The neurocognitive basis of preparing to stop action

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Authors
Greenhouse, Ian
Greenhouse, Ian

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The Neurocognitive Basis of Preparing to Stop Action

A dissertation submitted in partial satisfaction of the requirements for the degree
Doctor of Philosophy

in

Psychology

by

Ian Greenhouse

Committee in charge:

Professor Adam R. Aron, Chair
Professor Michael P. Caligiuri
Professor David E. Huber
Professor Douglas A. Nitz
Professor John T. Serences

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The Dissertation of Ian Greenhouse is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

2012
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2004 Bachelor of Arts, Tufts University
2004-2006 Research Assistant, McLean Hospital, Harvard Medical School
2006-2007 Research Assistant, University of California, Berkeley
2007 Master of Arts, University of California, San Diego
2012 Doctor of Philosophy, University of California, San Diego
ABSTRACT OF THE DISSERTATION

The Neurocognitive Basis of Preparing to Stop Action

by

Ian Greenhouse

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University of California, San Diego, 2012

Professor Adam R. Aron, Chair

Using contextual information to prepare to stop behavior is a key aspect of human self-control. For example, a child might chase a ball into the street, without stopping, if she does not know to check for cars. This thesis addresses the neurocognitive basis of how we prepare to stop. In three studies, we used behavioral tasks that require the subject to prepare to stop motor responses. The first study tested the idea that preparing-to-stop changes how outright stopping is achieved – specifically whether it affects task-irrelevant effectors. Accordingly, we used Transcranial Magnetic Stimulation to index the effect of stopping a
manual response on a task-irrelevant leg muscle. We found that when subjects slowed down in anticipation of stopping there was less suppression in the leg at the time of stopping than if they did not slow down. Thus, preparing-to-stop promotes selectivity in outright stopping. The second study tested the hypothesis that preparing to stop is implemented via an ‘associative/executive’ prefrontal-basal-ganglia circuit that passes through the ventral but not the dorsal subthalamic nucleus (STN). Accordingly, we stimulated either the ventral or dorsal STN in Parkinson's patients and measured the amount of response slowing in anticipation of stopping. Patients off stimulation did not slow as much as healthy controls. Notably, ventral, but not dorsal, stimulation remediated this deficit. This implicates the associative/executive circuit in preparing-to-stop. The third study tested the idea that preparing-to-stop makes outright stopping quicker by ‘priming’ a cortical mechanism involved in stopping. We recorded electroencephalography (EEG) in subjects while varying the degree of preparation for stopping. We found that preparing-to-stop led to faster stopping and an increased fronto-central EEG signature (the P3) that has previously been mapped to dorsomedial frontal cortex, a known node in stopping-related circuitry. This finding suggests that preparing-to-stop primes the mechanism for outright stopping. Taken together, these studies show that preparing to stop i) promotes selective stopping, ii) is probably implemented via an ‘associative/executive’ prefrontal-STN circuit, and iii) ‘primes’ cortical mechanisms to enable quicker stopping. This research speaks to the specialization of the human brain for preparing to control behavior.
Chapter 1:

INTRODUCTION

Imagine you are driving down the freeway. You are nearing the exit to your destination, so you signal to change lanes. Just as you begin to turn the steering wheel, out of nowhere, a car zips by in the lane you were entering. You immediately stop turning the steering wheel to avoid an accident. This example highlights an important kind of control that we refer to as ‘reactive stopping’. The tendency to move (i.e. turn the steering wheel) is stopped completely in response to an external signal. Much research implicates a fronto-basal-ganglia network for reactive stopping comprised of the right inferior frontal cortex (rIFC), pre-supplementary motor area (pre-SMA), and subthalamic nucleus (STN) (Aron et al., 2007a; 2007b). Deficits in reactive stopping suggest that this network is disrupted in a variety of disorders including attention deficit hyperactivity disorder (ADHD) (Schachar et al., 1993; Pliszka et al., 2000; Lijffijt et al., 2005; Pliszka et al., 2006; Liotti et al., 2010), Parkinson’s disease (Gauggel et al., 2004; Obeso et al., 2011), schizophrenia (Vink et al., 2006), bipolar disorder (Strakowski et al., 2010), obsessive compulsive disorder (Chamberlain et al., 2006; Menzies et al., 2007), as well as substance use disorders and gambling addiction (Monterosso et al., 2005; Li et al., 2008; Lawrence et al., 2009). Therefore, the study of this network for reactive stopping has widespread relevance.

However, reactive stopping is not the only kind of stopping. Returning to the driving example, imagine that you see the erratic driver approaching in your rearview mirror. In this case, you anticipate being passed and are able to prepare
to stop turning your steering wheel in advance. ‘Preparing to stop’ may be more prevalent in everyday life than outright, reactive stopping. Preliminary evidence (reviewed below) indicates that the same brain network implicated in reactive stopping is also involved in preparing to stop.

This thesis addresses the behavioral significance of preparing to stop and explores the underlying neural mechanisms. The experimental hypotheses were largely motivated by specific anatomical features of the brain network for stopping. For example, the identification of separate diffuse and selective projections from the STN to motor output nuclei of the basal ganglia led to the proposal that the STN’s efferent pathways determine whether stopping has global vs. selective effects on the motor system. Thus, if preparing to stop relates to the global vs. selective effects of stopping, this would suggest a relationship between preparing to stop and the recruitment of these two different STN output pathways. This issue is addressed in Chapter 2. Additionally, different STN subregions are hypothesized to participate in sensorimotor, associative (cognitive), and limbic (emotion) loops that connect the STN to separate areas of frontal cortex. Selectively manipulating activity within these separate loops could help to determine whether they are involved in preparing to stop and reactive stopping. This putative functional dissociation of these circuits is addressed in Chapter 3. Lastly, behavioral evidence indicates that preparing to stop speeds up reactive stopping. One way this could be accomplished is if preparing to stop primes the stopping network, possibly at the level of the cortex. This is addressed in Chapter 4.
1.1 Behavioral Tasks

This thesis addresses the relationship between preparing to stop and reactive stopping. A variety of psychological tasks have been developed for studying these two aspects of stopping behavior. Reactive stopping has traditionally been studied with the Stop Signal Task by measuring the cancelation of initiated actions in response to an external signal, whereas preparing to stop can be studied with the Conditional Stop Task and the Maybe-Stop No-Stop Task by measuring response slowing in anticipation of stopping (i.e. in the absence of an external stop signal). Additional useful measures of stopping behavior come from related paradigms, such as the Selective Stop Task and the Response Switching Task. These tasks provide measurements of the ability to selectively stop one response while initiating or executing another. This section reviews these behavioral tasks in detail and highlights the unique contributions of each.

1.1.1 The Stop Signal Task

The stop signal task (Lappin and Eriksen, 1966; Logan and Cowan, 1984) (Figure 1a) is a popular paradigm for measuring reactive stopping. On each trial of the task, participants execute speeded responses to a Go target. On a subset of trials, the Go target is followed by a stop signal, indicating that participants should attempt to cancel their initiated response. The delay between the target and stop signal is referred to as the stop signal delay (SSD). A longer SSD makes stopping more difficult, and a shorter SSD makes stopping easier.
Stop signal task performance has traditionally been modeled as a ‘horse-race’ between stochastic and independent Go and Stop processes toward a common threshold (Logan and Cowan, 1984; Band et al., 2003; Verbruggen and Logan, 2009a) (Figure 1b). Whichever process reaches the threshold first determines the behavioral outcome for a given trial. This model and its adaptations, e.g. (Boucher et al., 2007), have been useful to the study of reactive stopping because they make testable predictions. For example, the model assumes that the go and stop processes are independent, and this assumption generally holds up across different response domains, developmental stages, ages, diseases, and experimental contexts (Logan et al., 1997; Williams et al., 1999; Bedard et al., 2002; Band et al., 2003).

During stop signal task performance, it is possible to dynamically update the SSD according to an individual participant’s pattern of successful and failed stopping and thus determine the SSD that predicts a 50% success rate at stopping. Based upon the horse-race model assumption (i.e. that the Go and Stop processes are independent), subtracting this SSD from a participant’s mean Go RT provides an estimate of the speed of the stopping process, referred to as the stop signal reaction time (SSRT) (Verbruggen and Logan, 2009a). Several properties of the stop signal task and the behavioral measures it provides (e.g. the SSRT) make it a valuable paradigm to cognitive psychology and neuroscience research.

The stop signal task design has many practical characteristics that have contributed to its widespread application. It has been successfully adapted for
use with animals (Eagle and Robbins, 2003; Chen et al., 2010; Eagle and Baunez, 2010), populations affected by various disorders (Aron et al., 2003; Gauggel et al., 2004; Lijffijt et al., 2005; Vink et al., 2006), and even children (van den Wildenberg and van der Molen, 2004; Whelan et al., 2012). It has also been adapted to auditory, visual, and tactile sensory modalities. Moreover, the SSRT is a relatively stable behavioral measure throughout human adulthood with high test-retest reliability (Williams et al., 1999; Congdon et al., 2012). The robustness of the SSRT makes it especially useful for determining the effect of experimental manipulations on reactive stopping and for studying the underlying neural mechanisms discussed later.

1.1.2 Tasks for Measuring Preparing-to-Stop

While the standard stop signal task has been useful for studying reactive stopping in the laboratory, it does not measure the degree to which an individual prepares to stop. Therefore, minor modifications to the standard stop signal task have been made to study how stopping is prepared. For example, increasing the probability of the stop signal leads to longer Go RT, and this RT increase is believed to reflect preparation for stopping (Verbruggen and Logan, 2009b). In addition to adjustments in the probability of the stop signal, two adaptations of the stop signal task have been used to measure preparing to stop. In the Conditional Stop Task (de Jong et al., 1990; Aron et al., 2007a; Jahfari et al., 2010), the stop signal is only relevant for a subset of possible Go responses. For example, a participant might be instructed to press a left or right button in
response to a left or right target arrow. Following a stop signal, the participant should try to cancel the response only if the Go arrow points in the critical direction, e.g. left, and ignore the stop signal if the arrow points in the noncritical direction, e.g. right (Figure 1c). In another task, the Maybe-Stop No-Stop Task (Swann et al., 2011b), a ‘Maybe Stop’ or a ‘No Stop’ cue predicts the likelihood of a stop signal on the subsequent trial. For example, trials preceded by the ‘Maybe Stop’ cue might indicate that there is a 50% probability of stopping, and trials preceded by the ‘No Stop’ cue indicate that a stop signal will not occur (Figure 1d).

Both the Conditional Stop and the Maybe-Stop No-Stop Tasks allow for the comparison between a condition in which stopping is anticipated (i.e. critical or ‘Maybe Stop’) and a condition in which stopping is not anticipated (i.e. noncritical or ‘No Stop’). Comparing Go RT on critical to Go RT on noncritical trials, or the RT on ‘Maybe Stop’ Go trials to the RT on ‘No Stop’ Go trials, provides an index of slowing in anticipation of stopping. Such slowing may be attributable to four factors: i) slower processing of the target, ii) prolonged decision time, iii) less facilitation of the motor response, and iv) actively suppressing motor output (proactive inhibition). Interestingly, at least three separate studies have shown that increased slowing in anticipation of stopping correlates with faster SSRT (Chikazoe et al., 2009; Jahfari et al., 2010; Leotti and Wager, 2010). This finding suggests that preparing to stop facilitates reactive stopping.
1.1.3 Related Paradigms

One additional variation of the stop signal task, called the Selective Stop Task, is also worth mentioning here because it can be used to measure the selectivity of stopping (Coxon et al., 2007; Aron and Verbruggen, 2008; Claffey et al., 2010; Cai et al., 2011; Majid et al., 2011; Cai et al., 2012). In one version of this task a cue is presented that specifies which of a set of possible responses may need to be stopped. For example, a ‘Maybe Stop Left’ cue might precede a trial during which simultaneous responses are required with both the left and right hands. If a stop signal occurs following the Go stimulus, then only the left response should be stopped while the right response is completed. Thus, the Selective Stop Task requires the selective cancelation of a pre-specified response. This task also provides a measure of how much interference reactive stopping of one response poses to the alternative completed response, i.e. the ‘response interference effect’, and this serves as a behavioral index of stopping selectivity. This can be measured in the form of slower RT for the alternative completed response when the cued response is stopped successfully.

Another related task that may also measure a particular type of reactive and selective stopping is the Response Switching Task (Isoda and Hikosaka, 2007; 2008; Mars et al., 2009; Neubert et al., 2010; 2011). On each trial of this task, two different colored boxes flank a central white fixation box. The fixation box then changes color to match one of the two flanking boxes indicating that a response should be made for the matching side. The target matching color remains the same for a series of three to seven trials and then switches to the
other color, and this repeats throughout the task. The color switch requires a reconfiguration of the motor plan, and this reconfiguration is hypothesized to involve inhibition of the prepared response. The common finding with the Response Switching Task is that switch relative to nonswitch trials demonstrate increased RT and error rates, i.e. a switch cost.

1.2 Neural Mechanisms

This thesis also investigates the neural mechanisms involved in preparing to stop. Multiple lines of evidence suggest that preparing to stop involves the recruitment of the same cortico-basal-ganglia network implicated in reactive stopping. The recruitment of this shared brain network may have behavioral significance. Further to this point, specific anatomical features of this network motivate testable predictions concerning how preparing to stop is implemented and its resultant effects on reactive stopping. This section summarizes the relevant background and reviews evidence for i) the brain network involved in reactive stopping and switching, ii) the recruitment of this network for preparing to stop, and iii) the functional significance of the anatomic subdivision of cortico-basal-ganglia circuits into sensorimotor, associative, and limbic pathways.

1.2.1 Reactive Stopping and Switching

Neuroimaging studies in humans have identified a fronto-basal ganglia network for reactive stopping that connects the rIFC, pre-SMA, and STN (Aron et al., 2007a; 2007b) (Figure 2a). This network is hypothesized to accomplish rapid
stopping of a motor response by sending a command directly from the rIFC and pre-SMA to the STN via the hyperdirect pathway (Nambu et al., 2002; Aron et al., 2007a). The STN has diffuse excitatory projections to the output nuclei of the basal ganglia that send inhibitory projections to motor areas in the thalamus (Parent and Hazrati, 1995; Mink, 1996; Gillies and Willshaw, 1998). Thus, during reactive stopping, rapidly increasing STN activity could broadly reduce thalamic drive to the motor system and quickly inhibit ongoing responses. However, due to the diffusivity of the STN-GPi projections (Parent and Hazrati, 1995; Mink, 1996; Gillies and Willshaw, 1998), the hyperdirect pathway may lack specificity. Indeed, one study that used transcranial magnetic stimulation (TMS) to measure motor system excitability showed that during reactive stopping of manual responses both legs were suppressed, regardless of which hand was stopped (Badry et al., 2009). This global inhibitory effect could have the potential drawback of interfering with other ongoing and important behaviors when a particular behavior must be stopped. Referring back to the driving example above, imagine that you needed to stop turning the steering wheel and simultaneously press your foot on the brake pedal. You would be at greater risk for an accident if stopping the turning of the steering wheel also stopped your foot from pressing the pedal. Therefore, it is supposed that there is also a selective stopping mechanism.

The question of selective stopping has been investigated with the Selective Stop Task (Coxon et al., 2007; Aron and Verbruggen, 2008; Claffey et al., 2010; Cai et al., 2011; Majid et al., 2011). Based on behavioral and physiological findings, these studies point to a separate neural mechanism for
selective reactive stopping, i.e. a mechanism with non-global inhibitory effects.

The anatomy of the indirect cortico-basal ganglia pathway makes it a good candidate mechanism for having a selective inhibitory effect on the motor system (Figure 2b). The indirect pathway passes through the striatum and then the globus pallidus pars externa (GPe) and STN before reaching the output nuclei of the basal ganglia (Parent and Hazrati, 1995; Joel and Weiner, 1997). The STN efferents to GPi along this pathway have been shown to have a high degree of specificity (Shink et al., 1996; Joel and Weiner, 1997; Smith et al., 1998). This pathway is therefore well positioned to have a more focused inhibitory effect within the motor system, and could enable stopping of particular responses without globally interrupting other ongoing movements. This pathway’s putative involvement in preparing to stop will be discussed below.

The reactive stopping brain network has also been implicated in the performance of the response switching task, described previously. Single unit recordings from the monkey STN exhibited changes in firing rates for switch trials but not for nonswitch trials (Isoda and Hikosaka, 2008). Moreover, a study in humans that used the same task and applied single pulses of TMS over either the pre-SMA and then M1 or the rIFC and then M1 showed that the two frontal regions influenced M1 excitability following the cue to switch at delays that may have reflected the involvement of a connection to the STN (Neubert et al., 2010). Therefore, the pre-SMA, rIFC, and STN that comprise the reactive stopping network may also be important for successful response switching.
1.2.2 Preparing-to-Stop

Three TMS studies provide direct evidence that motor excitability is suppressed before and during the initiation of responses when stopping is anticipated. One of these studies used the Conditional Stop Task and measured motor excitability from the responding effectors during the early stages of response initiation (Jahfari et al., 2010). This study showed that RT slowing for critical trials was accompanied by an early and prolonged decrease in motor excitability, below baseline resting levels, as compared with noncritical trials. This finding suggests that preparing to stop a particular response may involve the active suppression of that response during its execution, and this is at odds with the idea that slowing in anticipation of stopping simply reflects decreased facilitation of the response. The two other studies used the Selective Stop Task and measured motor excitability following a cue that indicated which of two forthcoming simultaneously initiated responses might need to be stopped (Claffey et al., 2010; Cai et al., 2011). These studies showed that excitability in the effector that was cued for stopping was suppressed below baseline levels before the onset of the Go stimulus. The un-cued response was not suppressed. This finding indicates that preparing to selectively stop a particular response involves the suppression of that response, even before its initiation. Collectively, these studies strongly suggest that preparing to stop a response involves active suppression of the response before and during its execution.

Furthermore, studies that varied the likelihood of a stop signal, and observed increases in Go RT when stopping was more probable, also reported
changes in a set of EEG event related potentials, referred to as the N2/P3 complex, at the time of successful stopping (Ramautar et al., 2004; Enriquez-Geppert et al., 2010). These studies suggest that greater preparation for stopping may prime cortical mechanisms involved in the reactive stopping process. However, these previous studies suffer from the potential confound that changes in the N2/P3 complex reflect differences in processes that are sensitive to stop signal novelty rather than differences in the stopping process per se.

Nevertheless, simultaneous EEG and fMRI link the N2/P3 to many of the same brain regions that comprise the reactive stopping network, including the pre-SMA and basal ganglia, and strongly link the P3 in particular to the suppression and slowing of responses (Huster et al., 2011).

Further neuroimaging evidence strongly suggests that preparing to stop recruits all or part of the same network as reactive stopping. fMRI studies using the Conditional Stop Task and a version of the Maybe-Stop No-Stop Task reported increased BOLD responses in the rIFC and pre-SMA for critical and Maybe-Stop Go trials (Chikazoe et al., 2009; Jahfari et al., 2010). Moreover, slowing in anticipation of stopping correlated with faster SSRT in both these studies. Considered within the context of the above TMS results, these studies suggest that the recruitment of the stopping network in anticipation of stopping might slow down the execution of Go responses and this could facilitate reactive stopping. However, it remains an open question whether improvements in the speed of stopping also relate to differences in network dynamics at the time of stopping.
Several other fMRI studies that varied the probability of a stop signal have also observed increased BOLD activation in the rIFC, pre-SMA, and in the striatum when stop trials were more likely to occur, and this corresponded to increased slowing in anticipation of stopping (Vink et al., 2005; 2006; Zandbelt and Vink, 2010; Zandbelt et al., 2012). These findings agree with the other two studies mentioned above and further implicate the striatum in preparing to stop. The recruitment of the striatum during preparation for stopping is potentially interesting because the striatum participates in the indirect pathway and has been implicated in selective reactive stopping. The involvement of the striatum in both preparing to stop and selective reactive stopping suggests that these two processes may be related. For example, it may be that proactive recruitment of the striatum in anticipation of stopping prepares the indirect pathway for executing a selective reactive stop. Whether preparing to stop increases the selectivity of stopping, possibly via the recruitment of the indirect pathway, is another previously unanswered question.

1.2.3 Cortico-Basal Ganglia Circuits

Tract tracing studies in rodents and nonhuman primates demonstrated that there are parallel and largely non-overlapping sensorimotor, associative, and limbic circuits that loop from the cortex through the basal ganglia and back to the cortex, and these circuits pass through distinct STN subregions arranged along the dorsolateral to ventromedial axis of the nucleus (Alexander et al., 1986; Parent and Hazrati, 1995; Joel and Weiner, 1997). Although recent research
suggests that there is greater cross-talk between these circuits than was initially proposed (Haber and Calzavara, 2009), their structural parallelism suggests that the mechanism for controlling motor responses may share functional similarities with the mechanisms for controlling cognition and emotion. For example, the role of the STN in reactively stopping a motor response could mirror its role in suppressing thoughts or emotions. Thus, the careful characterization of the roles of the STN in behavioral action paradigms might provide useful information that could extend to other behavioral domains.

Deep brain stimulation of the STN is an increasingly popular treatment for Parkinson’s disease, essential tremor, and obsessive compulsive disorder (Benabid et al., 2009; Bronstein et al., 2011; de Koning et al., 2011; Fox et al., 2011), and may provide insight into the respective functions of the different cortico-basal ganglia circuits. The precise therapeutic mechanism of action is uncertain. However, there is suggestive evidence that stimulation of the different STN subregions can influence activity throughout each of the sensorimotor, associative, and limbic loops (Temel et al., 2005; Mallet et al., 2007; Hershey et al., 2010; Greenhouse et al., 2011; Marceglia et al., 2011; Swann et al., 2011a). The neuroimaging research reviewed above implicates the STN in preparing to stop, reactive stopping, and switching. However, it is not clear whether these behaviors depend on a particular pathway through the STN. This is an important and largely unanswered question that relates to the broader functional significance of cortico-basal-ganglia architecture in motor, cognitive, and emotion domains. One previous study showed that stimulation targeted at the ventral
STN, but not the dorsal STN, induced fewer hits on Go trials and more false alarms on NoGo trials during the performance of a Go/NoGo task (Hershey et al., 2010). This finding specifically implicates the ventral (associative/limbic) STN in response inhibition since no change in task performance was observed for stimulation of the dorsal STN. However, other studies have shown that therapeutic stimulation settings, which likely vary considerably individual-to-individual in terms of the targeted STN subregion, also influence outright/reactive stopping (van den Wildenberg et al., 2006; Ray et al., 2009; Mirabella et al., 2011; Swann et al., 2011a). It may or may not be the case that the ventral STN is particularly important for executive functions such as preparing to stop and switching.

1.3 Questions Addressed in the Current Thesis

Three studies were performed to examine the effect of preparation on reactive stopping and to identify the neural mechanisms involved in preparing to stop.

Chapter 2 addresses the hypothesis that preparing to stop a particular response increases the selectivity of reactive stopping. This was motivated by the fMRI and TMS experiments reviewed above which suggest that recruitment of the stopping network in anticipation of stopping suppresses a response before and during its execution (Jahfari et al., 2010; Cai et al., 2011). However, these studies did not investigate what happens at the time of stopping. Specifically, we hypothesized that proactively targeting control at a particular response when that
response may need to be stopped reduces the amount of interference to the rest of the motor system during reactive stopping. To test this idea, we used the Conditional Stop Task combined with the TMS methods of Badry et al. (2009) to measure motor excitability from the leg when the hand was being stopped. The degree to which the leg was suppressed during stopping served as a proxy for measuring the global vs. selective effects of stopping on the motor system. We predicted that greater slowing in anticipation of stopping (i.e. preparing to stop) would correspond to less suppression of the leg during successful stopping. This prediction was based on the idea introduced above that there are two kinds of stopping mechanism: global and selective.

Chapter 3 addresses the hypothesis that the ventral STN is important for the executive functions of switching and preparing to stop. As mentioned above, different sensorimotor and associative cortico-basal ganglia pathways are hypothesized to pass through dorsal and ventral STN subregions, respectively. Thus, stimulation of the dorsal and ventral STN could selectively modulate activity within these different circuits and help to determine their roles in switching and preparing to stop. We tested this hypothesis in a group of Parkinson’s patients treated with deep brain stimulation of the STN and a group of matched controls. We administered the Maybe-Stop No-Stop Task, which encourages preparing to stop, and the Response Switching Task. Patients were tested with stimulation delivered to the dorsal STN, the ventral STN, and with stimulation turned off. We hypothesized that these executive functions would be most sensitive to stimulation of the ventral STN due to this subregion’s putative
connections via the associative pathway to areas in the prefrontal cortex that have also been implicated in the same executive functions. Such a finding would indicate that the ventral (but not dorsal) STN, and its connected brain regions, are involved in executive functions in humans.

Chapter 4 addresses the hypothesis that preparing to stop ‘primes’ cortical mechanisms involved in reactive stopping to make stopping faster. Such a finding would provide additional evidence that preparing to stop changes the way in which the brain implements reactive stopping. This is important because it may help to validate the existence of different modes of stopping. Furthermore, whereas the previous studies reviewed above showed that EEG signatures observed during successful stopping change according to the probability of a stop signal, we kept the probability of a stop signal constant. We acquired scalp EEG during the performance of a version of the stop signal task with two reward conditions. In one condition, more points were awarded for stopping, and in the other, more points were awarded for going quickly. We expected that participants would prepare to stop more when stopping was rewarded over going than when going was rewarded over stopping and that this would lead to faster stopping. We also predicted the pattern of EEG during successful stopping would differ between the reward conditions. To test this, we compared the N2/P3 complex, a fronto-central EEG marker previously associated with stopping, for successful vs. failed stop trials between the two reward conditions. We expected that differences between successful and failed stop trials would be greater when
stopping was rewarded more than going. These results would indicate that preparing to stop ‘primes’ cortical processes involved in reactive stopping.

1.4 Summary

This thesis focuses on preparing to stop and its relationship to reactive stopping and switching. Part of the motivation for focusing on preparing to stop, as alluded to above, is that scenarios in which people reactively stop behavior instantly and completely are relatively uncommon. Instead, people often prepare to control themselves, whether they anticipate a need to stop (e.g. when crossing a busy street) or a need to switch (e.g. expecting an important phone call during dinner). This ability to prepare requires considerable forethought and is something that is evolutionarily well developed in humans. Specifically, preparing to stop requires the representation of a stopping goal and may involve proactive adjustments to a selected response in accordance with that goal. Such a mechanism may often be used to suppress inappropriate reflexive behavior or ‘primitive behavioral tendencies’, a characteristic that may separate humans from other animals. Therefore, the work in this thesis may indeed tap into aspects of response control that are characteristically and possibly even uniquely human.

Figure 2 of Chapter 1 is a reprinted with permission as it appears in Greenhouse, I; Swann, NC; Aron, AR Chapter 11 from "Neural Basis of Motivational and Cognitive Control" edited by Rogier B. Mars, Jérôme Sallet, Matthew F. S. Rushworth, and Nick Yeung, published by The MIT Press 2011.
Figure 1: A) The stop signal task provides an estimate of the duration of the stopping process. A reaction time distribution is generated for trials of the primary task during which responses are made to a target stimulus. On a subset of trials, a stop signal is presented at variable stop signal delays after target presentation indicating that a response should be stopped. B) A single trial on the stop signal task can be modeled as a horse-race between stochastic and independent Go (green arrow) and Stop (red arrow) processes toward a common threshold (dashed black line). The first process to reach the threshold determines the behavioral outcome: if the Go process wins the race then a response will be executed; if the Stop process wins the race then the response will be canceled. In this example, the Stop process will reach the threshold first resulting in the successful cancelation of a response. C) In the Conditional Stop Task, the stop signal is relevant only for critical and not noncritical responses. D) In the Maybe-Stop No-Stop Task, a ‘Maybe Stop’ cue predicts a stop signal with 50% probability and a stop signal never follows the ‘No Stop’ cue.
Figure 2: Proposed brain networks for A) globally stopping action via the hyperdirect pathway and B) selectively stopping action via the indirect pathway. STN = subthalamic nucleus, Str = striatum, GP = globus pallidus, Thal – thalamus, rIFG = right inferior frontal gyrus, pre-SMA = pre-supplementary motor area.
1.5 References


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Chapter 2:

Stopping a response has global or non-global effects on the motor system depending on preparation

ABSTRACT

Much research has focused on how people stop initiated response tendencies when instructed by a signal. Stopping of this kind appears to have global effects on the motor system. For example, by delivering Transcranial Magnetic Stimulation (TMS) over the leg area of primary motor cortex it is possible to detect suppression in the leg when the hand is being stopped (Badry R et al. 2009, Suppression of human cortico-motoneuronal excitability during the Stop-signal task. Clin Neurophysiol 120:1717-1723). Here we asked if such ‘global suppression’ can be observed proactively – i.e. when people anticipate they might have to stop. We used a conditional stop signal task which allows measurement of both an ‘anticipation phase’ (i.e. where proactive control is applied) and a ‘stopping’ phase. TMS was delivered during the anticipation phase (experiment 1), and also during the stopping phase (experiments 1 and 2) in order to measure leg excitability. During the anticipation phase we did not observe leg suppression, but we did during the stopping phase, consistent with Badry et al. (2009). Moreover, when splitting the subjects into those who slowed down behaviorally (i.e. exercised proactive control) and those who did not, we found that subjects who slowed did not show leg suppression when they stopped, while those who did not slow did show leg suppression when they
stopped. These results suggest that if subjects prepare to stop then they do so without global effects on the motor system. Thus, preparation allows them to stop more selectively.
2.1 INTRODUCTION

When reacting to changes in the environment, people are able to quickly stop actions that are already in progress. One way to measure this behavior in the laboratory is with the stop signal task (Logan et al., 1984; Verbruggen and Logan, 2009). For this task, participants initiate go responses on each trial and occasionally have to try to stop them when a signal occurs. Much research has examined outright stopping of this kind (Verbruggen and Logan, 2008). The research suggests that a fast mechanism is used to stop, perhaps via the subthalamic nucleus of the basal ganglia (Aron and Poldrack, 2006; Aron et al., 2007). The subthalamic nucleus sends a very broad output to the pallidum and so could have widespread effects on the motor system (Mink, 1996). Consistent with this, two studies have observed that if subjects stop the hand then there is suppression of the task-irrelevant leg (Badry et al., 2009; Majid et al., 2011). These studies used Transcranial Magnetic Stimulation (TMS) over the leg area in primary motor cortex to measure corticomotor excitability via concurrent electromyography, (also see (Leocani et al., 2000; Sohn et al., 2002; Coxon et al., 2006; van den Wildenberg et al., 2010) for further evidence).

Here we asked if such ‘global suppression’ can be observed proactively – i.e when people anticipate they might have to stop. To encourage subjects to engage proactive control, adjustments can be made to the basic stop signal paradigm. There are several ways to do this, for example increasing the proportion of stop trials, or comparing mixed go and stop blocks with pure go blocks (Bissett and Logan, 2011). The result in each case is a slowing down of
reaction time on trials where stopping is anticipated relative to trials where it is not (De Jong et al., 1995; Vink et al., 2005; Chikazoe et al., 2009; Jahfari et al., 2010; Leotti and Wager, 2010; Zandbelt and Vink, 2010). Such response slowing could arise from changes in several processes, including: a prolongation of the decision to respond; lesser facilitation of the motor system; and proactive suppression of the motor system (Verbruggen and Logan, 2009; Jahfari et al., 2010; Leotti and Wager, 2010). This last process of proactive suppression may contribute to response slowing by dampening response output (Jahfari et al., 2010). However, it is not known if proactive suppression has global or selective effects over the motor system when subjects slow down their responses in anticipation of stopping (Aron, 2010).

If preparing to stop involves the proactive recruitment of the same mechanism involved in stopping outright, then preparing to stop might also have a global effect over the motor system. A precedent for this prediction comes from the hold-your-horses theory proposed by Frank (Frank, 2006; Frank et al., 2007). According to this theory, the presence of conflict between competing responses recruits the subthalamic nucleus of the basal ganglia to momentarily withhold all response output. We acknowledge that a competition between going and stopping is conceptually quite different from a competition among alternative responses. Nevertheless, the subthalamic nucleus might exert its transient global inhibitory influence over the motor system in the presence of different kinds of conflict, including when there is conflict between the need to respond quickly and the need to possibly stop. Since the subthalamic nucleus is hypothesized to have
a broad effect on the motor system during successful stopping (Aron and Poldrack, 2006; Aron et al., 2007), we predicted that the corticomotor excitability of the leg should be reduced when there is proactive control of hand responses in anticipation of stopping (i.e. global suppression).

In experiment 1 we tested whether there is global suppression of the motor system during proactive control. We used the conditional stop signal task (De Jong et al., 1995; Jahfari et al., 2010). In this version of the stop signal task, participants are instructed to make responses to left and right pointing target arrows, and to inhibit responses following an auditory stop signal only if the arrow points in a ‘critical’ direction (e.g. left). Participants are instructed to ignore the stop signal when the arrow points in the ‘noncritical’ direction (e.g. right). Thus, participants can use proactive control if the target is critical, and this results in slower RT on critical than noncritical trials (De Jong et al., 1995; Jahfari et al., 2010). Here we refer to this as the ‘response delay effect’ (RDE). The RDE is accompanied by reduced excitability in the responding hand for critical relative to noncritical responses, and this difference has been detected as early as 160 and 200 ms after the Go signal (Jahfari et al., 2010). This early suppression of excitability for critical responses may be a marker for the recruitment of a proactive control mechanism. In order to test whether this putative mechanism influences only the responding hand or the entire motor system, here we measured the excitability of a task-irrelevant muscle within the same early response phase during the performance of the same task. We delivered single-pulse TMS over the primary motor cortex and recorded the resulting motor
evoked potentials (MEPs) from the leg while participants provided task responses with their hand. Consistent with prior work (Badry et al., 2009; Majid et al., 2011), we treated leg MEPs as the ‘signature’ of global motor suppression.

We delivered TMS stimuli with high temporal precision in the ‘anticipation’ phase and also in the ‘stopping’ phase. For the anticipation phase, we predicted that if participants globally suppress the motor system in anticipation of stopping, then leg MEPs would be suppressed during critical Go compared to noncritical Go trials. During the stopping phase we predicted leg suppression for successful stop trials, as shown before (Badry et al., 2009; Majid et al., 2011). Such a replication would serve to validate our methods for detecting global motor suppression.

In experiment 2 we used a very similar setup. The key difference was that leg TMS was only delivered during the stopping phase, at one of three specific time points: 200, 220, or 240 ms after the stop signal. We did this to replicate the results of experiment 1 and to better characterize the timing of global motor suppression during successful stopping and its relationship to proactive control.

2.2 METHODS

Subjects

In experiment 1, there were 19 young adult subjects (6 male and 3 left handed, 21.4 ± 2.8 years of age), and in experiment 2 there were 20 (9 male and 2 left handed, 20.7 ± 2.0 years of age). All subjects provided informed consent
according to a protocol of the University of California, San Diego Institutional Review Board. They also completed a TMS safety-screening questionnaire.

**Task**

We used a modified version of the conditional stop task of Jahfari et al. (2010) (see **Figure 3**). Stimuli were presented using PsychToolbox3 (http://www.psychtoolbox.org) running in Matlab (Mathworks, Natick, MA) on an iMac desktop computer (Apple Corporation, Cupertino, CA). Each trial began with a blank screen for 1400 ms followed by a white fixation cross for a variable period of 500 to 700 ms (steps of 100 ms, M = 600 ms). A leftward- or rightward-pointing arrow stimulus was then presented for 1000 ms or until a response was registered. Responses were executed with a leftward lateral movement of the right index finger or a downward movement of the right pinky finger.

In every four trials there were three go trials and one stop trial. On stop trials an auditory stop signal (500 Hz, 400 ms) sounded at a variable stop signal delay (SSD) following the presentation of the arrow. The stop signal indicated that the subject should try to cancel their response but only if the arrow pointed in the critical direction (e.g. rightward pointing). The critical direction was counterbalanced across subjects and was held constant for an individual subject throughout the experiment. The SSD was dynamically adjusted according to the subject's performance in order to converge on 50% stopping rate. If subjects failed to stop then the SSD was reduced by 50ms, if they succeeded in stopping then it was increased by 50 ms (Aron and Poldrack, 2006). Two different
staircases were used and were yoked to the critical trials. These started with SSD values of 200 and 250 ms.

Prior to the experiments, subjects were trained on four practice blocks of 24 trials during which TMS was not administered.

**EMG and TMS**

Surface electromyography (EMG) recordings were made with 10-mm-diameter Ag-AgCl hydrogel electrodes placed over the tibialis anterior (TA) muscle of the leg in a belly-tendon montage and over the lateral portion of the talus bone in the ankle to serve as a ground. In all subjects, EMG recording was done from the left leg only. The EMG signal was amplified using a Grass QP511 Quad AC Amplifier System Grass amplifier (Grass Technologies, West Warwick, RI), with a band-pass filter between 30 Hz and 1 kHz and a notch filter at 60 Hz. Data were sampled at 2 kHz with a CED Micro 1401 mk II and were recorded using CED Signal v4 (Cambridge Electronic Design, Cambridge, UK).

We used a 7 cm figure-of-eight ‘Batwing’ coil (type no. 15411) and a MagStim 200-2 system (Magstim, Whitland, UK) to deliver single pulse TMS stimuli over the scalp. The Batwing coil is optimized for stimulating the leg area. We were careful to observe a safe level of stimulation according to TMS guidelines (Wassermann, 1998). To locate the representation of the TA muscle of the left leg, pulses were first delivered 2 cm anterior of the vertex with the coil angled approximately 10° lateral to the midsagittal line and 15° above the vertex plane. The coil was then repositioned incrementally in order to locate the position
that produced the most reliable MEPs in the left leg. This locus was marked on a snug-fitting lycra swim cap worn by the subject throughout the experiment. Resting motor threshold was determined by finding the lowest stimulus intensity that produced MEPs of at least 0.05 mV amplitude on at least 5 of 10 trials (Rossini et al., 1994). The test stimulus intensity was 115% of the resting motor threshold.

**MEP Analysis**

MEP analysis was performed using custom software in Matlab R2009SV (The MathWorks, Natick, MA). All MEPs were visually inspected to exclude trials where the MEP was contaminated with EMG noise as well as trials with MEP peak-to-peak amplitudes of less than 0.05 mV or greater than 2 mV. No trials were excluded due to EMG noise in either experiment, likely because the leg muscle was not necessary for response execution and was at rest. However, 15.2 ± 4.2 % of MEPs in experiment 1 and 15.6 ± 8.1% of MEPs in experiment 2 were outside the allowable range. After excluding these MEPs, the remaining MEPs were Winsorized. Accordingly, MEPs with amplitudes that were more than 3 SD from the mean for each condition were assigned the value of the nearest MEP amplitude within 3 SD of the mean. Normalization of the data was performed after preprocessing and Winsorizing and is explained in more detail below because it differed between experiments 1 and 2.
Experiment 1

PROCEDURE

The experiment consisted of twenty blocks of 24 trials. TMS was delivered at 200 or 300 ms before the Go arrow to serve as a baseline and 120 or 200 ms after the arrow (Figure 3a). TMS was also delivered on stop trials at 100 ms before the mean critical Go RT as determined using correct critical Go trials from the practice blocks, based on prior methodology (Badry et al., 2009). On TMS trials, only one pulse was delivered at any one of these time points. TMS was delivered on 240 Go trials (120 critical) and 80 stop trials (40 critical). The p(TMS) at each time point was equal for critical and noncritical trials. Specifically, TMS was delivered during the baseline period on 40 critical and 40 noncritical trials; at 120 ms after the target on 45 critical and 45 noncritical trials; at 200 ms after the target on 45 critical and 45 noncritical trials; and during the stopping phase (i.e. Critical Go RT – 100 ms) on 30 critical and 30 noncritical stop trials. TMS was not delivered on the remaining 120 Go trials (60 critical) and 40 stop trials (20 critical). To normalize each subject’s data, the mean MEP amplitude for each condition was divided by the mean baseline MEP amplitude.

Measures of interest included mean critical Go RT, noncritical Go RT, failed stop RT, noncritical Stop RT, SSD, p(inhibit), the RDE (critical Go RT – noncritical Go RT), and stop signal reaction time (SSRT). SSRT is an estimate of the speed of stopping, which was calculated using the so-called ‘integration method’ (Logan et al., 1984; Verbruggen and Logan, 2009). Because TMS can interfere with task performance, these measures of interest were calculated
separately for TMS and no-TMS trials. Separate SSD staircases were used for TMS and no-TMS trials and these were yoked only to the critical direction.

**Experiment 2**

**PROEDURE**

The same conditional stop task and procedure were used as experiment 1, except that a) subjects performed thirty-two blocks of 24 trials during the experiment proper, b) TMS was delivered on every stop trial and only on stop trials, and it was delivered at 200, 220, or 240 ms after the stop signal (Figure 3b), c) for both behavioral and TMS analysis we performed a median split of subjects into a ‘RDE group’ and a ‘no-RDE group’ based upon the RDE measure, and d) as there was no TMS during the ITI we used a common average baseline for normalization: for each subject the mean MEP amplitude for each condition was divided by the average amplitude of all of the MEPs for that subject.

### 2.3 RESULTS

**Experiment 1**

**STIMULATION PARAMETERS**

Resting motor threshold was 55.8 ± 5.1% of the maximum stimulator output and the mean test stimulus intensity was 64.2 ± 5.8%. The baseline MEP amplitude was 0.53 ± 0.36 mV.
TASK PERFORMANCE

Table 1 shows a summary of all behavioral data for all TMS and no-TMS trials. Overall, the subjects performed satisfactorily on the task.

For no-TMS trials, SSRT was estimated at 334 ms with a mean SSD of 210 ms and \( p(\text{inhibit}) \) at 0.48. The critical Go RT for no-TMS trials was 578 ms, and noncritical Go RT was 506 ms, giving a RDE of 73 ms, \( t(18) = 4.3, \ p < 0.001 \). For TMS trials, SSRT was estimated at 373 ms with a mean SSD of 206 ms and \( p(\text{inhibit}) \) at 0.48. The critical Go RT for TMS trials was 579 ms, and noncritical Go RT was 508 ms, giving a RDE of 71 ms, \( t(18) = 4.6, \ p < 0.001 \).

During practice, critical Go RT was 585 ms and noncritical Go RT was 532 ms. Critical Go RT during practice did not differ significantly from critical Go RT for no-TMS trials measured during the experiment proper, \( t(18) = 0.53, \ p = 0.60 \). This is important because TMS pulse times were determined based upon the practice critical Go RT. However, noncritical Go RT for no-TMS trials was significantly faster during the experiment proper than during practice, \( t(18) = 5.93, \ p < 0.001 \). Practice SSRT was estimated at 360 ms with a mean SSD of 204 ms and \( p(\text{inhibit}) \) at 0.27. The low \( p(\text{inhibit}) \) value reflects the fact that there were not many stop trials and thus the staircases did not have time to stabilize around 0.5.

MEP AMPLITUDE

We predicted that if subjects prepare to stop using a global inhibitory mechanism then there would be suppression of leg MEPs in the anticipation
phase for critical vs. noncritical Go trials. The TMS data are presented in Figure 4a. We tested our hypothesis with an ANOVA that included the factors condition (critical vs. noncritical) and two time points (120 and 200 ms after the Go stimulus). There were no main effects or interactions, all $p \geq 0.10$.

To validate the leg TMS methodology, we examined MEPs in the stopping phase. There was significantly reduced MEP amplitude for successful vs. failed stop trials, $t(18) = 2.6, p < 0.05$ two-tailed, and for successful stop vs. noncritical stop trials, $t(18) = 2.7, p < 0.05$ two-tailed, replicating Badry et al. (2009) and Majid et al. (2011). The direction of the critical response (i.e. left or right) did not influence leg MEP amplitude during successful stopping, $t(17) = 0.98, p = 0.34$.

Thus, while there was a behavioral RDE, we did not detect global suppression of the motor system, contrary to our prediction. Nevertheless, we did detect reduced leg excitability during successful stopping. See Discussion for the implications of these results. We note that while leg excitability was reduced during successful stopping relative to the other conditions, it was not reduced below our inter-trial baseline, as was observed in previous studies (Badry et al. 2009; Majid et al. 2011). This may relate to different aspects of our experimental design such as the pulse timing. Previously, the effect of leg suppression associated with stopping was demonstrated to be transient (Majid et al. 2011). Therefore, variability in the timing of the TMS pulse relative to the stop signal in our experiment may have blurred across the moment at which the leg was maximally suppressed. We explore this pulse timing issue in greater detail below.
Interestingly, we noted that some subjects did not slow down on critical Go trials at all while others slowed down a lot. This raised the possibility that the degree of slowing might affect the way stopping is carried out. We therefore correlated the size of the RDE (Go critical RT – Go noncritical RT) for no-TMS trials against the amplitude of the leg MEPs on successful stop trials. There was a significant correlation, $r(19) = 0.60, p < 0.01$, indicating that those subjects who slowed more for critical vs. noncritical trials had less leg suppression when they stopped (Figure 4b). This suggests that there might be different mechanisms for stopping (global vs. non-global), and which one is used depends on the degree of behavioral slowing in anticipation of stopping.

We note a possible confound for this analysis in terms of the relative timing of the TMS pulse for different subjects. The TMS pulse was delivered at the practice period critical Go RT minus 100 ms and corresponded to a mean time of $279.7 \pm 78.2$ ms after the stop signal on successful stop trials. The high variability in pulse times across subjects raises the possibility that the pulse timing was systematically different for people who slowed in anticipation of stopping compared to those who did not. However, there was no evidence of a correlation between the timing of the TMS pulse (i.e. the interval between the stop signal and the TMS pulse) and MEP amplitude, $r(19) = -0.15, p = 0.55$. Nor was there evidence of a correlation between MEP amplitude and the timing of the TMS pulse relative to the critical Go RT from no-TMS trials, $r(19) = 0.2, p = 0.41$. While the difference in pulse timing across subjects is very unlikely to explain the observed relationship between the RDE and leg suppression during stopping, we
nevertheless performed a second experiment in which the timing of TMS relative to the stop signal was held constant across subjects.

**Experiment 2**

**STIMULATION PARAMETERS**

Resting motor threshold was 56.8 ± 7.2% of the maximum stimulator output and the mean test stimulus intensity was 65.3 ± 8.4%. The baseline MEP amplitude was 0.49 ± 0.33 mV.

**TASK PERFORMANCE FOR ENTIRE GROUP (n = 20)**

Table 2 shows a summary of all behavioral data for all TMS (i.e. stop trials) and no-TMS trials (i.e. Go trials). In this experiment, TMS was delivered on every stop trial. TMS was never delivered on Go trials. Overall, the subjects performed similarly to experiment 1. SSRT (TMS trials) was estimated at 307 ms with a mean SSD of 204 ms and p(inhibit) at 0.47. The critical Go RT (no-TMS trials) was 563 ms, and noncritical Go RT (no-TMS trials) was 508 ms, giving a RDE of 55 ms, $t(19) = 4.0$, $p < 0.001$.

**TASK PERFORMANCE FOR RDE (n = 10) AND NO-RDE (n = 10) GROUPS**

Experiment 1 showed that some subjects did not slow at all, and that there was a correlation between the RDE and leg MEP amplitude when stopping. Accordingly, we split the current group into a ‘RDE group’ and a ‘no-RDE group’ based upon a median split of the RDE (Go critical – Go noncritical RT) (Table 3).
The RDE was 100 ms for the RDE group and 11 ms for no-RDE group, and this was a significant difference, \( t(18) = 4.8, p < 0.0005 \). The RDE in the no-RDE group was not significantly different from zero, \( t(9) = 1.5, p = 0.16 \). The between-group difference in the RDE was predominantly due to a large difference in critical Go RT, which was significantly longer for the RDE group than the no-RDE group, \( t(18) = 5.4, p < 0.0001 \).

To examine how the RDE might change across time (i.e. experience with the task) we calculated the RDE separately for the training session and for the first and second half of the experiment proper. ANOVA with the factors session (training, first half, and second half) and group (RDE vs. no-RDE) yielded a significant main effect of group, \( F(2,18) = 20.2, p < 0.0001 \), but no significant main effect of session, \( F(2,18) = 0.5, p = 0.61 \), or session by group interaction, \( F(2,18) = 1.72, p = .21 \). Thus, participants in the two RDE groups showed stable behavioral performance throughout the experiment.

**MEP AMPLITUDE FOR ENTIRE GROUP (n = 20)**

We predicted that the leg would be suppressed during successful stop trials relative to failed stop and noncritical stop trials at all or one of 200, 220, or 240 ms after the stop signal. The normalized MEP data are presented in Figure 4c. We were not interested in comparing noncritical with failed stop trials. Therefore, we conducted two separate ANOVAs. The first ANOVA included stop trial condition (successful vs. failed) and the three time points (200, 220, and 240 ms after the stop signal). There was a significant main effect of stop trial
condition, $F(1,19) = 11.5, p < 0.01$, with greater leg suppression for successful than failed stopping but no other significant main effect or interaction. The second ANOVA included stop trial condition (successful vs. noncritical) and the three time points (200, 220, and 240 ms after the stop signal). There was a significant main effect of stop trial condition, $F(1,19) = 9.1, p < 0.01$, with greater leg suppression for successful than noncritical stop trials but no other significant main effect or interaction. Results from both ANOVAs replicate experiment 1 as well as Badry et al. (2009) and Majid et al. (2011). As in experiment 1, the direction of the critical response (i.e. left or right) did not influence leg MEP amplitude during successful stopping, $t(18) = 0.31, p = 0.76$.

**MEP AMPLITUDE FOR RDE (n = 10) AND NO-RDE (n = 10) GROUPS**

Based upon the findings of experiment 1, we predicted that the no-RDE group would show greater leg suppression during successful stopping than the RDE group at some or all of 200, 220, or 240 ms after the stop signal. We conducted an ANOVA with the factors of group (RDE vs. no-RDE) and time point (200, 220, or 240 ms after the stop signal) on the leg MEP data for successful stop trials only. There was a significant group by time point interaction, $F(2,17) = 3.9, p < 0.05$. Comparisons between the two groups at each time point revealed that the no-RDE group exhibited greater leg suppression than the RDE group only at the 240 ms time point, $t(18) = 2.3, p < 0.0167$, Bonferroni corrected for the three comparisons (Figure 4d).
We note however that there was an SSRT difference between the RDE and no-RDE groups. SSRT (with TMS) for the RDE group was 261 ms and for the no-RDE group was 354 ms. This was a significant difference, \( t(18) = 2.2, p < 0.05 \). However, SSRT during the practice session (no-TMS) was 264 ms for the RDE group and was 300 ms for the no-RDE group, and this was not a significant difference, \( t(18) = 0.9, p = 0.39 \). The groups did not differ in regards to \( p \) (inhibit) during the experiment proper, \( t(18) = 1.7, p = 0.11 \).

Yet, the difference in SSRT is unlikely to explain the MEP results for two reasons. First, SSRT was shorter for the RDE than the no-RDE group. If the two groups utilized the same stopping mechanism, only at different time points, then we might have expected significantly greater leg suppression for the RDE than the no-RDE group at the early TMS time point of 200 ms after the stop signal (as the SSRT difference was around 40 ms). But, leg excitability for the RDE group was not significantly reduced compared to the no-RDE group at any time point. Second, it is likely that the SSRT estimate in the TMS phase was affected by the TMS stimuli themselves. TMS has been shown to interfere with task performance, and it may have caused the difference in SSRT to emerge between the two groups. Notably, SSRT measured during practice did not differ between the RDE and no-RDE groups. Another alternative explanation is that the shorter SSRT observed for the RDE group could reflect a potential benefit afforded by the proactive recruitment of a selective stopping mechanism.
AUXILIARY RESULTS

We reanalyzed the data from experiment 1 using an average baseline (i.e. average of all pulses not administered during the inter-trial interval, to be consistent with experiment 2), and the overall pattern of results remained the same: ANOVA with the factors condition (critical vs. noncritical) and time points (120 and 220 ms after Go stimulus) yielded no significant main effects or interactions. Leg MEP amplitude was significantly reduced for successful stop vs. failed stop trials, $t(18) = 2.6, p < 0.05$, two-tailed, and for successful stop vs. noncritical stop trials, $t(18) = 3.0, p < 0.01$, two tailed. The correlation between the RDE and MEP amplitude on successful stop trials also remained significant, $r(19) = 0.47, p < 0.05$.

Additionally, we found evidence of ‘conflict-induced slowing’, i.e. slowing on noncritical stop trials (with stop signals, but for which stopping is not needed) vs. go trials in experiment 1, $t(18) = 2.43, p < 0.05$, and in experiment 2, $t(19) = 3.8, p < 0.001$, but this did not correlate significantly with leg MEP amplitude during noncritical stop trials across participants in either experiment 1 or 2, $r(19) = -0.03, p = 0.90$ and $r(20) = 0.13, p = 0.57$, respectively. While this pattern suggests that conflict-induced slowing may not depend on a global inhibition mechanism, we note that in experiment 2 the no-RDE group did exhibit greater conflict-induced slowing than the RDE group, $t(18) = 3.6, p < 0.01$. This suggests that the no-RDE group experienced motor inhibition following a stop signal on noncritical trials. Although the TMS methodology we used here may not have been sensitive enough, or timed correctly, to detect a global inhibitory effect at
the leg during conflict-induced slowing, the observed behavioral pattern leaves open the possibility that conflict-induced slowing recruits a global inhibitory mechanism.

2.4 DISCUSSION

Much research suggests that outright stopping is achieved by a fast system in the brain that has global effects on the motor system. In experiment 1 we asked if such ‘global suppression’ can be observed proactively – i.e. when people anticipate they might have to stop. We used a conditional stop signal task and leg TMS to measure whether there was global suppression during an anticipation phase and during a stopping phase. Leg suppression was not observed during the anticipation phase, but it was for the stopping phase. Further, we observed that those subjects who exhibited the most behavioral slowing (i.e. larger RDE) were those who also showed the least leg suppression when stopping. In experiment 2 we used a similar task and setup except that TMS pulses were only delivered in the stopping phase, and at specific time points. We found, again, that those subjects who slowed in anticipation of stopping did not have as much leg suppression at the time of stopping as those who did not slow in anticipation of stopping. These results provide further evidence for different modes of stopping – a global mechanism and a selective one – and they clarify the circumstances under which these are used. We specifically show that if subjects do not prepare to stop (manifest in minimal RT
slowing) then, if they are required to stop, they resort to using an emergency stopping mechanism with apparently global effects on the motor system.

**Does anticipating the need to stop lead to ‘global suppression’ of the motor system?**

Previous evidence suggests that the mechanism used to stop a response outright has a global inhibitory effect on the motor system (Badry et al., 2009; Majid et al., 2011). We predicted that if proactive control involves the recruitment of the same or a similar mechanism then exercising proactive control in anticipation of stopping should also globally suppress the motor system. Although we replicated the finding of global suppression during outright stopping (Badry et al., 2009; Majid et al., 2011), we did not detect global suppression during anticipation of stopping. One potential explanation for this is that the TMS methodology we used is insensitive to global suppression when it occurs proactively. Yet, a recent study showed that TMS is sensitive enough to detect the effects of proactive control on the motor system – at least for the hand, and for a paradigm where suppression is targeted at particular response channels before the go stimulus (Cai et al., 2011). A second explanation for not finding global suppression during anticipation of stopping is a lack of sufficient statistical power. For experiment 1, we calculated a Cohen’s $d$ value of 0.25 for the comparisons of leg MEP amplitudes between critical and noncritical trials at 120 ms after the Go stimulus. This is a small effect size and over 200 subjects would be required to reach significance. A third explanation is that this conditional stop
task may not be ideally suited to examine global effects of proactive control because the go stimulus that tells the subject which response to make is the same stimulus that tells the subject whether he/she may need to stop or not. Thus, if the subject uses a proactive control mechanism at all, it may be a selective one that is targeted at the single response that may need to be stopped rather than a global brake. Future studies could address whether there is a global suppression mechanism in the proactive control or hold-your-horses period for other kinds of decision-making tasks that would more clearly require multiple responses to be withheld.

**Relation to neural systems**

We suppose that subjects who slowed down their responses on critical Go trials were partially using a proactive suppression mechanism which was selectively targeted at the particular response that might need to be stopped, c.f. (Cai et al., 2011). We speculate that this selective mechanism engages the indirect pathway of the basal ganglia, including the striatum (Aron and Verbruggen 2008; Majid et al. 2011). This is consistent with an fMRI study which compared critical and noncritical Go trials and revealed striatal activation (Jahfari et al., 2010), see also (Vink et al., 2005; Vink et al., 2006; Chikazoe et al., 2009; Zandbelt and Vink, 2010; Jahfari et al., 2011). Additional neuroimaging studies have implicated the striatum in the tradeoff between response speed vs. accuracy (Forstmann et al., 2008; Forstmann et al., 2010), and this tradeoff could depend on the selective proactive control of particular responses when accuracy
is favored over speed. Such a striatal mechanism for selective proactive control might establish its influence gradually over particular responses, as opposed to transiently and globally inhibiting the entire motor system.

In contrast to the proposed selective stopping mechanism mediated by the indirect pathway, non-selective stopping may instead be implemented via the hyperdirect pathway, characterized by fast and direct projections from the cortex (i.e. right inferior frontal cortex and pre-supplementary motor area) to the subthalamic nucleus (STN) (Aron and Poldrack, 2006; Aron et al., 2007). The STN is a deep brain structure with diffuse excitatory projections to output nuclei of the basal ganglia that in turn exert an inhibitory influence over the motor system (Mink, 1996; Nambu et al., 2002). Therefore, recruitment of the STN could result in the rapid suppression of activity globally throughout the motor system.

Conclusions and Implications

In each of two experiments we found that, taking all subjects together, the leg muscle was suppressed when the hand was stopped. In each experiment we also found that those subjects who slowed down more in anticipation of stopping did not show as much leg suppression during the outright stopping phase as those who did not slow down. This suggests that if subjects do not prepare to stop then they have to resort to using an emergency stopping mechanism with global effects on the motor system. By contrast, if subjects do prepare to stop then they evidently stop with lesser global effects. While further research is
required to test the neural basis of this distinction, this study provides novel insights into the relationship between preparing to stop and stopping outright.

The results could have practical implications. There is evidently large variability in whether people bother to prepare to stop or not. It is possible that this individual difference reflects a degree of ‘motor caution’ that could relate to levels of impulsivity. That is testable in future studies that use personality rating scales. Further, the ability or disposition to prepare to stop in advance may help us to limit our dependence on ‘emergency’ behavioral inhibition mechanisms that could disrupt other ongoing behaviors. For example, a person who stops him or herself from uttering an offensive phrase mid-sentence may stop speaking altogether, whereas a person who proactively inhibits the urge to utter that offensive phrase may be able to continue speaking without interruption.

Chapter 2, in full, is a reprint of the material as it appears in the Journal of Neurophysiology 2012. Greenhouse, I., Oldenkamp, C. L., & Aron, A. R. (2012). Stopping a response has global or nonglobal effects on the motor system depending on preparation. *Journal of Neurophysiology, 107*(1), 384–392. The dissertation author was the primary investigator and author of this paper.
Figure 3: The conditional stop task consists of critical trials (dark grey) and noncritical trials (light grey). The auditory stop signal was only relevant for critical trials, e.g. when the target arrow points left. A) In experiment 1, TMS pulses were delivered during a baseline period (200 or 300 ms before the arrow) and at 120 or 200 ms after the arrow. Pulses were also delivered at 100 ms before each subject’s critical Go RT as measured during practice. B) In experiment 2, TMS pulses were delivered 200, 220, or 240 ms after the stop signal.
Figure 4: Normalized leg MEP results for experiments 1 and 2. A) In experiment 1, leg MEP amplitudes did not differ between critical and noncritical trials at 100 or 200 ms after the target, but were reduced during successful stop as compared with failed stop and noncritical stop trials. B) In experiment 1, those subjects who demonstrated a greater response delay effect (critical RT – noncritical RT) also demonstrated greater leg excitability during successful stopping. C) In experiment 2, leg MEP amplitudes were reduced at 200, 220, and 240 ms after the stop signal during successful stop as compared with failed stop and noncritical stop trials. D) Subjects in experiment 2 were divided into those who exhibited a response delay effect (‘RDE group’) and those who did not (‘no-RDE group’) by performing a median split based on the response delay effect. During successful stop trials, the RDE group demonstrated greater leg suppression than the no-RDE group at 240 ms, but not at 200 or 220 ms, after the stop signal. * indicates significance at $p < 0.05$. 
2.5 REFERENCES


Chapter 3:

Stimulation of the ventral subthalamic nucleus influences two measures of executive function

ABSTRACT

Research in non-human animals suggests that the subthalamic nucleus (STN) of the basal ganglia can be subdivided into functional territories that include separate sensorimotor (dorsal) and executive (ventral) sectors. While much research and clinical practice in humans focuses on a role for the STN in sensorimotor functions, a role for the human STN in executive functions is scarcely established. Here we focused on executive function and tested whether stimulation of the ventral STN would alter the functions of response switching, preparing to stop and stopping outright. We tested Parkinson’s disease patients at three visits each: once with bilateral dorsal STN stimulation, once with bilateral ventral STN stimulation, and once Off stimulation; and also matched healthy controls. Patients Off stimulation showed abnormal patterns of response switching and slowing in anticipation of stopping (i.e. preparing to stop). Stimulation of the ventral but not the dorsal STN restored behavior to a level more similar to controls. This provides evidence in humans that the ventral STN participates in fronto-basal ganglia circuitry that is important for executive functions.
3.1 INTRODUCTION

There is much current clinical and basic science interest in the human subthalamic nucleus (STN). Stimulation of this small structure via deep brain stimulation (DBS) leads to striking improvements in movement disorders such as Parkinson’s disease (PD) and is also being used to treat obsessive-compulsive disorder (Benabid et al., 2009; Bronstein et al., 2011; de Koning et al., 2011; Fox et al., 2011). However, while STN stimulation in PD generally improves motor function, it sometimes has side effects including changes in cognition, speech, and mood. The emergence of these side effects suggests that the human STN, and its connected brain circuits, do more than mediate motor functions.

Tract-tracing research in the rodent and monkey brain suggests the STN has three subregions, based upon its connectivity with other brain areas: the dorsal subregion (sensorimotor), the ventral subregion (executive/associative) and the ventro-medial tip (limbic) (Alexander and Crutcher, 1990; Parent and Hazrati, 1995a; 1995b; Joel and Weiner, 1997; Karachi et al., 2005; Temel et al., 2005), but see (Keuken et al., n.d.). Yet the functional subdivision of the STN is not well established in humans. While many studies have compared Off vs. On stimulation for various psychological processes, very few have assessed non-motor functions while stimulating or recording from different STN subregions (Mallet et al., 2007; Hershey et al., 2010; Greenhouse et al., 2011). Collectively, this animal and human research suggests the STN may be involved in functions traditionally attributed to the frontal cortex and, in primates, these functions may depend more on the ventral portion of the nucleus (Baunez and Lardeux, 2011).
Here, we test the hypothesis that stimulation of the ventral vs. dorsal STN affects executive function in humans. Based on the extant literature, we used two different computerized tests of executive function: a response switching and a Maybe Stop/No Stop task. Switching is a cardinal executive function that relates to the ability to flexibly change between tasks or response sets in everyday life. It is well established that the basal ganglia are important for switching (Aron et al., 2003; Cools et al., 2006; Robbins, 2007; Yehene et al., 2008; Cameron et al., 2009; Hikosaka and Isoda, 2010; Redgrave et al., 2010) and that patients with Parkinson’s disease are impaired at switching (Lees and Smith, 1983; Cools et al., 1984; 2001; Cameron et al., 2010). To test if the ventral STN might be important for switching in humans we used a task that was adapted for humans (Mars et al., 2009; Neubert et al., 2010) from a neurophysiological study in monkeys (Isoda and Hikosaka, 2008). Importantly, the monkey study found that single neurons in the ventral STN changed their firing pattern during a switch (Isoda and Hikosaka, 2008).

We also used a Maybe Stop/No Stop task (Swann et al., 2011b). This measures two kinds of action control: reactive stopping (i.e. what is often referred to as ‘response inhibition’ for Go/NoGo and stop signal tasks), and response slowing in anticipation of stopping. Stopping is also a cardinal executive function, being important in everyday life for controlling inappropriate responses (Verbruggen and Logan, 2008; Aron, 2011). Evidence for the selective involvement of the ventral STN in reactive stopping comes from research in monkeys and humans. The same monkey neurophysiology study mentioned
above also demonstrated that many STN neurons sensitive to switching also responded on NoGo trials (Isoda and Hikosaka, 2008). A study in humans showed that ventral but not dorsal STN stimulation caused patients to make fewer hits on Go trials and more false alarms on NoGo trials, possibly reflecting impaired response inhibition inter alia (Hershey et al., 2010). Several other studies in humans have pointed to the importance of the STN in response inhibition, but without subregional specificity (Kühn et al., 2004; Aron and Poldrack, 2006; van den Wildenberg et al., 2006; Ray et al., 2009; Mirabella et al., 2011; Swann et al., 2011a). Regarding preparing to stop, the STN has not yet been implicated, let alone the ventral STN specifically; however, studies of related phenomena such as favoring accuracy over speed and holding back responses while decisions are made do point to STN involvement (Frank et al., 2007a; 2007b; Bogacz et al., 2009; Forstmann et al., 2010; Mansfield et al., 2011).

Using these two tasks we studied PD patients Off stimulation and also On bilateral stimulation of either the ventral or dorsal STN. We also compared the patients with healthy controls. For each patient we targeted the stimulation at contacts estimated to lie in ventral or dorsal STN sectors using imaging and neurophysiological diagrams. Thus, the stimulation parameters for this study varied from the clinically-determined treatment settings.

Based upon multiple studies of switching and stopping deficits in PD (Cools et al., 1984; 2001; Gauggel et al., 2004; van den Wildenberg et al., 2006; Robbins, 2007; Kehagia et al., 2009; Cameron et al., 2010; Mirabella et al., 2011;
Swann et al., 2011a), we predicted that patients tested with DBS Off would exhibit abnormal task performance relative to controls on both behavioral tasks (i.e. greater switch costs, less slowing in anticipation of stopping, and impaired stopping). Furthermore, we hypothesized that ventral STN stimulation might rectify some of these executive function indices while dorsal STN stimulation would not. If so, this would provide evidence in humans that the ventral STN (and possibly the connected associative cortico-basal-ganglia circuit) implements executive function.

3.2 MATERIALS AND METHODS

Participants

Eleven patients diagnosed with Parkinson’s disease and treated with bilateral STN DBS were recruited from the Scripps Clinic in La Jolla, California. Ten age- and gender-matched healthy controls were recruited from the La Jolla community. All participants provided informed consent.

One patient was excluded from switching task analysis because of an error rate greater than three standard deviations above the group mean. There were therefore ten patients and ten matched controls in the switching task analysis. Two patients were unable to perform the Maybe Stop/No Stop task at one or more of the prescribed DBS settings. There were therefore nine patients and 10 matched controls in the Maybe Stop/No Stop task analysis. For each task, the groups were well matched on age, gender, handedness, MMSE, NAART (Table 1, all \( p \)'s > 0.05). For the patients, the time between the first and
second research visit was 14.0 ± 10.1 days, and the time between the second
and third research visit was 11.8 ± 11.8 days.

There were no significant differences in Unified Parkinson’s Disease
Rating Scale (UPDRS) III scores between OFF, Dorsal, and Ventral stimulation
conditions (Table 2). This is not surprising given that the experimental stimulation
settings were not intended to be therapeutic for PD motor symptoms and, in fact,
were substantially different from the patients’ typical settings.

**Neuroimaging and electrode contact selection**

Before DBS surgery, MRI was acquired on a Siemens Symphony 1.5T
scanner. This included scans with sagittal T1-weighting [TR = 2000 ms, TE =
2770 ms, flip angle = 15, 512 slices, 0.5 x 0.5 x 1 mm], coronal T2-weighting [TR
= 3630 ms, TE = 128 ms, flip angle = 180, 19 slices, 1 x 1 x 2 mm], and axial T2-
weighting [TR = 3400 ms, TE = 92 ms, flip angle = 180, 19 slices, 1 x 1 x 2 mm]).
The STN is hypointense in T2-weighted MRI due to higher iron content (Dormont
et al., 2004). After DBS surgery, a coronal CT image (0.5 x 0.5 x 0.625 mm, 120
kV, 320 mAs) was acquired on a GE LightSpeed CT scanner. The quadripolar
DBS lead (model 3389, Medtronic Activa System, Medtronic Inc.) is visible as an
artifact within the CT image.

Electrode localization proceeded as follows: First, the T2-weighted and CT
images were coregistered to the T1-weighted image using a mutual information
function (Collignon et al., 1995; Wells et al., 1996) in SPM 5 (Wellcome Dept. of
Cognitive Neurology, London, UK). Second, the artifact caused by the DBS lead
in the CT image was identified. Third, a model of the lead was scaled to match the voxel size of the artifact and overlaid on the image, see Figure 5a-c. Fourth, for each patient, two raters independently chose the best ventral and dorsal contacts for the study. Across the forty-four different electrode contacts (11 patients x 2 contacts x 2 hemispheres), there was strong inter-rater agreement (Spearman’s $\rho = 0.95$, $p < 0.001$). Fifth, reliability was also assessed in comparison with neurophysiological diagrams made from surgical recordings (see Figure 5d), and for more information (Hutchison et al., 1998; Greenhouse et al., 2011). For the 22 contacts in the ventral STN and the 22 contacts in the dorsal STN there was strong agreement in the contact chosen by the two raters (averaged) and the neurophysiological diagrams (Spearman’s $\rho = 0.91$, $p < 0.001$ and $\rho = 0.84$, $p < 0.001$, respectively).

**Behavioral protocol**

The patients were on typical medications throughout the experiment. They were tested at three separate visits: off stimulation (Off), with stimulation delivered to the dorsal STN (Dorsal), and with stimulation delivered to the ventral STN (Ventral). The visit order was counterbalanced across patients, and the patients and experimenter were double-blind to the Ventral/Dorsal conditions. Testing began at least thirty minutes after DBS adjustment. The UPDRS part III was administered to assess motor symptoms following DBS adjustment at each visit. For both tasks, stimuli were presented using the Psychtoolbox in Matlab R2009a (Mathworks, Natick, MA) running on a MacBook Pro laptop (Apple,
Cupertino, CA), and responses were recorded with an USB-interfaced two-button keypad. Participants responded using the index and middle fingers of the right hand.

THE SWITCHING TASK

This was adapted from prior studies (Isoda and Hikosaka, 2007; 2008; Mars et al., 2009; Neubert et al., 2010; 2011) (Figure 6a). At each visit, there were 30 practice trials and 180 test trials. Trials began with a white fixation square of 1 sec at center screen. The square was then flanked on each side by colored squares (one yellow and one pink) for a variable cue-period (450-600 ms, uniform distribution). The center square then changed color to match one of the two flanking squares. Participants were instructed to respond with a button press corresponding to the matching side (i.e. index finger for a left response or middle finger for a right response). The response window was 1 sec. The target stimulus was then replaced with the white fixation. A 400 ms 100Hz tone sounded if there was an incorrect response or if a response was not completed within the response window. Importantly, the matching color (e.g. yellow) repeated for a series of 4 to 8 consecutive trials (uniform distribution). This increased prepotency by encouraging participants to prepare a particular response during the cue-period based upon the matching color of the preceding trial. Trials for which the matching color remained the same as on the previous trial are referred to here as ‘nonswitch’ trials, and trials in which the matching color differed from the previous trial are referred to as ‘switch’ trials. Each trial
was further categorized depending upon whether the response on that trial was the same (i.e. repeat) or different (i.e. alternate) from the previous trial. This resulted in four trial categories: switch-repeat, switch-alternate, nonswitch-repeat, and nonswitch-alternate (see Figure 6a). This was done based upon the classic finding that switch cost differs for repeat and alternate responses (Rogers and Monsell, 1995; Cooper and Mari-Beffa, 2008; Kiesel et al., 2010). During the experiment proper, participants completed 180 trials; totaling thirty switch trials and 150 nonswitch trials.

THE MAYBE STOP/NO STOP TASK

We used the ‘Maybe Stop/No Stop’ (MS/NS) version of the stop signal task (Swann et al., 2011b) with slight modifications (Figure 6b). At each visit, there were 24 practice trials and then eight blocks of 24 test trials. Trials began with a preparatory cue, either the words ‘Maybe Stop’ or ‘No Stop,’ for .6 sec. The cue was followed by a .4 sec blank screen, and then a target left- or right-pointing arrow for up to 2 sec or until a key was pressed. Trials were separated by a blank 1.2 sec inter-trial interval. There were 96 ‘Maybe Stop’ (MS) trials and 96 ‘No Stop’ (NS) trials in total.

Two thirds of the MS trials (i.e. 64 trials) were stop trials where the arrow was followed, at a short stop signal delay (SSD), by an auditory stop signal (500 Hz, .4 sec). A mixture of four independent SSD staircases (two for each response, initial SSDs of .15 and .2 sec) moved up and down in increments of .05 sec according to the participant’s performance to converge on an
approximate $p(\text{stop} \mid \text{signal}) \sim .5$ (Logan et al., 1997). For reactive stopping, we computed the speed of stopping, i.e. stop signal reaction time (SSRT), using the integration method (Verbruggen and Logan, 2009a). For preparing to stop, we calculated the amount of slowing down that occurs when stopping is anticipated as MS Go RT minus NS Go RT. However, since the PD Off group responded significantly more slowly than controls on the NS Go trials, we created a proportional index i.e. $(\text{MS Go RT} - \text{NS Go RT})/\text{NS Go RT}$ in keeping with much research in ageing and patients, e.g. (Faust et al., 1999). We refer to this as the proportional response delay effect ($pRDE$).

### 3.3 RESULTS

**The Switching Task**

**CONTROLS VS. PATIENTS OFF DBS**

For RT, ANOVA was performed with the factors trial type (switch vs. nonswitch), response type (repeat vs. alternate), and group (PD-Off vs. control). There was a main effect of trial type with switch trials slower than nonswitch

$[F(1,18) = 6.1, P < 0.05]$; Table 3 and **Figure 7a**. There was a small but significant main effect of response type, with longer RT for repeat (529 msec) than alternate (521 msec) responses $[F(1,18) = 7.1, P < 0.05]$. There was a significant interaction between trial type and response type $[F(1,18) = 7.7, P < 0.05]$, replicating the well-established finding that there is a greater RT switch cost for repeat than alternate responses. The interaction between response type and group was also significant $[F(1,18) = 4.4, P = 0.05]$, indicating that controls
showed a larger difference between repeat and alternate response RT than did patients. Most noteworthy was a highly significant three-way interaction of trial type, response type, and group for RT \([F(1,18) = 10.8, P < 0.01]\). There were no other significant main effects or interactions.

To further examine the three-way interaction for RT, follow-up ANOVAs were run for the control and PD groups separately and included the factors trial type (switch vs. nonswitch) and response type (repeat vs. alternate). For controls there was a main effect response type, i.e. longer RT for repeat (520 ms) than alternate (506 ms) responses \([F(1,9) = 14.3, P < 0.01]\) and a significant trial type by response type interaction for RT \([F(1,9) = 23.6, P < 0.001]\), but no other significant main effects or interactions. Follow-up paired t-tests showed that the trial type by response type interaction was due to a significant switch cost for repeat response trials \((t = 4.4, P < 0.01)\) and the lack of a significant switch cost for alternate response trials \((t = -0.72, P = 0.49)\) (Figure 7b). Alternate responses were in fact slightly faster for switch (501 ms) than nonswitch (511 ms) trials, albeit not significantly so. This pattern of behavior replicates previous studies of task switching in healthy populations that reported a switch cost for repeat and not for alternate responses (Rogers and Monsell, 1995; Aron et al., 2003).

For the PD group there was a trend toward slower RT for switch than nonswitch trials \([F(1,9) = 3.2, P = 0.11]\), but no other significant main effects or interactions. In stark contrast to the control group, patients Off DBS did not exhibit any relationship between switch cost and repeat vs. alternate responses (Figure 7b). Thus, the control group showed a difference in the switch cost for
repeat vs. alternate trials whereas the PD group did not, and this resulted in the significant three-way interaction observed in the overall ANOVA.

For errors, ANOVA was performed with the factors trial type (switch vs. nonswitch), response type (repeat vs. alternate), and group (PD-Off vs. control). There was a main effect of trial type, with more errors on switch vs. nonswitch trials \( F(1,18) = 13.0, P < 0.01; \text{Figure 7c} \), but no other significant main effects or interactions.

EFFECTS OF DBS

ANOVA was performed for the factors DBS condition (Off, Dorsal, Ventral) trial type (switch, no switch) and response type (repeat, alternate). Patients were significantly slower on switch than nonswitch trials \( F(1,9) = 5.0, P = 0.05; \text{Figure 7a} \). There was also a significant trial type by response type interaction \( F(1,9) = 6.5, P < 0.05 \) (i.e. a greater switch cost for repeat than alternate response trials). The three-way (trial type x response type x DBS condition) interaction for RT was also significant \( F(2,18) = 6.5, P < 0.01, \text{Figure 7c} \). There were no main effects of DBS condition or response type.

To interpret the three-way interaction for RT, follow-up ANOVAs were run separately for the Ventral and Dorsal DBS conditions and these included the factors trial type (switch vs. nonswitch) and response type (repeat vs. alternate). Results from the OFF condition were reported above. For the Ventral DBS condition there was a significant interaction \( F(1,9) = 26.9, P < 0.001 \) indicating a larger switch cost for repeat than alternate responses, but there were no
significant main effects. For the Dorsal DBS condition switch RT was significantly slower than nonswitch RT \([F(1,9) = 8.1, P < 0.05]\), but there was no significant effect of response type and no interaction. This pattern of results shows that patients in the Ventral DBS condition had a larger switch cost for repeat vs. alternate responses while this was not the case for the Dorsal or OFF DBS conditions (Figure 7b). Moreover, every patient in the Ventral DBS condition demonstrated a greater switch cost for repeat than for alternate responses, and this more closely resembled the pattern of the control group than the Dorsal or OFF DBS conditions (see Figure 8).

For errors, ANOVA was performed for the factors DBS condition (Off, Dorsal, Ventral) trial type (switch, no switch) and response type (repeat, alternate). There were more errors on switch than nonswitch trials \([F(1,9) = 11.6, P < 0.01; \text{Figure 7c}]\). However, there was no significant effect of DBS condition or response type, and there were no significant interactions.

The Maybe Stop/No Stop Task

CONTROLS VS. PATIENTS OFF DBS

For preparing to stop, the key index was how much slowing there was on trials where stopping was anticipated compared to those on which it was not (i.e. MS – NS RT). As explained above, the PD-Off group was slower than controls on the ‘baseline’ NS trials \((t = 2.9, P = 0.01, \text{two-tailed}; \text{Figure 9a})\); thus we created a proportional index of proactive control for RT (i.e. MS – NS / NS), which we refer to as \(pRDE\). For this index, there was a significant difference between
groups, with controls showing greater proactive control (0.44) than the PD-Off group (0.22) \((t = 2.2, P < 0.05, \text{two-tailed; Figure 9b})\).

For reactive stopping (SSRT), the PD-Off group was slower to stop than controls (PD-OFF: 358; controls: 273 ms), consistent with several prior studies (Gauggel et al., 2004; van den Wildenberg et al., 2006; Mirabella et al., 2011; Swann et al., 2011a), however this was only at trend level \((t = 1.4, P = 0.09, \text{one-tailed; Figure 9c})\).

Patients and controls did not differ in their error rates on Go trials (Fig. 5D).

**EFFECTS OF DBS**

A repeated-measures general linear model ANOVA was performed on the \(p\)RDE measure across the three DBS conditions (Off, Dorsal, Ventral), following the analysis method of a previous study (Hershey et al., 2010). There was a significant effect with the largest \(p\)RDE observed for the Ventral condition (0.28), followed by the Dorsal condition (0.27), and Off (0.22) \([F(1,8) = 6.4, P < 0.05; \text{Figure 9b}]\). Follow-up paired \(t\)-tests indicated that the \(p\)RDE was significantly larger in the Ventral than the Off condition \((t = 2.5, P < 0.05, \text{one-tailed, Bonferroni corrected})\). Significant differences were not observed between the Ventral vs. Dorsal or the Dorsal vs. Off comparisons \((t = 0.5, P = 0.3 \text{ and } t = 1.4, P = 0.1, \text{respectively, one-tailed})\).
For reactive stopping, repeated-measures general linear model ANOVA revealed that there were no significant differences in SSRT across the three DBS conditions (Off, Dorsal, Ventral) (Figure 9c).

A repeated-measures ANOVA was performed for the proportion of errors on Go trials and included the factors DBS condition (Off, Dorsal, Ventral) and trial type (MS, NS). There were no significant main effects or interactions (Figure 9d).

### 3.4 DISCUSSION

We used a double-blind and counterbalanced design to test a group of PD patients on two different tasks of executive function while DBS was targeted at either the ventral or dorsal STN. We also tested patients Off DBS as well as a matched group of controls. We found that patients Off DBS exhibited abnormal patterns of switching and slowing in anticipation of stopping. Specifically, patients showed an equivalent switch cost for repeat and alternate responses, whereas controls showed a typical pattern of a larger switch cost for repeat than alternate responses. Patients also demonstrated reduced slowing in anticipation of stopping relative to healthy controls. These abnormal patterns of behavior became more like those of controls when stimulation was targeted at the ventral but not dorsal STN. We attribute these findings to a role for the ventral STN in modulating executive functions, probably via the ‘associative’ prefrontal-basal ganglia circuit.
Switching

The controls exhibited the classic pattern of an RT switch cost for repeat, but not alternate responses (Rogers and Monsell, 1995; Cooper and Mari-Beffa, 2008; Kiesel et al., 2010). This pattern may result from: (i) a tendency to switch the rule and response simultaneously (i.e. a ‘change all’ signal), (ii) increased difficulty uncoupling recently established stimulus-response mappings, or (iii) the selective suppression of the last-executed (and possibly still active) response (Rogers and Monsell, 1995). Current behavioral evidence supports the latter, selective suppression, hypothesis (Hübner and Druey, 2006; Cooper and Mari-Beffa, 2008; Hübner and Druey, 2008). Interestingly, the PD patients Off stimulation exhibited equivalent switch costs for repeat and alternate response trials. While we cannot be sure of the mechanism underlying this difference between PD Off and controls, one possibility is that pathology of the basal ganglia in PD rendered these patients unable to selectively suppress particular responses; specifically, when they switch they may not suppress the response just made, instead they may suppress more globally. Hence there is a switch cost regardless of whether there is a repeat or alternate response. Importantly, ventral but not dorsal STN stimulation restored the switching pattern in the PD patients to that observed in controls: i.e. there was now the classic pattern of a switch cost for repeat, but not alternate, responses.

A neural mechanism that may underpin the selective suppression of a just-executed movement is the indirect pathway of the basal ganglia. The indirect pathway is comprised of a projection from the striatum to the external pallidum
and then to the STN and internal pallidum (striatum-GPe-STN-GPi, or alternatively, striatum-GPe-GPi) (Albin et al., 1989; Alexander and Crutcher, 1990). It has been proposed that the indirect pathway is important for controlling particular responses (Mink, 1996; Shink et al., 1996; Joel and Weiner, 1997; Nambu et al., 2002), and this pathway is believed to be affected in PD (DeLong, 1990; Nambu, 2005; Redgrave et al., 2010). As stated before, it is possible that the pathology of basal ganglia pathways in PD induces an overdependence on global suppression of the motor system at the expense of selective suppression, and therefore a putative basal-ganglia mechanism for selectively suppressing the just-made-response cannot be engaged when a switch occurs. Further studies, at the neural/physiological level, are needed to validate the idea that switching involves suppression of the just-made-response via basal ganglia circuitry, and that this ability is disrupted in PD.

Whereas previous studies in PD have reported deficits in primary switch cost (i.e. independent of response type; repeat vs. alternate), here we did not detect such an effect. Instead, we observed an effect of DBS on the comparison of switch costs for repeat and alternate response trials. However, we note that most studies of switching in PD only looked at the overall switch cost and did not break it down by repeat/alternate responses [although see (Shook et al., 2005; Cools et al., 2006; Helmich et al., 2009)]. Further, the current task is a particular form of switching, response switching, which is different from many of the switching paradigms used in previous PD studies. In any event, the current results clearly show, in humans, that ventral STN stimulation modifies at least
one type of switching, thus buttressing the results from monkey neurophysiology (Isoda and Hikosaka, 2008) and pointing to the ventral STN and/or its influence on the associative cortico-basal ganglia circuit as being important for switching.

**Preparing to stop**

Whereas controls showed substantial slowing down when stopping was anticipated, the amount of proportional slowing was reduced in PD patients Off DBS. Notably, as for switching, DBS of the ventral STN had an effect (increasing the preparatory slowing) relative to DBS Off while dorsal STN DBS did not.

There are several explanations for the slowing down of RT when stopping is anticipated. It could relate to prolonging the decision to go, reduced facilitation of the go process, and active suppression of the unfolding response (i.e. braking) (Verbruggen and Logan, 2009b; Jahfari et al., 2010). While fMRI studies show that prefrontal brain regions associated with reactive stopping are activated when preparing to stop (Vink et al., 2005; Chikazoe et al., 2009; Jahfari et al., 2010; Swann et al., 2011b; Zandbelt et al., 2012), perhaps consistent with the braking account, these studies have not identified STN activity. However, the STN has been implicated in response slowing that occurs to a stop signal that should be ignored (Aron et al., 2007), and in paradigms that stress accuracy over speed (Frank et al., 2007b; Bogacz et al., 2009; Forstmann et al., 2010), and by other tasks that require subjects to hold back their responses while decisions are made (Frank et al., 2007a; Mansfield et al., 2011; Zaghloul et al., 2012). Thus, it is possible that the ventral STN and its connected circuitry are important for slowing
down RT when stopping is anticipated, perhaps via partial suppression of basal ganglia output. An alternative explanation is that ventral STN stimulation actually impaired rather than improved executive aspects of Maybe Stop trial performance. On this account the longer RT on Maybe Stop Go trials for ventral STN stimulation reflects the extra time required to apply proactive control rather than an increased level of proactive control. However, this is difficult to reconcile with the result from the response switching experiment in which ventral stimulation clearly restored switching behavior to the same pattern as controls. Thus, a seemingly more parsimonious interpretation is that ventral STN stimulation improves executive function deficits in PD.

It is possible that ventral STN stimulation acts on a mechanism that is important for the selective suppression of responses and is commonly recruited for response switching and preparing to stop. While response switching involves many processes, one of these may be the selective suppression of the response just-made (Hübner and Druey, 2006; Cooper and Mari-Beffa, 2008; Hübner and Druey, 2008). And while preparing to stop also involves many processes, one of these may be the selective suppression of particular response channels (Cai et al., 2011; Jahfari et al., 2011; Majid et al., 2011; Greenhouse et al., 2012). We speculate that such selective suppression relates to the indirect pathway of the basal ganglia. If PD impairs the recruitment of the indirect pathway, this could explain both types of executive function deficits seen here.
Reactive Stopping

Several studies have reported that PD patients stop more slowly than controls (Gauggel et al., 2004; van den Wildenberg et al., 2006; Mirabella et al., 2011; Swann et al., 2011a), and we also observed this difference between groups, albeit at trend level. Yet, unlike previous studies, we did not observe an effect of DBS on stopping performance (van den Wildenberg et al., 2006; Mirabella et al., 2011; Swann et al., 2011a). Importantly, however, these other studies tested patients On therapeutic DBS treatment settings compared to Off, whereas here we compared dorsal vs. ventral STN stimulation at non-therapeutic settings. One previous study found that ventral STN stimulation caused patients to make fewer correct Go responses and more failures of inhibition on NoGo trials during the performance of a Go/NoGo task (Hershey et al., 2010). However, a comparison with that study is complicated because it involved unilateral stimulation, whereas here there was bilateral stimulation. Notably, of the existing STN DBS investigations of motor response inhibition, those that used unilateral stimulation have reported performance impairments (Hershey et al., 2004; Ray et al., 2009; Hershey et al., 2010), whereas those that used bilateral DBS showed performance improvements (van den Wildenberg et al., 2006; Mirabella et al., 2011; Swann et al., 2011a). Unfortunately, we did not test patients On their treatment DBS settings, and consequently we are unable to make claims about whether or not the therapeutic benefit of DBS for motor symptoms translates to stopping. We speculate that DBS settings selected for the purpose of treating PD
motor symptoms are also important for reactive stopping, whereas the anatomically defined targets in the dorsal and ventral STN that we used here are not. This is corroborated by the fact that we did not observe UPDRS improvements for our experimental DBS settings. Thus, the reactive stopping deficit commonly observed in PD may have a different etiology than the switching and proactive slowing deficits we observed here.

Conclusions and Implications

Stimulation of the ventral but not the dorsal STN in Parkinson’s patients remediated abnormal patterns of switching and response slowing in anticipation of stopping and caused patients to behave more similar to healthy controls. These findings suggest that the ventral STN and the connected associative cortico-basal ganglia circuit are involved in these two types of executive functions. This is some of the first evidence that executive functions of switching and proactive control are sensitive to the manipulation of basal-ganglia mechanisms in humans.

The results strongly suggest that there may indeed be an ‘associative/executive’ cortico-basal ganglia circuit in humans that includes the ventral STN. This pathway appears to be particularly important for the executive functions of switching and preparing to stop – two types of goal-directed response control. We speculate that these types of goal-directed response control share a common process that involves the selective inhibition of a response, and may relate to the recruitment of the indirect cortico-STN pathway.
For switching, this mechanism could selectively inhibit the just-made-response. For preparing to stop, this mechanism could target a selected response to slow its execution when stopping is anticipated.

Deficits in switching and proactive control are common across a wide range of neurological and psychiatric disorders including obsessive-compulsive disorder (Menzies et al., 2007; Gu et al., 2008), schizophrenia (Vink et al., 2006; Wylie et al., 2010), attention deficit/hyperactivity disorder (Schachar et al., 2004; Kenemans et al., 2005), and Huntington’s disease (Aron et al., 2003) in addition to Parkinson’s disease [for a review also see (Robbins, 2007)]. It is possible that the executive function deficits observed across these different disorders arise from the direct or indirect disruption of associative cortico-basal ganglia circuitry. The ventral STN may be a candidate target for treating these types of executive function deficits with DBS. Similar studies in these populations may help to further characterize the role of the ventral STN and its connected circuitry in executive functions.

In summary, this study supports the existence of separate functional circuits through the human STN and provides valuable insights into a putative role for the STN and its connections in executive functions in humans. Specifically, the ventral STN and its connected circuitry may be important for response switching and preparing to stop (i.e. slowing in anticipation of stopping). The associative cortico-basal ganglia circuit may depend upon this STN subregion to selectively control goal-directed responses.
Chapter 3 is a manuscript of an article being prepared for submission.

Greenhouse, I; Gould, S; Houser, M; Aron, AR 2012.
<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Gender (F/M)</th>
<th>Handedness (L/R)</th>
<th>MMSE ± std</th>
<th>NAART ± std</th>
<th>Off ± std</th>
<th>Ventral ± std</th>
<th>Dorsal ± std</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD Stopping</td>
<td>62.6 ± 7.3</td>
<td>2/7</td>
<td>1/8</td>
<td>28.3 ± 2.0</td>
<td>37.9 ± 9.0</td>
<td>8.8 ± 3.4</td>
<td>8.1 ± 3.8</td>
<td>10.3 ± 4.5</td>
</tr>
<tr>
<td>PD Switching</td>
<td>63.3 ± 7.3</td>
<td>2/8</td>
<td>1/9</td>
<td>28.2 ± 1.9</td>
<td>37.4 ± 8.6</td>
<td>8.7 ± 3.2</td>
<td>8.3 ± 3.6</td>
<td>10.2 ± 4.3</td>
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<tr>
<td>NC</td>
<td>61.8 ± 9.7</td>
<td>2/8</td>
<td>1/9</td>
<td>29.3 ± 0.8</td>
<td>42.5 ± 10.1</td>
<td></td>
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</tr>
</tbody>
</table>

PD = Parkinson’s disease, NC = normal control, Stopping = Maybe Stop/No Stop task, Switching = switching task, MMSE = Mini-Mental State Examination, NAART = North American Adult Reading Test, UPDRS III = Unified Parkinson’s Disease Rating Scale motor score, OFF = off deep brain stimulation, Ventral = deep brain stimulation of ventral subthalamic nucleus, Dorsal = deep brain stimulation of dorsal subthalamic nucleus.
Table 2: Patient characteristics and DBS parameters.

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age</th>
<th>Gender</th>
<th>Handedness</th>
<th>Ventral Contact</th>
<th>Dorsal Contact</th>
<th>Ventral Voltage</th>
<th>Dorsal Voltage</th>
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<tr>
<td>PD01</td>
<td>76</td>
<td>F</td>
<td>R</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>PD02</td>
<td>54</td>
<td>M</td>
<td>R</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>PD03*†</td>
<td>63</td>
<td>F</td>
<td>R</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>PD04</td>
<td>70</td>
<td>M</td>
<td>R</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>PD05</td>
<td>64</td>
<td>M</td>
<td>R</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>PD06</td>
<td>56</td>
<td>M</td>
<td>R</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>PD07*</td>
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<td>M</td>
<td>R</td>
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<td>7</td>
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<tr>
<td>PD08</td>
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<td>7</td>
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<tr>
<td>PD09</td>
<td>55</td>
<td>M</td>
<td>R</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>PD10</td>
<td>65</td>
<td>M</td>
<td>R</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>PD11</td>
<td>60</td>
<td>M</td>
<td>R</td>
<td>0</td>
<td>4</td>
<td>2</td>
<td>7</td>
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</tbody>
</table>

* = excluded from stop task analysis, † = excluded from switching analysis.
Table 3: Switching task reaction time and proportion of errors (mean ± std).

<table>
<thead>
<tr>
<th></th>
<th>RT (ms)</th>
<th>Proportion of Errors (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Switch</td>
<td>Nonswitch</td>
</tr>
<tr>
<td></td>
<td>Repeat</td>
<td>Alternate</td>
</tr>
<tr>
<td>Control</td>
<td>544 ± 52</td>
<td>501 ± 56</td>
</tr>
<tr>
<td>PD-OFF</td>
<td>599 ± 128</td>
<td>590 ± 101</td>
</tr>
<tr>
<td>PD-Dorsal</td>
<td>611 ± 117</td>
<td>608 ± 131</td>
</tr>
<tr>
<td>PD-Ventral</td>
<td>604 ± 97</td>
<td>561 ± 88</td>
</tr>
</tbody>
</table>
Table 4: Maybe Stop/No Stop task reaction time and proportion of errors (mean ± std).

<table>
<thead>
<tr>
<th></th>
<th>RT (ms)</th>
<th>Proportion of Errors (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Maybe Stop</td>
<td>No Stop</td>
<td>SSRT</td>
</tr>
<tr>
<td>Control</td>
<td>909 ± 169</td>
<td>636 ± 96</td>
<td>273 ± 137</td>
</tr>
<tr>
<td>PD-OFF</td>
<td>945 ± 102</td>
<td>735 ± 121</td>
<td>359 ± 117</td>
</tr>
<tr>
<td>PD-Dorsal</td>
<td>986 ± 152</td>
<td>735 ± 112</td>
<td>382 ± 150</td>
</tr>
<tr>
<td>PD-Ventral</td>
<td>994 ± 157</td>
<td>776 ± 103</td>
<td>403 ± 121</td>
</tr>
</tbody>
</table>

SSRT = stop signal reaction time, pRDE = proportional response delay effect.
Figure 5: Deep brain stimulation electrode contacts were localized within the subthalamic nucleus. (A) The subthalamic nucleus (outlined) was identified bilaterally in T2-weighted MRI scans. (B) The electrodes were visible as an artifact in a CT image (yellow) overlaid on the MRI. (C) A model of the electrode was scaled to the voxel size of the image. This allowed for the identification of those electrode contacts inside or overlapping with the dorsal and ventral borders of the subthalamic nucleus. (D) Neurophysiological diagrams were created from intraoperative single-unit recordings made during the implantation of the deep brain stimulation electrodes. The location of the dorsal and ventral borders of the STN were determined based upon cell firing rates. A model of the electrode was then overlaid on a corresponding plate from the Schaltenbrand and Wahren Atlas for Stereotaxy of the Human Brain (in this example -12 mm lateral).
Figure 6: On each trial of the switching task (A) participants responded to the target box that matched the color of the central fixation box. White dashed circles indicate the correct response. The target color stayed the same for a series of 4-8 trials and then switched to the other color for the next series of 4-8 trials. There were four categories of trials based upon the target color and response history: switch-repeat, nonswitch-repeat, switch-alternate, and nonswitch-alternate. The Maybe Stop No Stop Task (B) consisted of a cue, either the words ‘Maybe Stop’ or ‘No Stop,’ followed by a target arrow. On 2/3 of Maybe Stop trials, the arrow was followed by an auditory stop signal at a short dynamic stop signal delay (SSD). Participants were instructed to try to cancel their response following the stop signal.
Figure 7: A) Reaction time data (mean ± SEM) for controls and Parkinson’s disease patients in the OFF, Dorsal, and Ventral STN DBS conditions for switch repeat, nonswitch repeat, switch alternate, and nonswitch alternate trials. B) Switch cost (mean ± SEM) for controls and Parkinson’s disease patients in the OFF, Dorsal, and Ventral STN DBS conditions represented separately for repeat and alternate trials. C) The proportion of errors (% mean ± SEM) for controls and Parkinson’s disease patients in the OFF, Dorsal, and Ventral STN DBS conditions for switch repeat, nonswitch repeat, switch alternate, and nonswitch alternate trials.
Figure 8: The switch costs (switch RT – nonswitch RT) in milliseconds for repeat and alternate responses for the individual Parkinson's patients (dots) in the Dorsal, Ventral, and OFF STN DBS states and the individual controls (diamonds). The dashed diagonal line represents repeat switch cost = alternate switch cost. All of the patients in the Ventral STN DBS state and the majority of controls show a smaller switch cost for alternate than repeat responses.
Figure 9: Results from the Maybe Stop/No Stop Task. (A) Reaction time data (mean ± SEM) for controls and Parkinson’s disease patients in the OFF, Dorsal, and Ventral STN DBS conditions for Maybe Stop and No Stop trials. (B) The proportional response delay effect (\(p_{RDE}\); mean ± SEM) for controls and Parkinson’s disease patients in the OFF, Dorsal, and Ventral STN DBS conditions. (C) Stop signal reaction time (SSRT) estimates (mean ± SEM) for controls and Parkinson’s disease patients in the OFF, Dorsal, and Ventral STN DBS conditions. (D) The proportion of errors (%; mean ± SEM) for controls and Parkinson’s disease patients in the OFF, Dorsal, and Ventral STN DBS conditions for Maybe Stop and No Stop trials.
3.5 References


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Yehene E, Meiran N, Soroker N (2008) Basal ganglia play a unique role in task switching within the frontal-subcortical circuits: Evidence from patients with


Chapter 4:
A frontal EEG signature associated with stopping is sensitive to preparation

ABSTRACT
Evidence suggests that preparing to stop improves the speed and selectivity of outright stopping, but the underlying mechanism is uncertain. One hypothesis is that preparing to stop ‘primes’ the outright stopping network. If so, then preparing to stop may induce an observable change in brain activity at the time of stopping. Much electroencephalography (EEG) research has studied the N2/P3 complex over fronto-central electrodes during outright stopping. These EEG components may be useful for determining if and when the cortical regions active at the time of stopping are sensitive to the effects of preparation. Here we used differential reward of the stop and go processes in a stop signal task to manipulate the degree of preparation for stopping and held the probability of a stop signal constant. Our manipulation was successful because stopping was significantly faster when it was rewarded compared to when going was rewarded. For EEG, we found that the fronto-central P3 amplitude was larger for successful vs. failed stopping, and this difference was greater when stopping was rewarded compared to when going was rewarded. In contrast, the frontal N2 component was only observed on failed stop trials. This shows, like other studies, that the P3 amplitude is sensitive to whether stopping is successful or not; however it goes
further by showing that the P3 was sensitive to our reward manipulation. Thus, we propose that fronto-central cortical mechanisms active at the time of stopping are sensitive to preparation.
4.1 INTRODUCTION

Much research has addressed how initiated responses are stopped. Recent evidence from a handful of studies suggests that preparing to stop can influence the stopping process (Chikazoe et al., 2009; Verbruggen and Logan, 2009a; Jahfari et al., 2010; Leotti and Wager, 2010; Sinopoli et al., 2011; Greenhouse et al., 2012). For example, rewarding successful stopping induces response slowing in preparation for stopping and also speeds up the stopping process (Leotti and Wager, 2010; Sinopoli et al., 2011). This change in the speed of stopping could result from proactive adjustments in motor excitability by reducing the amount of inhibition required to override an initiated response without directly influencing the mechanism involved in stopping. This could mean that the stopping process remains stable and that the difference in the speed of stopping results from reduced excitability associated with the response.

Alternatively, the stopping mechanism could be ‘primed’ to execute stopping more quickly. Indeed, several fMRI studies lend support to this idea and observed that preparing to stop activates the stopping network (Vink et al., 2005; 2006; Chikazoe et al., 2009; Jahfari et al., 2010; Zandbelt and Vink, 2010; Swann et al., 2011; Zandbelt et al., 2012). However, no studies have explicitly investigated whether preparing to stop directly influences neural mechanisms at the time of stopping to determine if the stopping mechanism is primed by preparation. Here, we used electroencephalography (EEG) and a modified stop signal task to test whether rewarding stopping over going vs. going over stopping
changes the speed of stopping and the pattern of brain activity at the time of stopping.

Preliminary evidence from studies that used transcranial magnetic stimulation suggests that preparation engages an inhibitory mechanism before and during response initiation and execution, i.e. proactive inhibition. One of these studies showed that during the initiation of a response that might need to be stopped there was a prolonged decrease in motor excitability, below baseline levels (Jahfari et al., 2010). This finding indicates that response inhibition occurs during response execution when stopping is anticipated. Another pair of studies showed that motor excitability was suppressed, also below baseline levels, following an informative cue that indicated a particular forthcoming response may need to be stopped (Claffey et al., 2010; Cai et al., 2011). This result suggests that responses can be inhibited, even before their initiation, when stopping is anticipated. Such proactive reductions in motor excitability could facilitate stopping by limiting the amount of inhibition required to override an active response without necessarily influencing the mechanism for stopping.

It remains a question whether preparing to stop directly influences aspects of the stopping process that occur after the presentation of a stop signal, i.e. reactive stopping mechanisms. It could be the case that preparation does not influence reactive stopping, but instead only involves proactive adjustments in motor excitability like those just mentioned. This is important because specific brain mechanisms involved in the reactive inhibition of responses may be sensitive to the effects of preparation, and determining their sensitivity to
preparation could help to further characterize their functional contribution to stopping. One way to test for such changes at the time of stopping is with EEG because of its high temporal resolution, which enables the dissociation of activity changes that occur before and after the stop signal.

The N2/P3 complex is a set of EEG event related potential (ERP) components that has, for over thirty years, been associated with reactive inhibitory control processes during the performance of the Go/NoGo and stop signal tasks (de Jong et al., 1990; van Boxtel et al., 2001; Kok et al., 2004; Ramautar et al., 2004; Dimoska et al., 2006; Ramautar et al., 2006; Schmajuk et al., 2006; Dimoska and Johnstone, 2008; Huster et al., 2010; Liotti et al., 2010; Huster et al., 2011; van Gaal et al., 2011). The established finding from these studies is that both the N2 and P3 components demonstrate fronto-central scalp topographies and are enhanced on NoGo and stop trials relative to Go trials.

Recent evidence suggests that these two EEG components may represent different processes associated with novelty detection and reactive inhibitory control. One EEG study implemented a combined Go/NoGo and stop signal task and also incorporated different proportions of Go vs. reactive control trials (i.e. NoGo and stop trials) (Enriquez-Geppert et al., 2010). This study found that the fronto-central N2 amplitude was larger for relatively infrequent events, regardless of whether the trial was a Go trial, a NoGo trial, or a Stop trial. In contrast, the P3 amplitude was the largest for successful stop trials, smaller for NoGo trials, and smallest for Go trials. This pattern was exaggerated when reactive control trials were less frequent. The implications of this functional
dissociation between the N2 and P3 components are two-fold. First, these findings suggest that the N2 is a marker for relatively infrequent or unlikely events, possibly related to the conflict that arises from unexpectedly reconfiguring responses or an increased attentional demand required for such reconfiguration. Second, they suggest that the P3 component is selectively sensitive to reactive control processes. These results extended those of a previous study that also found increased P3 amplitude for infrequent relative to frequent stop trials (Ramautar et al., 2004), but see (Dimoska and Johnstone, 2008). However, all these previous studies only manipulated the likelihood of a stop signal, and therefore were unable to fully determine whether differences in the P3 amplitude during successful stopping were due to the novelty of the stop signal or due to the influence of preparing to stop. This is an important distinction because in the former case, P3 amplitude differences could occur in the absence of any influence of preparation, while in the latter case differences in P3 amplitude could index preparedness to stop. Ruling out one of these possibilities would help to elucidate the functional significance of the P3 in stopping. A more precise characterization of the functional significance of the P3 would be useful in determining whether changes in stop signal task performance represent differences in novelty detection or inhibitory control processes. Therefore, in addition to characterizing the influence of preparation on reactive stopping mechanisms, the current experiment has implications for determining the functional significance of the different N2 and P3 components.
Here, we set out to test whether preparing to stop influences brain mechanisms associated with the reactive stopping of initiated responses. We did this by measuring the N2/P3 complex that has previously been associated with stopping. We developed a modified stop signal task that incorporated a points system. In one condition stopping was emphasized over going, and in the other condition going was emphasized over stopping. The probability of a stop trial was the same in both conditions. We then compared the EEG signatures of interest between the two different conditions. Thus, it was possible to test if the N2/P3 complex that occurs during successful stopping relates to the speed of stopping and also demonstrates sensitivity to our reward manipulation. Such a finding would suggest that preparing to stop primes a brain mechanism involved in reactive stopping.

4.2 METHODS

Participants

Fifteen participants (9 female, 24.7 ± 8.5 years of age, 2 left-handed) were recruited from flyers posted on the University of California, San Diego campus. All participants were screened to rule out any neuropsychological or psychiatric disorders and were not taking any neuropsychiatric medication. One subject was excluded from the analysis due to a very high frequency of eye-blinking and other noise in their EEG data.
**Task**

We used a modified stop signal task with two conditions. In one condition more points were awarded for stopping than going and in the other condition the point contingencies were reversed (Figure 10). The task was administered in blocks of 12 trials. A 3 s fixation screen and then one of two possible instruction screens preceded each block. The instructions were either ‘going = 10 points / stopping = 1 point’ or ‘going = 1 point / stopping = 10 points’. These different point contingencies were selected to emphasize going over stopping (G > S) or stopping over going (S > G), respectively, and alternated from block to block. The starting instruction was counterbalanced across participants. Participants completed one block with each instruction as practice, and a total of 1200 trials in total during testing. This resulted in 50 blocks (600 trials) for each of the two points conditions during testing.

Each trial of the task consisted of the presentation of a left- or right-pointing white arrow stimulus presented in the center of a black computer screen for 1 s or until a response was made. On one third of trials, a red letter ‘X’ occluded the arrow at a brief delay. This ‘X’ served as a visual stop signal and remained on the screen until 1 s from target onset or until a response was made. The delay between the arrow and the stop signal (i.e. the stop signal delay, SSD) was dynamically adjusted in increments of 50 ms. Eight independent stop signal staircases were used. Two were mapped to the left arrow (starting at 150 and 200 ms) and two were mapped to the right arrow (starting at 150 and 200 ms) for each of the two instruction conditions. This resulted in 50 stop trials within each
staircase, or 200 stop trials from each of the two different instruction conditions (400 stop trials in total).

All trials were followed by a 500 ms blank screen interval and then a 500 ms feedback screen that displayed the points earned on the immediately preceding trial (i.e. 0 points, 1 point, or 10 points). A jittered ITI was used (1.2 ± 0.1 s) to prevent anticipation of the target onset. Additionally, following every 6 blocks of the task, participants were presented with a feedback graph of their overall mean RT, averaged across the two different instruction conditions. This informed participants of their overall tendency to change the speed of responding across the testing session.

Participants were seated with their hands in their laps and their pinkies facing downwards. Button boxes were suspended beneath the edge of a desk on which the stimulus computer was positioned. This positioning necessitated an upward movement of the index fingers to make a response and permitted the recording of electromyography (EMG) from the first dorsal interosseous muscles of each hand. These EMG data will not be discussed here. Participants were instructed to respond quickly and accurately to the target arrows using the index fingers of their left and right hands and to try to stop to the stop signal, although it may not be possible to stop on about half of the stop trials. Additionally, participants were instructed to earn as many points as possible.

The point system was constructed to selectively manipulate the preparedness for stopping. For the G > S condition, 10 points were awarded on trials in which the correct Go RT fell within the fastest 25% of the cumulative Go
RT distribution for that condition, and 1 point was awarded for successful stopping. For the S > G condition, 1 point was awarded on trials in which the correct Go RT fell within the fastest 25% of Go RTs for that condition, and 10 points were awarded for successful stopping. Otherwise, zero points were awarded for trials with slow Go RTs, choice errors, or failed stopping in both conditions. For the initial G > S and S > G blocks, the 25% RT cutoff was determined using the practice RT distributions.

This point system had two particularly important features. First, awarding points only for fast Go RTs and successful stopping encouraged participants to respond quickly and also to try to stop in both conditions. Second, the total number of points that could be earned was largely predetermined since points were awarded on only 25% of Go trials (i.e. the fastest 100 trials within each condition) and approximately 50% of stop trials (i.e. approximately 100 successful stop trials in each condition), based upon the dynamic staircase adjustments. Therefore, one condition was not expected to result in a greater number of points earned than the other.

**Behavioral Analysis**

Mean Go RT, total points earned, the mean SSD, the probability of successful inhibition (i.e. \( p(\text{inhibit}) \)), failed stop RT, and the stop signal reaction time (SSRT) were calculated separately for each of the two task conditions, i.e. S > G and G > S. SSRT is an estimate of the duration of the stopping process. Here, we used the integration method to calculate SSRT (Verbruggen and
Logan, 2009b). In brief, the integration SSRT is calculated by determining which RT values from the Go RT distribution fall at percentiles that correspond to the \( p(\text{inhibit}) \) for the three most common SSDs. Each SSD is subtracted from its corresponding Go RT value. The average of these differences is the integration SSRT.

**EEG Acquisition**

EEG data were sampled at 512 Hz, using a 32 + 8 channel Biosemi ActiveTwo system (Biosemi Instrumentation). Four extra electrodes were placed as follows: one on each mastoid (used for subsequent re-referencing), one lateral to the left eye, and one below the left eye (as EOG’s to monitor eye movements.)

**EEG Pre-processing and Analysis**

The EEG data were preprocessed using a combination of EEGLab (Delorme and Makeig, 2004) (http://www.sccn.ucsd.edu/eeglab) and custom Matlab scripts in the following stages. First the mean of each channel was removed to eliminate baseline shift. Second the data were re-referenced to external electrodes placed on the left and right mastoids. Third a 0.5 Hz high pass filter was applied to remove low frequency drift and a 30 Hz low pass filter was applied to remove high frequency noise using the EEGLab “eegfilt” function, a two-way FIR filter. Data were then binned into trial epochs, and trials with signal greater than 3 standard deviations from the mean probability distribution within each epoch were excluded from subsequent analysis. The remaining eye
movement and blink artifacts were removed using independent component analysis. Components that corresponded to eye blinks/movements were identified using a published technique that compares favorably with other artifact rejection techniques (Jung et al., 2000). For each subject at least one component was found and removed which corresponded to eye movements/blinks. Visual inspection before and after rejection confirmed the effectiveness of this procedure.

All the remaining stop trials were time-locked to the onset of the stop signal, and these epochs were then averaged within each of the two task conditions. Thus, it was possible to make direct comparisons between the two task conditions for the ERP of interest, i.e. the ERP to the stop signal.

4.3 RESULTS

Behavior

For stopping, the mean SSRT was significantly longer for the G > S condition (288 ± 26 ms) than the S > G condition (249 ± 46 ms), [t(13) = 3.6, p < 0.005] (Figure 11b). This pattern of behavior confirmed that the reward manipulation was influencing subjects’ stopping behavior and replicated the findings of two previous studies (Leotti and Wager, 2010; Sinopoli et al., 2011).

The mean SSD was significantly shorter for the G > S condition (63 ± 39 ms) the S > G condition (291 ± 121 ms), [t(13) = 7.6, p < 0.001] (Figure 11b). The mean p(inhibit) was also significantly smaller for the G > S condition (0.35 ± 0.14) than the p(inhibit) for the S > G condition (0.58 ± 0.05), [t(13) = 5.7, p =
0.001], and the mean failed stop RT was significantly later for the S > G condition (420 ± 20 ms) than the G > S condition (328 ± 9 ms), $[t(13) = 5.7, p < 0.0001]$ (Figure 11a). The pattern of $p_{\text{inhibit}}$ and failed stop RT also replicated the results of the previous study (Leotti and Wager, 2010). However, the $p_{\text{inhibit}}$ was relatively low in the G > S condition, and although every subject provided at least 44 successful stop trials, the resulting SSRT estimate may be unreliable (Verbruggen and Logan, 2009b).

The mean Go RT was significantly faster for the G > S condition (373 ± 36 ms) than the S > G condition (494 ± 78 ms), $[t(13) = 6.1, p < 0.001]$ (Figure 11a). The mean total points earned for the G > S condition was 1205 ± 249 and for the S > G condition was 1148 ± 66, and this was not a significant difference $[t(13) = 0.92, p = 0.4]$. Again, this pattern of Go RT and points earned indicates that participants were modifying their proactive control strategies in accordance with the different point contingencies, i.e. they favored stopping over going in the stop-rewarded condition and vice versa.

**EEG**

Three distinct ERP components were identified for successful and failed stop trials in both task conditions. The first was a posterior occipito-parietal N1 that peaked approximately 190 ms after the onset of the stop signal, centered over electrode Oz (Figure 12). The second was a fronto-central N2 that peaked around 210 ms after the stop signal, centered over Cz (Figure 13b). The third
was a P3 component that peaked around 300 ms after the stop signal, with a fronto-central topography, centered over Cz (Figure 13).

For each subject, we derived the minimum (N1 and N2) and maximum (P3) peak amplitude of the ERPs at their corresponding electrode sites for successful and failed stop trials in each of the two task conditions. We ran separate ANOVA for each of the three ERPs with the factors condition (S > G vs. G > S) and type of stop trial (successful vs. failed).

The P3 amplitude was larger for successful vs. failed stopping and was also larger for the S > G than G > S condition, \( F(1,13) = 117.3, p < 0.0001 \) and \( F(1,13) = 8.3, p = 0.01 \), respectively (Figure 13b). Moreover, there was a significant interaction, \( F(1,13) = 16.3, p = 0.001 \) (Figure 13c). Follow up \( t \)-tests indicated that the P3 amplitude difference between successful and failed stop trials was larger for the S > G condition than the G > S condition, \( t(13) = 4.0, p = 0.001 \), two-tailed.

The posterior N1 showed a much larger amplitude for the S > G condition for both successful and failed stop trials, \( F(1,13) = 25.7, p < 0.0001 \) (Figure 12b and c). There was no main effect of successful vs. failed stopping and no interaction.

Notably, at electrode Cz, we did not observe an N2 component for successful stop trials in either the S > G or G > S condition. However, we did observe an N2 at electrode Cz emerging around 200 ms for failed stop trials in both reward conditions, (Figure 13b). The N2 peak amplitude on failed stop trials was larger for the S > G than the G > S condition, \( t(13) = 3.6, p < 0.005 \).
4.4 DISCUSSION

Here, we manipulated the numbers of points that could be earned for stopping successfully vs. going quickly while keeping the probability of a visual stop signal constant. To our knowledge, this is the only study that has used a points system to manipulate the relative value of stopping vs. going to investigate EEG signatures associated with successful stopping. Other EEG studies have only manipulated the likelihood of a stop signal and were therefore unable to disentangle the effects that result from the occurrence of an infrequent event (e.g. an oddball) from those that result from endogenous processes involved in preparing to stop (Ramautar et al., 2004; Dimoska and Johnstone, 2008; Enriquez-Geppert et al., 2010). Our experimental design ensured that the probability of a stop signal was identical between the two reward conditions. Therefore, any differences in the EEG signatures of interest between our task conditions cannot be attributed to differences in the probability of task stimuli. The effects we observed can only be attributed to the way in which subjects modified their behavior in accordance with the different task instructions.

We found that stopping was faster when it was rewarded over going and that the amplitude of a well-characterized EEG signature that emerges at the time of stopping, the fronto-central P3, was also sensitive to the reward manipulation. Specifically, the P3 amplitude was larger for successful than failed stopping and this difference was more pronounced when stopping was rewarded over going. Interestingly, we also observed that the occipito-parietal N1 component to the stop signal, commonly associated with visual attention (Luck et
showed increased amplitude when stopping was rewarded over going quickly. However, N1 amplitude did not differ between successful and failed stop trials. Thus, manipulating reward for stopping influenced brain activity over middle frontal cortex (indexed by the P3) that related to both stopping speed and success. This implies that preparing to stop facilitates stopping by priming the dorsomedial frontal cortex and/or its connected regions.

The P3

We found that the fronto-central P3 showed greater amplitude for successful vs. failed stop trials and that this difference was larger when successful stopping was rewarded over going. Notably, these changes in the P3 amplitude coincided with changes in SSRT. Therefore, the P3 may reflect a neural mechanism that is involved at the time of stopping and is also sensitive to preparation. Thus, preparing to stop could prime the dorsomedial frontal cortex for stopping.

Although the P3 peak occurred after the estimated completion of the stopping process for most subjects, the peak amplitude may result from earlier neural events. Importantly, differences in the P3 wave started to emerge around 200 ms after the stop signal, within the time frame of the stopping process. One previous study that also reported a P3 amplitude difference between successful and failed stopping noted that the difference reached significance approximately 20 ms before completion of the estimated SSRT for that study (Kok et al., 2004). Our results are in accordance with that previous finding.
It is commonly accepted that the P3 is comprised of two positive-going potentials that occur in close temporal proximity, an early P3a with a frontal distribution that peaks around 240 ms after a stimulus and a later P3b with a parietal distribution that peaks around 350 ms after a stimulus (Squires et al., 1975). The P3 waves we observed here contain two peaks at the approximate latencies of the P3a and P3b. The P3a and P3b are believed to occur when working memory is updated with new information (Polich and Kok, 1995), and the P3a is specifically hypothesized to reflect an attentional process that initiates the inhibition of ongoing activity (Polich, 2007). The largest peak amplitude differences across our task conditions were found for the P3a, particularly for the successful stop trials in the S > G condition (Figure 13b). Therefore, the larger difference between successful and failed stop trials that we observed for the S > G condition than the G > S condition may reflect a larger change in an underlying attention-driven inhibitory process. This putative mechanism could facilitate the initiation of the stop command and lead to faster stopping.

**The N2**

We observed a fronto-central N2 component for both task conditions at electrode Cz but only for failed stop trials (Figure 12a and 13b). Therefore, the fronto-central N2 that we observed may reflect error awareness on failed stop trials, and may be classified as a feedback-related negativity (Simons, 2010; Wessel, 2012). This pattern replicates a previous study that observed changes in the fronto-central N2 for failed but not successful stopping (Kok et al., 2004) and
extends the results of two previous studies that reported greater sensitivity to changes in stop signal frequency for the P3 than the N2 component (Ramautar et al., 2004; Enriquez-Geppert et al., 2010). Thus, the fronto-central N2 may be sensitive to the reward manipulation implemented here, but only when there is a failure to stop.

The N1

We also detected a large difference between the two reward conditions in the posterior occipito-parietal N1 component, centered at electrode Oz. This component is believed to reflect visual attention processes (Luck et al., 2000), and in this case likely reflects differences in attention to the visual stop signal. Interestingly, we did not observe a difference between successful and failed stop trials in either reward condition. This pattern suggests that visual attention to the stop signal may not have related to stopping success, at least in this task. Moreover, it suggests that the differences in the P3 amplitude for successful vs. failed stopping are unlikely to have resulted from changes in visual attention.

Neural Mechanisms

Putative neural sources of the N2/P3 complex were recently identified in a study that utilized simultaneous EEG and functional MRI (Huster et al., 2011). This study reported that the N2/P3 complex was associated with increased BOLD signal within the pre-supplementary motor area (pre-SMA), striatum, anterior midcingulate, and anterior insula. These brain regions largely overlap
with those believed to participate in a frontal-basal ganglia network for stopping (Aron et al., 2007). Therefore, it is reasonable to assume that the P3 component reflects activity changes at fronto-central cortical nodes within this network during stopping, e.g. the pre-SMA and its connected regions.

Furthermore, a transcranial magnetic stimulation study showed that individuals who slow their Go responses in anticipation of stopping exhibit less suppression of muscles in the leg during reactive stopping than individuals who do not prepare to stop (Greenhouse et al., 2012). This result suggests that greater preparation for stopping increases the selectivity of reactive control processes. The findings from the current study extend this previous finding by showing that within-individual adjustments in preparation for stopping, reflected in changes in Go RT, related to changes in the P3 and SSRT. Considered together, these findings suggest that the P3 amplitude may also index the selectivity of reactive stopping. For example, an increase in the P3 amplitude at the time of stopping could reflect both faster stopping and more selective inhibition of the particular response that is stopped. Future studies that combine transcranial magnetic stimulation and EEG methods will be able to test for a relationship between the P3 amplitude and the selectivity of stopping.

Moreover, the ability to modulate P3 amplitude may be impaired in certain populations and this could relate to a specific type of stopping deficit. For example, several previous studies have reported that the stopping P3 differs between more and less impulsive individuals (Jonkman et al., 2003; Dimoska and Johnstone, 2007; Lansbergen et al., 2007; Ruchsow et al., 2008). The extent
to which an individual is able to modulate the P3 amplitude (e.g. through preparing to stop) may help to elucidate the mechanisms that underlie impulsivity. Individuals who prepare to stop but are unable to modulate the P3 at the time of stopping may have a different underlying problem than individuals who do not prepare in the first place. Thus, measuring the influence of preparation on stopping P3 amplitude may help to discriminate between deficits resulting from an inability to properly prepare or an inability to influence inhibitory control mechanisms. This dissociation could be useful in determining whether the underlying cortical mechanism is disrupted.

**Conclusion**

We implemented a modified stop signal task to investigate the effects of rewarding stopping vs. going on EEG signatures associated with stopping. We observed that rewarding stopping over going resulted in faster SSRT as well as increased amplitude of the posterior occipito-parietal N1 and the fronto-central P3 at the time of stopping. The posterior N1 difference likely reflects increased visual attention to the stop signal. Interestingly, this component did not differ between successful and failed stopping. In contrast, the fronto-central P3 component exhibited increased amplitude for successful vs. failed stopping, and this effect was greater when stopping was rewarded over going. This finding suggests that the P3 reflects a reactive control process that is sensitive to changes in the level of preparation. Such a process may depend upon a fronto-central cortical brain region such as the pre-SMA that can be primed for stopping
through preparation. Moreover, this provides strong evidence linking the stopping processes to the P3 component.

Chapter 4 is a manuscript of an article being prepared for submission.

Greenhouse, I; Aron, AR 2012.
Figure 10: The stop signal task was administered in blocks of twelve trials. An instruction screen indicated the number of points that could be earned for successful stopping and going quickly for the following block (within the fastest 25% of the Go RT distribution). Either going quickly earned 10 points and successful stopping earned 1 point (G > S) or successful stopping earned 10 points and going quickly earned 1 point (S > G). The stop signal was a red ‘X’ that appeared over the Go target-arrow at a short and dynamically adjusted stop signal delay (SSD). At the end of each trial, the number of points earned was presented as feedback.
Figure 11: A) Reaction time in milliseconds on Go trials and failed stop trials. B) The stop signal delay (SSD) and stop signal reaction time (SSRT). G > S = going quickly earned 10 points and successful stopping earned 1 point; S > G = successful stopping earned 10 points and going quickly earned 1 point. ** indicates significance at $p < 0.01$ and *** indicates significance at $p < 0.001$. 
Figure 12: A) Scalp topographies for the peak amplitude of the occipito-parietal N1 are presented for successful and failed stop trials for each condition along with the difference and t-value maps. The emergence of the fronto-central N2 is also visible for failed stopping. B) The average ERP measured at electrode Oz is presented for successful and failed stop trials for the two different task conditions. C) The ERP difference wave for successful – failed stopping is presented for the two different task conditions and indicates that there were no condition differences in the N2. SS = successful stop; FS = failed stop; G > S = going quickly earned 10 points and successful stopping earned 1 point; S > G = successful stopping earned 10 points and going quickly earned 1 point.
Figure 13: A) Scalp topographies for the peak amplitude of the fronto-central P3 are presented for successful and failed stop trials for each condition along with the difference and t-value maps. B) The average ERP measured at electrode Cz is presented for successful and failed stop trials for the two different task conditions. The N2 for failed stop trials and the P3 for all trial types are visible. C) The ERP difference wave for successful – failed stopping is presented for the two different task conditions and shows a prominent difference between the two task conditions from ~200 to 300 ms after the stop signal. SS = successful stop; FS = failed stop; G > S = going quickly earned 10 points and successful stopping earned 1 point; S > G = successful stopping earned 10 points and going quickly earned 1 point.
4.5 REFERENCES


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Chapter 5:

CONCLUSION

A large body of research on behavioral inhibition has focused on how responses are canceled after their initiation. However, in the real world, this type of reactive control is relatively uncommon. Instead, the need to inhibit a particular behavior is often anticipated and may be set up in advance, possibly by targeting control proactively at a specific response. Whereas previous investigations of stopping have seldom considered the influence of preparing to stop, the studies included in this thesis were designed to address questions concerning how stopping is prepared, even before a situation demands the cancelation of behavior, and how this type of preparation influences the stopping process.

Three specific questions were addressed: i) Does preparing to stop increase the selectivity of reactive stopping? ii) Are the subthalamic nucleus (STN) and its connected circuitry, which have previously been implicated in stopping, also important for preparing to stop? and iii) Does preparing to stop ‘prime’ cortical mechanisms involved in reactive stopping? The findings have implications for understanding the behavioral and neural mechanisms involved in preparing to stop and for the reactive stopping of motor responses.

The following sections elaborate the research implications. The first section discusses the relationship between preparing to stop and reactive stopping. The second section covers implications for the diagnosis and treatment of disorders that affect control over motor, cognitive, and limbic functions.
5.1 Preparing to Stop and Reactive Stopping

The stop signal task (Lappin and Eriksen, 1966; Logan and Cowan, 1984) has proven to be a valuable tool for studying the reactive stopping of motor responses in part because it provides an estimate of the speed of stopping, the stop signal reaction time (SSRT) that has high test-retest reliability and remains fairly static throughout adult life (Williams et al., 1999; Congdon et al., 2012). The SSRT has traditionally been thought to represent an independent psychological process that does not interact with other processes (Logan and Cowan, 1984; Verbruggen and Logan, 2009a). However, recent evidence suggests that the stopping process is not a completely independent process. Indeed, several studies indicate that the speed of the stopping process is sensitive to preparation for stopping (de Jong et al., 1990; van den Wildenberg et al., 2002; Band et al., 2003; Boucher et al., 2007; Leotti and Wager, 2009; Verbruggen and Logan, 2009b; Jahfari et al., 2010). This thesis provides additional evidence that preparing to stop can influence some aspects of the reactive stopping process, possibly through the recruitment of neural mechanisms implicated in both preparing to stop and reactive stopping.

5.1.1 Global vs. Selective Reactive Stopping

Prior experiments that used TMS to measure motor system excitability found that stopping a hand response resulted in the suppression of activity in a task-irrelevant leg muscle (Badry et al., 2009; Majid et al., 2011). Thus, reactive stopping can have a non-specific, or global, inhibitory effect on the motor system.
Chapter 1 extended this finding and showed that increased slowing in anticipation of stopping corresponded to less leg suppression at the time of stopping. Specifically, individuals who demonstrated greater slowing on critical relative to noncritical Go trials during the performance of a Conditional Stop Task also demonstrated larger leg MEPs at the time of successful stopping. This finding suggests that preparing to stop may reduce the global effect of stopping on the motor system by targeting inhibitory control at the specific response to be stopped.

This result predicts that individuals who are less capable of preparing to stop suffer a more widespread interruption to the motor system at the time of stopping. This could have adverse consequences in situations where one action must be stopped while others must be continued. For example, if a car were to cut you off while you were changing lanes you might suddenly stop turning the steering wheel and simultaneously push your foot down on the brake pedal. If you were unprepared, stopping the turning of the steering wheel might cause your leg muscles to be inhibited and temporarily impair your ability to push your foot down. But, if you prepared to stop turning the wheel, you might be better able to dissociate the motor processes involved in steering and pressing your foot down. Your ability to prepare to stop turning the wheel in such a situation might determine whether or not you press the brake in time to avoid an accident. However, future work is needed to determine whether this type of interference is practically detrimental and which factors govern individual differences in preparing to stop.
Two separate cortico-basal-ganglia pathways through the STN may determine whether stopping has a global or selective effect on the motor system. The STN is a particularly good candidate for quickly inhibiting motor system output because it receives input directly from the cortex through the hyperdirect pathway (Nambu et al., 2002; Aron et al., 2007), and has diffuse projections to the motor output nuclei of the basal ganglia which could broadly reduce thalamic drive of primary motor cortex (Mink, 1996; Gillies and Willshaw, 1998). Thus, this circuitry is set up to have a quick and global inhibitory effect over the motor system (Figure 14a). In addition to the cortico-subthalamic hyperdirect pathway, recent studies have proposed that the STN might stop action via the striatal-pallidal-subthalamic indirect pathway (Aron and Verbruggen, 2008; Aron, 2011; Majid et al., 2011). In contrast to the putative global effect of the hyperdirect pathway, the indirect pathway is proposed to result in the selective, focused inhibition of particular responses (Figure 14b). Thus, based upon the architecture of these two pathways, whether output from the basal ganglia has a focused or non-focused effect on the motor system may be determined at the level of the STN.

5.1.2 A Shared Mechanism for Preparing to Stop and Switching

Cortico-basal-ganglia circuits may also underlie preparing to stop. We tested this in Chapter 2 by stimulating different parts of the STN that are hypothesized to participate in different cortico-basal-ganglia circuits. Tract tracing studies in rodents and monkeys have shown that the STN can be divided into
three functional subregions (Monakow et al., 1978; Alexander and Crutcher, 1990; Parent and Hazrati, 1995a; 1995b; Karachi et al., 2005; Temel et al., 2005). The dorsal STN subregion receives input from primary motor and premotor cortices and sends output to the globus pallidus. This subregion is hypothesized to play a role in sensorimotor functions. The ventral and more medial STN receives input from dorsolateral prefrontal and lateral orbitofrontal cortices via the striatum and sends output along the ‘direct pathway’ to the substantia nigra pars reticulata (SNr) and along the ‘indirect pathway’ to the globus pallidus pars externa (GPe). This ventral STN subregion is hypothesized to participate in associative (executive) functions based upon its connections with the prefrontal cortex. The third subregion makes up the medial tip of the STN and has reciprocal connections with the ventral pallidum. This subregion is hypothesized to be involved in limbic functions. Based upon this circuitry, the three STN subregions may serve homologous functions in the control of movement, cognition, and emotion. This hypothesis is further motivated by the mostly non-overlapping and parallel anatomical architecture of the broader sensorimotor, associative, and limbic cortico-basal-ganglia loops that divide the STN (Alexander and Crutcher, 1990).

These three functional-anatomic STN subregions are also believed to exist in the human. However, only a handful of studies have been able to stimulate (Mallet et al., 2007; Hershey et al., 2010; Greenhouse et al., 2011) or record [for a review see (Marceglia et al., 2011)] from specific STN subregions in humans. Chapter 2 used image-guided deep brain stimulation (DBS) methods in
a group of Parkinson’s disease patients to determine if the human ventral STN is important for the performance of two tests of executive function. We hypothesized that if stimulation of the ventral but not the dorsal STN induced changes in executive function, then this would provide supporting evidence for the functional subdivision of the STN in humans. This is indeed what was found. In summary, patients off DBS exhibited patterns of abnormal behavior when compared to healthy, matched controls on both executive function tasks. On a response switching task, controls only showed a switch cost when repeating the response from the preceding trial, whereas patients exhibited a switch cost on every switch trial, regardless of whether repeating a response or making a different response. On a modified stop signal task, patients did not slow as much as controls when cued to anticipate a stop signal. Stimulation of the ventral (but not the dorsal STN) caused the patients to behave more similarly to the controls on both tasks. Some caution is required in the interpretation of these results because the observed changes in behavior may have resulted from non-specific effects of stimulation that spread throughout the connected circuit and therefore may not have been restricted to the STN. Nevertheless, the observed differences in the effect of stimulation between the dorsal and ventral STN imply that human STN subregions participate in different functional circuits. This is some of the first evidence to support the existence of such a functional subdivision within the human STN.

Based upon our findings that both preparing to stop and response switching were influenced by ventral STN stimulation, we speculate that these
two behaviors share a common subprocess. This subprocess may entail the selective suppression of an activated response. In the case of preparing to stop, a response may be actively suppressed before or during its execution if stopping is anticipated, and this could contribute to response slowing. Indeed, evidence for such an early inhibitory process comes from diffusion modeling of stop signal task performance (Verbruggen and Logan, 2009b) and also from TMS studies (Claffey et al., 2010; Jahfari et al., 2010; Cai et al., 2011). In the case of switching, the last-executed response may have lingering activation making that response more susceptible to premature re-execution. In order to prevent such an error when the task rule switches, the last-executed response may be suppressed. Behavioral evidence strongly suggests that such a process is engaged during response switching (Cooper and Mari-Beffa, 2008). Thus, for both preparing to stop and successful response switching an active response may need to be selectively suppressed. This interpretation implies that performance deficits on both executive function tasks could arise from interference to the same underlying behavioral subprocess, as may be the case in Parkinson’s disease. Additionally, as may also be the case in Parkinson’s disease, the inability to properly engage this selective control process could result from a pathologically overactive global stopping mechanism.

Considered together, the results in Chapters 2 and 3 provide insight into the neural relationship between preparatory and selective control mechanisms in the brain. The specific pattern of results presented in Chapter 3 implicates the ventral STN in preparing to stop (i.e. slowing in anticipation of stopping) as well
as selective control when switching (i.e. global vs. selective stopping when switching). These results fit with the TMS findings presented in Chapter 2 and provide corroborative evidence that preparing to stop a particular response and selective response inhibition are related. Moreover, they suggest that pathways passing through the STN mediate this relationship. Together, these findings support the idea that the STN is involved in executive processes that influence the extent to which motor control is applied globally vs. selectively.

5.1.3 Preparing to Stop and Stopping Speed

Chapter 4 identified a specific EEG marker that may index the influence of preparing to stop on the speed of stopping. Previous studies reported that the fronto-central P3 elicited in response to the stop signal is sensitive to stop signal likelihood (Ramautar et al., 2004; Dimoska and Johnstone, 2008; Enriquez-Geppert et al., 2010). By differentially rewarding stopping vs. going while keeping the probability of a stop signal constant, we were able to demonstrate that preparing to stop results in increased P3 amplitude and also faster stopping, independent of stop signal likelihood. This result suggests that preparatory processes can influence the pattern of cortical activity during the stopping process (about 200 ms after the stop signal). Thus, brain activity associated with faster stopping appears to be sensitive to preparation for stopping.

Nevertheless, the precise behavioral significance of the P3 is unclear. One possibility is that the P3 indexes the effects of motivation to stop. Our findings that adjustments in the amount of reward received for stopping vs. going
influenced response slowing in anticipation of stopping as well as the speed of stopping agrees with the results of a previous study in which adjustments in monetary reward resulted in the same pattern of behavior (Leotti and Wager, 2010) in addition to another study that showed reward mediates the speed of stopping in children (Sinopoli et al., 2011). While these previous studies showed that the speed of stopping is sensitive to such reward manipulations, they were unable to determine whether such effects were due to changes in attention to the stop signal or changes in inhibitory control mechanisms. Chapter 4 suggests that changes in attention to a visual stop signal may not fully account for changes in stopping speed or rates of success. This is because a posterior N1 component associated with visual attention did not differ between successful and failed stop trials. Instead, the observed changes in the P3 amplitude suggest that changes in the success and speed of stopping may be attributed to differences in a stimulus-driven inhibitory control mechanism situated in dorsomedial frontal cortex (Polich, 2007). Studies that used simultaneous EEG and fMRI in humans (Huster et al., 2011), electrocorticography in humans (Swann et al., 2011b), TMS in humans (Chen et al., 2009; Cai et al., 2012), and neurophysiological recordings in the monkey (Isoda and Hikosaka, 2007; Chen et al., 2010; Scangos and Stuphorn, 2010) suggest that the P3 might relate to activity specifically in the pre-supplementary motor area and connected circuits during reactive stopping. Our findings suggest that reward-mediated adjustments to this inhibitory control mechanism could account for changes in the speed of stopping. Interestingly,
this finding points to a possible relationship between stopping mechanisms and reward circuitry in the brain.

To further characterize the neural mechanisms involved, future studies could combine the image-guided DBS and EEG methods used in Chapters 3 and 4 to test if the stopping P3 is sensitive to DBS when it is targeted at the ventral vs. dorsal STN. One previous study showed that non-image-guided STN stimulation changed an EEG signature associated with stopping (Swann et al., 2011a). The use of image-guided stimulation and scalp EEG could inform whether specific connections between the sensorimotor or associative/limbic STN subregions and the dorsomedial cortex determine the speed of stopping. Moreover, evidence from electrocorticography in humans suggests that different cortical regions are engaged at different time points during the reactive stopping process (Swann et al., 2011b). Stimulating different STN territories and recording EEG during successful stopping could help to determine whether different cortico-STN pathways are recruited at different stages of the stopping process. Thus, targeting stimulation at different STN subregions could provide further insights into the communication between subcortical and cortical nodes during reactive stopping.

5.1.4 Summary

Collectively, the three studies included in this thesis suggest that preparing to stop determines the extent to which different cortico-basal ganglia pathways may be recruited at the time of stopping. Future studies that combine
the methods we used will be able to test whether changes in executive function are associated with signatures of global vs. selective reactive inhibitory control. Such investigations will help to dissociate the functions of the different cortico-STN pathways and different STN subregions as well as characterize the role of different cortical regions involved in response control.

5.2 Clinical Implications

5.2.1 Parkinson’s Disease

Chapter 3 has clear implications for the diagnosis and treatment of cognitive symptoms in Parkinson’s disease. Multiple studies have reported Parkinsonian deficits in stopping (Gauggel et al., 2004; Mirabella et al., 2011; Swann et al., 2011a) and switching (Lees and Smith, 1983; Cools et al., 1984; 2001; Cameron et al., 2010). Yet, the specific abnormal patterns of switching and slowing in anticipation of stopping that we observed have not previously been reported. Moreover, we found that these abnormalities were sensitive to image-guided DBS directed at a specific anatomical target, the ventral STN. This result indicates that executive impairments caused by Parkinson’s disease may be treatable with stimulation of the ventral STN. Furthermore, the study of these specific executive function abnormalities and their sensitivity to DBS has implications for i) understanding the cognitive changes that occur in Parkinson’s disease, ii) the identification of the pathological mechanisms underlying these cognitive changes, and iii) the targeting of treatment and the ability to measure its effectiveness.
Parkinson’s is a progressive disease that gradually extends across different territories within the basal ganglia, and therefore cognitive symptoms are likely to emerge when particular neural circuits involved in cognitive functioning are affected. Understanding the time course of cognitive changes in Parkinson’s disease has clinical value. Previous studies indicate that cognitive symptoms in Parkinson’s disease emerge at different stages of the illness (Rowe et al., 2008). Measures of switching and preparing to stop could potentially supplement standard assessments of Parkinson’s motor symptom severity for the purpose of determining disease progression. It may be the case that the abnormal behavioral patterns we observed are most pronounced at a particular stage of the illness. Since our results mapped specific behaviors to the ventral STN subregion, the detection of these behavioral deficits in Parkinson’s patients might indicate that disease processes have affected the ventral STN or its connected circuits.

Moreover, the specific switching and response slowing measures that we acquired could potentially serve as indices of treatment efficacy. We found that both behavioral measures of switching and slowing in anticipation of stopping were sensitive to DBS. Future studies may be able to determine whether or not these measures are also sensitive to dopamine replacement therapy, the most common treatment for Parkinson’s disease. If dopamine treatment does not have the same effect on executive function as DBS, it would suggest that these two treatment methods operate through different mechanisms of action, at least for
associative functions. Furthermore, this would imply that switching and preparing to stop are not dopamine-dependent. The degree to which these executive functions are sensitive to DBS (or other treatments) may be predictive of treatment efficacy for other executive functions as well. Diagnosing executive function impairments and determining their sensitivity to treatment in a clinical setting is a challenge. Therefore, behavioral measures of preparing to stop and switching may be useful for diagnosing cognitive symptoms in Parkinson’s disease, as well as other populations, and also for assessing treatment efficacy.

The use of image-guided DBS, implemented for experimental purposes in Chapter 3, has proven useful in treating Parkinson’s motor symptoms (Wodarg et al., 2012). Our findings suggest that this technique may extend to the treatment of non-motor symptoms as well. The incorporation of imaging methods that provide more detailed anatomical information about the pathways being targeted for stimulation possesses great potential for improving DBS therapy. For example, diffusion weighted images of the tracts that pass near the STN have been used to successfully model the field of stimulation (Butson et al., 2007), and this information could be useful for focusing stimulation at disease-affected circuits as determined through behavioral testing. Future research that incorporates such tract-based imaging may supplement the experimental methods described in Chapter 3 to better determine if the effects of DBS on different behavioral domains map to the different functional cortico-basal ganglia circuits.
5.2.2 Other Clinical Implications

The findings from Chapters 2 and 4 also have potential clinical relevance. We identified a TMS marker in Chapter 2 (i.e. leg excitability during stopping) and an EEG marker in Chapter 4 (i.e. P3 amplitude) that both demonstrated sensitivity to changes in preparation for stopping and may relate to reactive control processes. These markers may have utility for detecting impairments in reactive control processes. For example, disorders characterized by sporadic and uncontrolled movement restricted to particular groups of muscles, such as dystonia, essential tremor, and chorea, may result from the impaired recruitment of a selective inhibitory control mechanism. TMS measures of motor excitability from unaffected limbs during stopping of responses with the affected limb could help determine if deficits in selective control contribute to symptom severity. Likewise, differences in the stopping P3 amplitude for an affected vs. unaffected limb could point to disease related changes at the cortex. Moreover, these TMS or EEG measures could be used as feedback to train patients to inhibit affected muscles more effectively.

More generally, Chapter 4 suggests that reward-driven motivation to stop can influence the speed of stopping a motor response. Future studies may be able to test for this type of improved stopping in non-motor domains. If rewarding successful inhibition of unwanted thoughts and emotions helped to prevent their emergence it could have important implications for the treatment of impulse control disorders, Tourette syndrome, obsessive compulsive disorder, schizophrenia, mood disorders, generalized anxiety disorder, and addiction in
addition to motor disorders. Cognitive behavioral therapy techniques could be combined with neurofeedback, using tools such as TMS or EEG, for the purpose of training individuals to prepare to control themselves.

5.3 Summary

We are constantly synthesizing sensory input and behaving in accordance with our goals. During this ongoing cycle of sensing and behaving, rarely is it the case that we are presented with an unambiguous external cue that tells us to stop our behavior. Instead, we often anticipate the need for control and prepare to control specific behaviors that could compete with our goals. The results from the three studies included in this thesis support the overarching hypotheses that circuits between the cortex and subthalamic nucleus of the basal ganglia are involved in preparing to control behavior and that this preparation helps to target inhibition at specific behavioral responses when they must be stopped. Specifically, we showed that preparing to stop i) influences the selectivity of motor system inhibition during stopping, ii) depends on the ventral subthalamic nucleus and/or connected brain areas, and iii) alters EEG signatures associated with reactive stopping.

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Figure 14: Proposed brain networks for A) **globally** stopping action via the hyperdirect pathway (e.g. when stopping is not prepared in advance) and B) **selectively** stopping action via the indirect pathway (e.g. when stopping is prepared and targeted at a specific response). STN = subthalamic nucleus, Str = striatum, GP = globus pallidus, Thal – thalamus, rIFG = right inferior frontal gyrus, pre-SMA = pre-supplementary motor area.
5.4 References


Chen C-Y, Muggleton NG, Tzeng OJL, Hung DL, Juan C-H (2009) Control of


Swann NC, Cai W, Conner CR, Pieters TA, Claffey MP, George JS, Aron AR, Tandon N (2011b) Roles for the pre-supplementary motor area and the right inferior frontal gyrus in stopping action: Electrophysiological responses and functional and structural connectivity. If you read this, please look me up, and I will buy you a beer. NeuroImage.


