response inhibition. In chapter two

we found that although performance differed between the two hemispheres, both J.W.'s right and left hemisphere could complete the inhibitory control tasks independently of the other. In chapter three, we found significant widespread activation in both the left and right hemispheres during successful inhibition of a motor response in the 538 adolescents both at age 14 and at age 19. In chapter four, we selected the ten regions that exhibited the greatest magnitude of stop-related activity. These ten regions were comprised of regions from both the right and left hemispheres, and included both the left and right inferior frontal gyri. Early reports on the stop task have indicated that only the right hemisphere exhibited significant activation during successful response inhibition (Aron, Robbins, & Poldrack, 2004; Garavan, 2002; Garavan, Ross, & Stein, 1999), however here we are demonstrating that both hemispheres are involved during successful inhibition. It is possible that the large sample sizes used here (538 in chapter three and 210 in chapter four) provided sufficient power to capture bilateral activation during the task.

Second, our findings provide insight on the lateralization of performance correlates of inhibitory control tasks. We found in chapter two that the right hemisphere of a split-brain patient performed better than the left hemisphere on three tasks of inhibitory control, however the left hemisphere could still perform the task relatively well. We found in chapter three that greater activity in a region including the right inferior frontal gyrus and anterior insula was correlated with faster SSRT at both baseline and follow-up. In chapter four we found that the right inferior frontal gyrus and the right superior temporal gyrus exhibited greater activity in superior inhibitors compared to poor inhibitors. We also found in chapter four that the left inferior frontal gyrus exhibited greater activation in superior

inhibitors compared to poor inhibitors. These results together suggest that there are functional correlates of inhibitory performance in both the right and left hemispheres.

However, these results may suggest an age-related effect in the lateralization of correlates of performance whereby the left hemisphere emerges as a correlate of performance with age. Chapter three reported that at baseline (age = 14), only the right inferior frontal gyrus was correlated with SSRT. At follow-up (age = 19), only the right inferior frontal gyrus exhibited a significant whole-brain correlation with SSRT, but region of interest data extracted from the left inferior frontal gyrus exhibited greater activation in superior inhibitors compared to poor inhibitors. Furthermore, when thresholds are lowered in the whole-brain correlation with SSRT, the left IFG exhibits a correlation at follow-up but not at baseline. Although this effect is sub-threshold, the left inferior frontal gyrus trending towards a correlate of SSRT at follow-up but not at baseline may indicate that as age increases the left inferior frontal gyrus becomes more involved with the task and thus more related to performance.

Third, our findings suggest interesting effects of hemispheric differences in the age-related changes in stop-related activity. In chapter three we found age-related decreases in the right inferior frontal gyrus and anterior insula but age-related increases in the left inferior frontal gyrus and anterior insula from age 14 to 19. This effect agrees with the potential age-related shift in lateralization. Along with an age-related increase in stop-related activity from 14 to 19, at 14 the left inferior frontal gyrus and anterior insula exhibit no relationship with performance but at 19 greater activity is apparent in superior inhibitors. Thus, as age increases, activation increases, and this activation becomes associated with better task performance. This model has been proposed previously and has

been referred to as "hemispheric asymmetry reduction in old adults" (HAROLD; (Cabeza et al., 1997; Dolcos, Rice, & Cabeza, 2002). The HAROLD model was originally proposed for older adults, where asymmetry in a cognitive task declines with cognitive decline, hypothetically indicating the emergence of contralateral aid during the task. In the current report, we may be observing patterns congruent with hemispheric asymmetry reduction, but in adolescents and in the absence of cognitive decline.

It is possible that the hemispheric differences in age-related effects between the right and left inferior frontal gyrus and anterior insula are indicative of a developmental trend. Here, in a sample of participants examined at age 14 and again at age 19, we found age-related decreases in activity in the right inferior frontal gyrus and anterior insula but an age-related increase in activity in the left inferior frontal gyrus and anterior insula. In a previous study examining children at 9 and again at 11, researchers found a significant increase in activity in the right inferior frontal gyrus in a response inhibition task (Durston et al., 2006). Previous research on normal brain development have indicated that the right hemisphere matures before the left hemisphere (Thatcher, Walker, & Giudice, 1987). Thus, the age-related increase in left inferior frontal gyrus and anterior insula stop-related activity found here may reflect similar, but relatively delayed, developmental patterns as previously reported for the right inferior frontal gyrus (Durston et al., 2006).

3.2 Development

The current report explored age-related changes in stop-related activity and SSRT from 14 to 19 in a large, longitudinal sample of adolescents. Here, although there was no significant within-subject change in SSRT from baseline to follow-up, there were

interesting changes in the magnitude of activation from baseline to follow-up. Notably, there were widespread decreases in activation in areas that typically exhibit positive activation during successful inhibition. That is, this decrease in activity is not a decrease in "noise" per se, but rather a decrease of activation in regions that are involved with the task. There are multiple potential explanations for decreased activation from age 14 to age 19 while performance remained stable.

First, there may be underlying functional connectivity between regions associated with response inhibition that are developing during this time. As these functional networks develop, perhaps less activation is required of the nodes in the network to complete the task. Multiple reports addressing the development of response inhibition functional networks have found increased strength and number of connections from the prefrontal cortex to various areas of the brain (Hwang, Velanova, & Luna, 2010). This may indicate that decreased cortical activity occurs concurrently with increased functional connectivity. However, other research has indicated that in disorders such as ADHD and Autism, patients exhibit reduced cortical activation as well as reduced functional connectivity compared to controls, suggesting that activity and connectivity may be positively correlated with one another (Cubillo et al., 2010; Kana, Keller, Minshew, & Just, 2007; Wolf et al., 2009). Future research on the simultaneous development of activation and connectivity would greatly improve our understanding of age-related changes in cognition and executive functioning.

Second, the decrease in activation may coincide with an increase in the flexibility of the magnitude of activation required to inhibit a response. In chapter four, we show that in 19-year old participants, activation from areas involved with successful response

inhibition is influenced by the difficulty of the stop trial. When we compared activation from more difficult trials in superior inhibitors to the easier trials in poor inhibitors, group differences were greater than when we compared the groups on the same difficulty of trials. These results might suggest that as difficulty of the trial increases, the magnitude of activation increases to meet the demands of the task. It would be interesting to test if the flexibility of activation based on task demands is the same at age 14 as it is at age 19. A previous study by Durston and colleagues examined if task difficulty influenced activation in children differently than in adults (Durston et al., 2002). Participants were presented with easy, medium, and hard inhibitory motor tasks. As difficulty of the task increased, activity in ventrolateral prefrontal areas in adults increased. In children, activity was greatest during easy trials and decreased on medium and hard trials. Additionally, adults performed well on all levels of the task while children only performed well on the easy trials. These results suggest that in a mature adult system, activation can increase to meet the demands of the task. In a relatively immature child system, activation peaks at easy trials, subsequently cannot increase at harder trials, and the child is unable to inhibit in more difficult conditions. These data support the hypothesis stated above suggesting that as activity decreases with age, flexibility of activation increases.

3.3 Questions for Future Research

The results from the three chapters of this dissertation open interesting questions that remain on the neural mechanism of inhibitory control and the development of these mechanisms.

3.3.1 *Does flexibility of stop-related activation based on task demands increase with age?*

Results from the current dissertation suggest that age-related decreases in activation occurred while SSRT remained stable over time. As proposed above, one possibility for the age-related activation effects is a more flexible activity that adapts to meet tasks demands. It would be interesting to replicate the study performed in chapter four in the same participants at age 14 to examine if task difficulty influences activation to the same degree. Based on the work of Durston and colleagues (Durston et al., 2002), we hypothesize that task difficulty would influence stop-related activity greater at follow-up than at baseline.

3.3.2 *Does the lateralization of inhibitory control change over time, and what is the exact role of the left hemisphere in this task?*

Here, we found an interesting trend suggesting that the left hemisphere, particularly the left inferior frontal gyrus and anterior insula, increases activation during adolescence and this activation may become more correlated with performance over time. The nature of left inferior frontal gyrus activation in response inhibition remains unclear. In the current report, we found that stop-related activation in the left inferior frontal gyrus was influenced by task difficulty, which supports previous hypotheses suggesting the role of the left inferior frontal gyrus is to supplement the right inferior frontal gyrus during difficult inhibitory conditions (Hirose et al., 2012). Future studies should examine if the flexibility of activation based on task difficulty is equal in the left and right inferior frontal gyri, and if flexibility of activation in these areas changes at the same rate over time.

3.3.3 *What is the nature of activation in the inferior frontal gyrus and anterior insula?*

In the whole-brain analyses conducted here, effects observed in the right and left inferior frontal gyri were also found in the right and left anterior insulae, respectively. In age-related increases or decreases in activity, or in functional SSRT correlates, the inferior gyri were coupled with the anterior insulae. Previous research has attempted to separate the roles of these regions, suggesting that the anterior insula is involved with relevant stimulus detection while the inferior frontal gyrus is involved with inhibitory control (Cai, Ryali, Chen, Li, & Menon, 2014). Supporting this separation, we found in chapter four that task difficulty influences activity in the right and left inferior frontal gyri but not in the right and left anterior insulae. However, it is interesting that the regions are coupled in so many of the whole-brain analyses conducted here. It is possible that intra- and inter-individual differences in inhibitory control systems are correlated with intra- and inter-individual differences in stimulus detection systems, thus explaining the coupling of the two regions. Future research should explore the nature of these regions during response inhibition. One way to potentially separate the roles of these regions further would be to map the functional and structural connections to and from these regions, to examine if they are indeed involved with separate systems used during response inhibition.

3.3.4 *What is the best way to measure stop-related activity?*

There are two main findings that question if average activity on all successful stop trials is the best way to capture individual differences in response inhibition. First, despite the strong, widespread activation patterns of stop-related activity at baseline and follow-up, minimal activity is correlated with performance. Second, activation in several regions

is influenced by the distribution of stop trials used to derive the activity. That is, stop-related activity may be meaningfully dependent on the difficulty of the trial, and extracting activity from the average of all successful stop trials may minimize the variance associated with individual differences. When we controlled for objective task difficulty by selecting only the trials both superior and poor inhibitors could successfully inhibit, there were no group differences in activation. When we maximized differences in objective task difficulty by selecting difficult trials that only the superior inhibitors could successfully inhibit and compared them to the easy trials that only the poor inhibitors were exposed to, we found greater activity in the superior inhibitors.

It is possible there is a different measure of stop-related activity that better captures these subtle differences in activation that would correlate with performance. One possibility is that it is the activity associated with the most difficult trials an individual can inhibit that best explain individual differences in performance. Or, perhaps performance is correlated with the rate of activation increase relative to task difficulty that best explain performance differences. Future studies should investigate the degree to which activity is influenced by task demands, and if, or what aspects of, this activation flexibility best explains why some individuals are better inhibitors than others.

3.4 Limitations

There are two main limitations of the current dissertation that need to be addressed. First, the reliability of the Stop Signal Task to measure SSRT over time is poorly understood. Here, we assume that the adaptive algorithm in the task ensures participants perform to their maximum ability, and the SSRTs extracted from the task is a reliable index

of inhibitory control (Congdon et al., 2012). However, other reports have indicated that the task has weak retest reliability in children and young adults (Kuntsi, Stevenson, Oosterlaan, & Sonuga-Barke, 2001; Weafer, Baggott, & de Wit, 2013; Wöstmann et al., 2013). We argue that the results from the current study align with developmental reports from previous work, indicating a within-subject stability in SSRT from age 14 to 19 (Huizinga, Dolan, & van der Molen, 2006; Williams, Ponesse, Schachar, Logan, & Tannock, 1999), and the widespread activation during the task argue that here the task is properly assessing inhibitory control.

Second, the current dissertation only examines the functional BOLD activation associated with successful stopping. Ideally, to understand better the neurodevelopment from 14 to 19 and how this is related to inhibitory control, one would want to explore this question from multiple modalities. We decided to limit the focus of the current dissertation to functional activation because of the multitude of age-related findings observed within this modality alone. We argue it is best to understand the trends of one modality before trying to converge multiple imaging techniques together cohesively. Furthermore, we found interesting effects of task difficulty on magnitude of activation. These effects led us to believe that average activation from all successful stop trials is not the best measurement, and this question needed to be addressed.

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