Domain Specific Lateralization of the Frontal Processes Informing Inhibition: A TMS Study

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Abstract

Response inhibition is the suppression of actions that are inappropriate given some wider context or goal, a capacity that is vital for everyday functioning. In this thesis the theoretical backdrop of executive functioning is discussed, before exploring current research into response inhibition and its neural underpinnings. A theory by Mostofsky and Simmonds (2008) holds that when the decision to inhibit a behavior is a complex one, task dependent parts of an inhibitory network in the prefrontal cortex are utilized. The current thesis argues on the basis of observed biases in the literature, for the possibility that this task dependent engagement features domain specific lateralization. In order to investigate this, a transcranial magnetic stimulation [TMS] experiment is then presented where four go/no-go tasks, spread across language and spatial domains in complex and simple forms, are performed following TMS. Stimulation sites include the right posterior inferior frontal gyrus, the left posterior inferior frontal gyrus, and sham stimulation. Results are then discussed, however implications are limited, likely due to low statistical power.

Keywords: Response Inhibition, Executive Function, TMS, pIFG

Preface

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Chapter 1: Introduction and Theoretical Perspective

Imagine yourself in a group of people, waiting to cross the road at a busy intersection. While impatiently waiting to cross your chosen street, the light on the left that controls the perpendicular crossing changes to green, and this is accompanied as it usually is by a buzzer for the vision impaired. At this point you may notice that some of those around you take a half step forward. You may even notice that you yourself, cued by the buzzer, lean forwards before stopping the impulse to cross. The impulse to step out arises due to the consistent pairing of the buzzer sound with the action of stepping out in the past. In this case however, the context indicates that this impulse is a bad one; your light is still red, and stepping out in front of traffic does not align with your current goal set. Therefore, you inhibit the impulse to step forward. If you are under the influence of alcohol or distracted by a good conversation, you may find yourself failing to halt the impulse to step out in front of the traffic and placing yourself and others in danger. In this situation, a failure to inhibit this impulse could be catastrophic.

The halting of this impulse is an example of '*response inhibition'*, the suppression of actions that are inappropriate given some wider context or goal. Broadly speaking, the capacity to inhibit a response is crucial to success in everyday life. At work, saying exactly how you feel to your employer is not always the best choice of action. Similarly, giving in to the urge to dance at a classical music concert may result in some social embarrassment!

Given the importance of response inhibition for everyday life, a difficulty involving some or all of these skills is likely to be highly debilitating. A deficit in response inhibition has been proposed as a significant component of the difficulties described by Attention Deficit Hyperactivity Disorder [ADHD], or at least certain permutations of this condition (Aron &

Poldrack, 2005; Mark A. Bellgrove, Hawi, Gill, & Robertson, 2006; Oosterlaan, Logan, & Sergeant, 1998; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Sergeant, Geurts, & Oosterlaan, 2002; van Rooij et al., 2015). Other disorders have also been associated with an inability to inhibit certain cognitions or behaviors; Obsessive-Compulsive Disorder [OCD] and Substance Abuse [SA] both seem to constitute an inability or extreme difficulty with inhibiting particular compulsions in the presence of an obsessive thought or substance related stimulus respectively, even when to do so is contextually inappropriate or disadvantageous for the individual (Coles, Schofield, & Pietrefesa, 2006; Fillmore & Rush, 2002; Monterosso, Aron, Cordova, Xu, & London, 2005; Penades et al., 2007). It is obvious then that response inhibition is a human capacity well worth studying.

Exploration of the literature in this area, as well as of tasks used to measure response inhibition, will begin in Chapter Two. This discussion will lead to the presentation of an experiment in chapters three, four and five. The remainder of this first chapter serves as a prefatory comment on broader theoretical context, and can happily be skipped if the reader does not share an interest in the ontology of the cognitive processes occurring within the frontal lobes of the human brain.

Executive Function and Modulatory Control Theory

Response inhibition is usually considered to be an example of a wider set of high level skills known as executive function. Executive function is a somewhat elusive construct that refers to the ability to modulate one's cognitions and behaviors according to one's goals (Alvarez & Emory, 2006; Aron, 2007; Miller & Cohen, 2001). This concept is usually further broken down into different categories which unfortunately vary depending on which researcher you are talking to. As reported in a review by Diamond (2013), there is some consensus in regard to

three commonly purported primary executive functions; ‘working memory’ or one’s ability to take in, maintain and manipulate information (Baddeley, 1992, 2012; Barbey, Koenigs, & Grafman, 2013; Gazzaley & Nobre, 2012; Kane & Engle, 2002); ‘set shifting’, or the capacity to shift fluidly between behaviors directed towards different goals (Koch, Gade, Schuch, & Philipp, 2010; Monsell, 2003); and of course ‘inhibition’, the ability to inhibit a cognition or behavior which is highly activated, but inappropriate or disadvantageous under the current circumstances (Friedman & Miyake, 2004; Jurado & Rosselli, 2007; Nigg, 2000). However, in the broader literature, a wide number of other skills and behaviors have also been identified as falling under the rubric of executive function, betraying the fragile nature of this consensus. These other skills and behaviors include: the monitoring of one’s own activity and external circumstances so as to ensure behaviors are successfully meeting goals within a changing context, commonly referred to as simply ‘monitoring’ (Stuss, 2011); decision making and logical reasoning (Toplak, Sorge, Benoit, West, & Stanovich, 2010); goal-oriented planning (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005); the ability to think creatively and flexibly, for example, as is required to generate novel ideas, or multiple solutions for a complex open-ended problem (Dietrich, 2004); the ability to rapidly establish novel stimulus response-associations needed for a task, even when they are inconsisntet with prioir learning, commonly refered to as ‘task setting’ (Stuss, 2011); the ability to inititate behavior in the absence of external cues, commonly referred to as ‘energization’ or ‘initiation’ (Stuss et al., 2005); the ability to remember to do something in the future, known as prospective memory (Kliegel, Martin, McDaniel, & Einstein, 2002); as well as more generally, sustained attention, and top down attentional control. For a more formal review of different conceptions of executive function see Jurado and Rosselli (2007), but needless to say, this is an area of lively debate.

Worse than this however, the debate is not over just what functions should be included under the label "executive function", but also over the conceptual borders of these functions. For example, consider the ability to shift between response sets such as when you are listening to a friend's story on the phone while also frying yourself some bacon. To successfully shift back and forward between these tasks one must be able to maintain both response sets in working memory (such as responding to your friend at the appropriate times, and remembering to take the pan off the heat in response to the sight and smell cues of perfectly cooked bacon), and of course inhibit the non-target response set while performing the currently appropriate set (i.e. don't accidently tell your friend that they smell really good). This function then, also encompasses other 'executive functions' like inhibitory control and working memory. Similarly, to plan future goal-oriented actions effectively, one needs to be able to maintain and manipulate multiple pieces of information, functions that are often described under the rubric of working memory. More and more the literature is pointing to the overlap between executive functions; working memory requires focused cognitive resources and is therefore greatly influenced by selective attention abilities (Gazzaley & Nobre, 2012; Kane & Engle, 2002), and task switching likely involves inhibition as a central mechanism (Kiesel et al., 2010; Koch et al., 2010). In short, when it comes to the conventional categorical model of "executive function", there is an issue with internal consistency. Even within functions that would appear to be more specific and well defined, such as response set shifting, inhibition, and monitoring, distinctions are not as clear as they may seem. A latent variable analysis by Miyake et al. (2000) showed that performance across these areas is not completely dissociable, describing this as the 'unitary yet diverse nature' of executive functions. Most pertinently for this thesis, virtually all of the proposed categories involve some sort of inhibition, as the proposed mechanism for executive function is usually some sort of

complex modulating network, a process that by definition includes inhibition as a large part (Miller & Cohen, 2001).

These issues with internal consistency seem to stem from a broader ontological problem; the status quo model does not make clear what exactly these functions are meant to be. It is unclear whether they constitute discrete cognitive functions, capacities arising from some combination of disparate functions, or simply useful metaphors to describe phenomena emerging from near-indescribable complexity. To answer or even properly discuss these questions is well beyond the scope of this thesis, but what can be said is that the categorical model that has emerged like a behemoth from the literature does not speak to the "unitary yet diverse nature" of executive functions (Miyake et al., 2000), and thereby does not do justice to the complexity and elegancy of the brain. It is obvious, even if only for pragmatic reasons, that a more parsimonious perspective that captures the observed complexity in an internally consistent way is required.

There are models that attempt to fix these problems, and some of the more common of these are briefly outlined here. Norman and Shallice (1986), proposed the supervisory attentional system (SAS) as a model of frontal lobe function. This describes the prefrontal cortex [PFC] of the brain as a unitary component of the brain that biases lower level functions to optimize behavior in unique situations, where more automatic functioning would be problematic. While accounting for the functional integration of executive control, this model does not differentiate between separate anatomical areas of the PFC; this is in contrast to the component theory of Stuss and Co. which has gained popularity in more recent years. Theirs is a model that holds that three broad executive functions can be observed (and that others may arise as research continues), and that executive functioning *per se* does not exist, but rather is a combination of these processes which occur in distinct areas. These three functions are: task setting, occurring in

the left lateral prefrontal cortex; monitoring, occurring in the right lateral frontal lobe; and energization, occurring within superior medial areas of the frontal cortex (Stuss, 2011; Stuss & Alexander, 2007; Stuss, Shallice, Alexander, & Picton, 1995)). Other models include those of Badre (Badre, 2008; Badre & D'Esposito, 2009), and Koechlin (Koechlin & Jubault, 2006; Koechlin, Ody, & Kouneiher, 2003; Koechlin & Summerfield, 2007), which are based on the idea of a hierarchical organisation of the lateral PFC, where progressively more posterior regions support more concrete or temporally proximate levels of actions respectively. A review of these theories and others like them is far beyond the scope of this thesis (for a taxonomy of some of these theories see Koechlin and Summerfield (2007)), but it should be noted that these theories differ in regard to an important attribute: the degree of unitary function proposed. At the extremes, theories such as the SAS propose complete unity, while Stuss's component theory proposes quite clear functional specialisation for different areas. Taking a middle line the hierarchical organisation models attempt to rectify the observation of functional specialisation with the integration of the different executive functions, by demonstrating how the over-arching structure allows the different functions to work together.

Debate in this area will continue, likely for quite a while. Rather than attempt to delve into such an area this thesis will work from a conservative framework of assumptions which will now be outlined. In this way the framework makes no strong claims in regard to functional organization, allowing for the nesting of different models as research in this area develops. On the continuum of unity to disparity described above this framework takes a middle ground, much like the hierarchical organisation models; however it arrives at this point not via structural claims, but via an ontological observation in regard to the nature complex systems, such as the brain most certainly is.

To begin, we will assume in accordance with a long standing consensus in the literature that it is the PFC of the brain that is largely responsible for the various executive functions. We will also assume that such processing draws on the 'lower-level' processing in other areas of the brain; for a critical meta-analytic review of this basis see Alvarez and Emory (2006). Going on, the theoretical outlook of this thesis assumes that the dominant process occurring within the PFC is a complex network of synthesis and modulation, as described in Miller and Cohen (2001). Theirs is a theory that explains the human capacity for top-down control of behavior by postulating that the PFC takes the information it receives from diverse areas of the brain, including areas intrinsic to itself, synthesizes this information, and modulates external and internal behavior (including the biasing of sensory experiences) in accordance with certain parts of this information such as goals, emotional associations, and contextual factors. Within this theory, functionally specialized areas do play a role. Essentially, Miller and Cohen propose that the observed capacity for 'executive function' emerges from this complex network. Full exploration of this theory is also beyond the scope of this thesis, but the fact that it successfully describes how the PFC performs a "supervisory" role, without the existence of some magic box or homunculi, while also accounting for the functional integration of different executive functions, makes it a viable basis from which to start. Given this basis we will label the equivalent term to executive function as 'modulatory control' given its roots in the work of Miller and Cohen (2001). From this point onward the current framework will be referred to as the 'modulatory control framework' for the sake of clarity between models, and because this seems a more descriptive term, the referent of which does not fall to the homunculus fallacy with the same necessity as 'executive' function.

Given that the current model is building on the basis of such a complex mechanism, it has drawn on the method of integrative pluralism explored in Mitchell (2009), which concerns the use of realist-pluralism to describe and manage complexity within systems in a practical way. This is most relevant to the fact that under this model the capacities sought to be explained (including key functions such as maintenance, top-down attentional control, inhibition/response set modulation, and monitoring), are not described as categorical processes in and of themselves, but rather stay as they are observed; as capacities that arise as products from a complex network of modulation. Importantly, if one looks close enough, iterations of such capacities, while appearing to be the same outcome or serve a similar purpose, may arise from different causal networks within the brain system. For example, it is practical to view the capacity of inhibiting a response as a robust phenomenon, but it is also important to recognize that each real world iteration of response inhibition will arise from different neural substrates contingent upon both the nature of the task at hand, as well as the states, traits, and history of the individual.

The use of this method allows for integration of understandings across different levels of granularity. It is this that allows the ontological observation alluded to earlier, that within a system as complex as the brain, unity versus disparity is a somewhat false dichotomy. From a large grainsize such a system will act with unity, yet on closer inspection partially independent subsystems will emerge. An apt metaphor for this is the murmuration of starlings. This is the name given for when a flock of birds fly together in a way that appears to demonstrate self-organization at a group level. Investigation of this phenomenon has shown that it emerges from complex interactions between the simple responses of each bird to the other six to seven birds in its immediate vicinity (King & Sumpter, 2012). Each bird then, is in essence its own semi-independent subsystem, but as a whole it still makes sense to say that the flock acts with unity.

This demonstrates that the apparent independence or unity of a system is influenced by the granularity of your perspective. Use of Mitchell's method of integrative pluralism, which layers multiple understandings together, coupled with Miller and Cohen (2001)'s description of a complex self-modulating network, allows us properly capture the "unitary yet diverse nature" of frontal processes described by Miyake et al. (2000), without falling to issues of internal consistency. It is therefore from this basis that this thesis will work from.

For clarity this modulatory control framework can be summarized into the following five guidelines:

1. Executive functions are capacities rather than processes and should be described as such.
2. These capacities arise as products from a complex network of synthesis and modulation occurring within the PFC.
3. This network is unitary in the sense that it modulates cognitions and behavior in accordance with other information including goals and values, but is also disparate in that specialized functional areas do exist.
4. Each performance of some executive capacity will be achieved in a different way dependent on the requirements and context of the task, as well as the historical context of the individual.
5. It is pragmatic to cluster these capacities under titles such as inhibition, monitoring, etc., but as we continue to inspect these abilities they will continue to be subcategorized into different patterns of neural cascade.

Different Types of Inhibition

Turning now to inhibition specifically, even this ostensibly simple function may be subcategorized. Nigg (2000) presents a taxonomy that denotes four major kinds of "effortful" inhibition. These include: interference control (the effortful ignoring of task irrelevant stimuli), cognitive inhibition (the effortful suppression of wandering thoughts in order to protect working memory/attention), oculomotor inhibition (effortful suppression of reflexive saccades), and finally the focus of this thesis, behavioral inhibition (the effortful suppression of inappropriate actions or behaviors). Nigg's taxonomy fits well with modulatory control theory as it does not describe some common process of inhibition, but rather describes separate processes dependent on what it is that is being inhibited. At the same time Nigg's description does not miss the fact that these processes share a conceptual similarity, in that they all involve the capacity of inhibition. The modulatory control framework further predicts that Nigg's processes, when studied in greater detail, will continue to separate depending on what is being modulated and what it is being modulated in light of. Accordingly, some separations have already been proposed in the literature such as the difference between 'action restraint', and 'action cancelation' which will be discussed in more detail later on. In the following chapter an argument will be presented for such a separation within the capacity of response inhibition, on the basis of the kind of information informing the decision to inhibit a response. This will be followed by a supporting experiment. First however, we must explore what exactly response inhibition is, how to measure it, and what we already know about its occurrence in the brain.

Figure 1. *A Murmuration of Starlings, Demonstrating Unity Emergent from a Complex Network of Subsystems. Photograph courtesy of ISC-CNR, Starflag Project.*

Chapter 2: Literature and Task Review

Tasks Used to Measure Response Inhibition

The capacity to inhibit inappropriate responses can be measured in the laboratory in a number of ways. For example, one classic task which is considered to tap into this group of skills is the Stroop task (Stroop, 1935). This involves a participant being presented with the names of colors written in various colors of ink. Their task is to name the colour that the word is written in, irrespective of what the word actually says. Sometimes, the ink color is congruous with the referent colour (e.g. "red" written in red ink), and sometimes it is incongruous (e.g. "red" written in blue ink). Participants are consistently slower, and make more errors, on incongruous items, and this is attributed to the cognitive effort of inhibiting the competing attributes of the stimulus (the word name). In this way the Stroop task measures response inhibition in that it involves the inhibition of a highly activated response so that it can be replaced by an alternative response, less highly activated but more appropriate for the current context. Of course, this task could also be seen as involving not just response inhibition, but also cognitive inhibition (inhibition of inappropriate cognitions) and even controlled selective attention (the participant may try to attend more to the color of the word and less to its name).

Other tasks that measure behaviors related to response inhibition are go/no-go tasks (Georgiou & Essau, 2011) and stop signal tasks (Morein-Zamir & Sahakian, 2010). Go/no-go tasks are comparatively simple. A series of stimuli is presented, most of which require a key press response ('go' trials). However, on a (usually) small percentage of 'no go' trials, the participant must refrain from responding altogether, dependent on some rule. For example, imagine a participant being shown a series of letters. They are to press a key in response to every letter they see, unless it is an 'X', in which case they must withhold their response. Using this

paradigm, participants will often incorrectly respond to the ‘no go’ trials, even though they are supposed to refrain from doing so. Since the ‘go’ trials usually outnumber ‘no go’ trials, the go response becomes ‘prepotent’, and thus difficult to inhibit.

The stop signal task is slightly more complicated in construction, involving repeated trials of some basic response, such as pressing one of two keys depending on whether a stimulus is for example red or green. On critical trials, some salient visual cue is presented shortly after the stimulus, and on these trials, the participant must withhold a response. The stop signal is presented at a variable interval after the onset of the stimulus, and the effect of this interval on the probability of making an inhibitory error (responding despite the presence of the stop signal), is used to generate an estimate of the time taken to inhibit a ‘go’ response known as the stop signal reaction time (SSRT).

Comparing these two tasks, the most obvious difference is the nature of the stop cue. Within the go/no-go task the cue to withhold a response is inherent in some property of the stimulus, while in the stop signal task the cue always follows the stimulus, and therefore presumably after some degree of response preparation has occurred. This difference has led some researchers to label the go/no-go task as a measure of ‘action restraint’, and the stop signal task as a measure of ‘action cancelation’, with both representing different flavors of response inhibition (Eagle, Bari, & Robbins, 2008; Schachar et al., 2007). Considering this, as well as the breadth of processes that the Stroop task may draw on, it can be seen that different tasks measure distinctly different inhibitory processes. Focus of this discussion will now shift to the neurological processes behind our capacity to inhibit responses during performance of both go/no-go and related tasks.

Neural Localization and Domain Specificity

Much work has been done on locating the brain areas that may be involved during response inhibition. This section is concerned with overviewing and critiquing this literature. To begin, a meta-analysis by Buchsbaum, Greer, Chang, and Berman (2005) amalgamated the results of 17 separate functional magnetic resonance imaging [fMRI] studies, each looking at the brain areas active during no-go trials of go/no-go tasks (various contrasts used). Their results suggested that a highly right lateralized frontal network may be active during these trials, with particularly strong activation in the right posterior inferior frontal gyrus [pIFG]. However, there was also some activation of the left IFG. Looking at the studies included in this meta-analysis it is worth noting that none of the tasks used word stimuli, a point that I will return to later (Asahi, Okamoto, Okada, Yamawaki, & Yokota, 2004; Mark A Bellgrove, Hester, & Garavan, 2004; Braver, Barch, Gray, Molfese, & Snyder, 2001; De Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; Fassbender et al., 2004; Garavan, Ross, Murphy, Roche, & Stein, 2002; Garavan, Ross, & Stein, 1999; Hester et al., 2004; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Kelly et al., 2004; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Liddle, Kiehl, & Smith, 2001; Maguire et al., 2003; Menon, Adleman, White, Glover, & Reiss, 2001; Mostofsky et al., 2003; Rubia et al., 2001; Watanabe et al., 2002).

Outside of the imaging literature, investigation has supported this picture of a predominantly right lateralized inhibitory network in the PFC. Aron, Fletcher, Bullmore, Sahakian, and Robbins (2003) demonstrated that patients with right hemisphere damage produced slower SSRTs during a stop signal task in comparison to healthy controls. The degree of this slowing correlated highly with the degree of damage to the right IFG, particularly the posterior components (i.e. the pars triangularis and pars opercularis), with much lower

correlations with damage to other frontal areas. Response times when no stop signal was given were also slower for right hemisphere patients, but this measure did not correlate with damage to any particular area. This supports the functional role of the right pIFG during response inhibition tasks; however it should be noted that left hemisphere patients were not studied. Chambers et al. (2006) demonstrated similar results using Transcranial Magnetic Stimulation [TMS], a method which temporarily disrupts processing in targeted areas of the cortex. An increase in SSRT and a decrease in the number of correct inhibitions during a stop signal task was found following stimulation of the right IFG, defined as the dorsal midpoint of the pars opercularis. Stimulation of the middle frontal gyrus, and the angular gyrus, did not have such an effect. Supporting evidence has also been found using electroencephalography [EEG], which is a way to measure brain responses during cognitive tasks; Swann et al. (2009) placed electrodes within the skulls of participants completing a stop signal task and compared activation of different brain areas on successful stops to unsuccessful stops, finding greater activations over the pars triangularis and opercularis of the right IFG during correct inhibitions. Again however, leftward areas were not studied. In summary, literature in this area strongly supports a functional role of the right posterior IFG, but the possible role of the left IFG is less clear, as it is often ignored.

One study that does include the left IFG was Swick, Ashley, and Turken (2008). This paper looked at the performance of lesion patients on a go/no-go task, showing that those with damage to the left IFG had made a greater number of inhibitory errors compared to both heathy subjects and patients with damage to orbito-frontal areas, especially when the percentage of no-go trials was lowered to %10 (e.g. when the task was more complex due to the infrequency of no-go trials). This study did not make comparison to patients with damage to the right IFG, but still suggests contrary to the majority of literature in the area, that left IFG may be playing a

causal role. Unfortunately the wider picture is not entirely this clear. Chambers et al. (2007) once again used TMS to demonstrate that stimulation of the right IFG impairs performance on a stop signal task much like their earlier study, however this time the researchers also stimulated the left IFG, which interestingly showed no such effect. In comparing these studies it is of note that Chambers et al. used spatial stimuli involving the direction of arrows, while Swick, Ashley, and Turken used letters of the alphabet.

It is important to remember that it is not only the IFG that is of interest, for example the pre-supplementary motor area [pre-SMA] and supplementary motor areas [SMA] are also often implicated. Floden and Stuss (2006) demonstrated that patients with damage to the SMA/pre-SMA area show higher SSRTs on a stop signal task while Picton et al. (2007) showed similar results using a go/no-go task, where patients with damage to SMA/pre-SMA areas showed a greater number of inhibitory errors. Together these results support the proposal of a network within the PFC supporting response inhibition, with the right pIFG and pre-SMA areas being key nodes.

There is also reason to believe that this network is utilized across response modalities; an interesting study by Chikazoe, Konishi, Asari, Jimura, and Miyashita (2007) used fMRI on healthy subjects during an anti-saccade task, a task which is quite different to the tasks focused on in the rest of this discussion. The anti-saccade task involves moving the direction of eye gaze either toward (control condition) or away from a target stimulus (anti-saccade condition). These conditions are usually presented at equal rates, with the ‘toward’ response being seen as reflexive and the ‘away’ response being seen as requiring inhibition of the reflexive response. This task usually activates various frontal areas, but is not usually associated with prominent activation in the IFG. Within their study however, Chikazoe et al. (2007) modified the task by introducing a

third ‘baseline’ reflexive saccade condition which required a reflexive saccade toward the stimuli, much like the control condition. This decreased the proportion of trials requiring an anti-saccade response, increasing the prepotency of toward stimuli responding. This effectively increased the inhibitory demand in a similar way to a go/no-go task. Compared to the traditional anti-saccade task, Chikazoe et al. (2007) found increased activation of the right posterior IFG during anti-saccade trials. This suggests that activation in this area seems to be dependent on the inhibitory nature of the task at hand rather than on response modality. Further comparison was then made to the meta-analysis of Buchsbaum et al. (2005), which revealed overlap in the coordinates of peak activation points including those referencing the right posterior IFG.

Reviews of this response inhibition literature can be found in Chikazoe (2010), and Chambers, Garavan, and Bellgrove (2009). In summary however, support for a right lateralized inhibitory network featuring the pIFG and pre-SMA areas, is relatively strong. That said, as alluded to above it is noteworthy that the left IFG is often not studied, and that the tasks used in this literature do not often utilize language based stimuli. Of the seventeen studies used in Buchsbaum et al. (2005)’s meta-analysis, which has played a significant role in the development of this lateralized network hypothesis, seven used letter stimuli, while ten used colours, shapes or objects. Of the seven that used letter stimuli only three used the complete alphabet, while the other four used such task constructions such as using ‘Y’ as a go stimulus and ‘X’ as a no-go stimulus. None of the studies in the meta-analysis used more complex language oriented stimuli.

This brings us to a meta-analysis by Simmonds, Pekar, and Mostofsky (2008) and the associated theory of Mostofsky and Simmonds (2008). This meta-analysis of fMRI studies divided go/no-go studies into those that used ‘simple’ tasks, where the no-go stimulus was always the same, and those that used complex tasks, where the no-go stimulus was visually

different each time and depended on some more complex rule. An example of a simple task might involve presentation of the letters of the alphabet with the rule that the participant 'goes' on every letter, but doesn't go when the letter is an 'X'. This task is 'simple' because the no-go stimulus is always the same. An example of a complex task might involve the presentation of various pictures of food items, with the rule being that the participant 'goes' on each food item they see, but withholds the response when the food item is a vegetable. This task is complex because the no-go stimuli will not always be the same, many different vegetables will require the withholding of a response. This meta-analysis indicated that the pre-SMA (as well as the fusiform gyrus which the authors ascribe to the performance of a template matching function) shows reliable activation across both kinds of go/no-go tasks, while increased activation of the previously observed right lateralized inhibitory network, including the right IFG, was only seen during the complex tasks.

Mostofsky and Simmonds (2008) offer a theoretical explanation of these findings. In their account, response selection and response inhibition are viewed as "two sides of the same coin", in that response inhibition is simply selection against a more automatic or dominant response. They propose that response selection/inhibition in its most basic sense is occurring within the pre-SMA as it is essentially preparation for motor action which is the apparent function of this area (Isoda & Hikosaka, 2007). In contrast, the cognitive processes used to *inform* the selection/inhibition within the pre-SMA recruit different frontal and parietal areas depending upon on the nature of the task. This task dependency sits well with the modulatory control framework underlying this thesis and is the proposition that will be the focus going on.

Seemingly, Simmonds et al. (2008)'s analysis and the accompanying theoretical contribution of Mostofsky and Simmonds (2008) support the right lateralized inhibitory network

hypothesis, with the addition that the majority of this network is only activated under ‘complex’ conditions, where response selection requires context dependent modulation. However, the simple implication of this task dependency is that when attempting to study response inhibition the requirements of the task at hand should be carefully considered. Looking at the ten studies included in the Simmonds et al. (2008) meta-analysis more closely, the same lack of language based stimuli seen in Buchsbaum et al. (2005) is apparent, and perhaps even more prevalent, for none of the six studies that used letter stimuli presented more than two letters, and again, none used more complex language based stimuli (Fassbender et al., 2004; Garavan et al., 2002; Garavan et al., 1999; Garavan, Ross, Kaufman, & Stein, 2003; Hester et al., 2004; Kelly et al., 2004; Kiehl, Liddle, & Hopfinger, 2000; Liddle et al., 2001; Mostofsky et al., 2003; Watanabe et al., 2002). This therefore represents a potentially important bias, as does the lack of investigation into the left hemisphere in non-imaging studies pointed out earlier.

When we consider that the left pIFG is more highly activated than the right in tasks that require word production, such as verb generation, leading to it often being seen as a language specialized area (Schnur et al., 2009; Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997), and that in the frontal cortex more broadly there is some evidence to support a slight rightward bias for spatial information (Vogel, Bowers, & Vogel, 2003), the implications of these biases become clear. The illusion of a rightward lateralization of inhibitory processing is exactly what we would expect to see from such a biased literature and may therefore be artefactual. In fact, the apparent fixed lateralization of this network may be domain specific. The left PFC, particularly the pIFG, may actually be playing a role in informing response selection/inhibition, but only when the task at hand is language oriented. A novel experiment will now be presented in order to explore this possibility.

Chapter 3: The Experiment

Overview and Hypothesis

This thesis is focused on the proposition by Mostofsky and Simmonds (2008) that the utilization of processing in the frontal lobes to inform response inhibition is functionally specific. Specifically, we propose that, in the context of a task that involves withholding a response, the network of structures that are engaged in response inhibition will vary depending upon the domain of the stimulus that indicates the need to withhold. Broadly speaking, the intended study takes what are arguably the two most lateralized domains of cognitive processing, language versus spatial reasoning (Vigneau et al., 2006; Vogel et al., 2003), and compares performance on inhibition tasks rooted in these domains. Specifically, we focus on the posterior section of the Inferior Frontal Gyrus (pIFG), also known as the pars opercularis, within each hemisphere. We use a go/no-go paradigm, in which we manipulate both the nature of the stimuli (whether language or spatial) and the complexity of the rule that determines how participants should respond. Based on the observed greater frontal engagement during complex go/no-go tasks (Simmonds et al., 2008), we predict that frontal areas particularly the pIFG will contribute minimally during simple task versions, but will play a stronger role in the complex versions. Given that the right pIFG is highly activated in go/no-go tasks involving spatial stimuli (Chambers et al., 2009; Chikazoe, 2010), and the left pIFG is highly activated in tasks involving selection of words and/or their meanings (Schnur et al., 2009; Thompson-Schill et al., 1997), we predict that go/no-go tasks using spatial stimuli will utilize the right pIFG, and that go/no-go tasks using language stimuli will utilize the left pIFG.

Transcranial Magnetic Stimulation (TMS), the use of electromagnetic pulses directed at the cortex, is a tool well suited to test this proposition as it allows us to disrupt processing within a targeted area of the brain (Rossi, Hallett, Rossini, & Pascual-Leone, 2009; Sandrini, Umilta, & Rusconi, 2011). Based on Mostofsky and Simmonds (2008)'s theory, the predictions regarding the effect of TMS stimulation on go/no-go performance are as follows: TMS of the right pIFG should reduce performance on the spatial based inhibition task compared to both stimulation of the left as well as sham TMS. Similarly, stimulation of the left pIFG should impair participants' ability to inhibit responses on "no-go" trials on a language based inhibition task compared to both stimulation of the right as well as sham TMS. Also based on Mostofsky and Simmonds (2008), we predict that this effect will primarily be shown in the complex task versions, and will be comparatively smaller or in fact minimal, in the simple task versions. The alternative hypothesis of a right lateralized inhibition network, referred to earlier, will be supported by domain general reduced performance under conditions of rightward stimulation. Reduced performance will be primarily indicated by an increase in the number of errors made on no-go trials, also known as an inhibitory error. Response times will also collected in order to check for speed accuracy trade off.

Method

Design. A within-subjects 3x4 design was used. The independent variables were: TMS condition (sham TMS, left pIFG, and right pIFG), and task (Simple Spatial, Complex Spatial, Simple Language, Complex Language). While our tasks were intended to manipulate domain and complexity independently, this was not a fully orthogonal manipulation in a statistical sense, and therefore for statistical purposes the four tasks were considered to be different levels of one factor. Briefly, the four different tasks were: 'Simple Spatial', where the no-go stimulus was a

reoccurring shape; ‘Simple Language’, where the no-go stimuli were two reoccurring letters; ‘Complex Spatial’, where the no-go stimuli were symmetrical shapes; and ‘Complex Language’, where the no-go stimuli were words that fitted a specific category. Each participant completed three sessions, each involving one of the three different TMS conditions.

Participants. A total of 18 participants took part in this study (Sex: 9 male, 9 female; Age: 18-34, M=24.89, SD=4.25), and were offered two movie vouchers per session for their time. All participants were right-handed and were screened and excluded for the following; epilepsy or history of seizure, family history of epilepsy, head trauma resulting in loss of consciousness, previous stroke, previous brain surgery, intracranial pathology, hearing problems or tinnitus, use of cochlear implants, recent fainting spells/syncope, recent or major history of headaches, pregnancy or chance thereof, metal in the body in proximity to the head, intracorporal devices (specifically including but not limited to: implanted neurostimulators, cardiac pacemaker or intracardiac lines, medication infusion device), current medications (specifically including: antidepressants, antipsychotics, anxiolytics, analgesics, anticonvulsants, amitriptyline, haloperidol), albinism, neurological or psychiatric disorder, multiple sclerosis, and previous problems during MRI or TMS. The presence of any other medical conditions was also queried. In sum, no participants were excluded. All participants had received an MRI scan at Wellington Hospital, New Zealand, prior to their participation in the current study as part of the Victoria University of Wellington’s School of Psychology TMS program. Ethical approval for this study was granted by the Victoria University of Wellington, School of Psychology Human Ethics subcommittee.

Tasks and Materials. A go/no-go paradigm was used. This is because during these tasks the nature of the stimuli is what cues inhibition, thereby allowing for true manipulation across

domain. Comparatively, the domain of the stimuli in stop signal tasks seems less relevant to the process of inhibition as it is simply the sudden appearance of the stop cue that triggers cancelation of pre-potent response. All tasks were created using Open Sesame version 3.0.X (Mathôt, Schreij, & Theeuwes, 2012). The four go/no-go tasks used in the study were as follows.

Simple Language Task. This task was based on a similar task reported in Swick et al. (2008). In each trial, a single lowercase letter from a-z was presented. The participant's task was to respond to each letter "as quickly as possible" using a single marked key on the computer keyboard using the index finger of the right hand. However, when the lowercase letter corresponded to one of two prespecified targets, participants were to withhold a response altogether. They were instructed that they "must not press anything" on these trials. Two targets were used in an attempt to balance error rate across the two simple tasks. This was decided on the basis of piloting, where a similar task with only one target letter was found to produce minimal error rate. Prior to commencing the task, participants were again reminded to respond as quickly as possible followed by presentation of a fixation point. Trials proceeded as follows. Each stimulus was presented for 1500ms or until the participant responded. There was then a 300ms blank screen before presentation of the next trial. The letters used as targets varied across participants and sessions. There were 128 trials in total, 25% of trials were no-go trials.

Complex Language Task. For this task, the stimuli were 32 different words presented in a random order. Target words were those that described a role or position that somebody could take (e.g. *acrobat, politician, poet*). The role/position words were chosen to contain a variety of different word endings to ensure that semantic engagement with each stimulus would be required. Two alternate lists of 32 words were created, and these lists were controlled for word frequency and length. Specifically, both lists had target and non-target words with an average

length of 6.5 letters (*Min*=3-4, *Max*=10) and an average $LogSUBTL_{WF}$ of 2.5 (*Min*=1.5-2.0, *Max*=3.1-3.9). This frequency information was sourced from 'The English Lexicon Project'(Balota et al., 2007). The lists were counterbalanced across participant and session. Other aspects of the procedure were the same as for the Simple Language task.

Simple Spatial Task. For this task, stimuli were 26 different abstract geometric shapes composed of straight lines. Shapes were nameless in order to minimize language based processing. Examples of the shapes used are shown in Figure 2. In this task, the no-go stimulus was a single target shape, which was presented to the participant prior to the trials, accompanied by the instruction "if the shape presented is this one, you must not press anything!" Other aspects of the procedure were the same as for the Simple Language task.

Complex Spatial Task. For this task, the stimuli again consisted of 32 different nameless shapes presented in a random order. These shapes incorporated curved lines in order to differentiate them from those used in the simple spatial task. Some shapes were symmetrical about the vertical or horizontal axis, and some were not. Examples are shown in Figure 2. The no-go stimuli were those that were symmetrical, either vertically or horizontally. Prior to the task, participants were given examples of symmetrical shapes, but these examples were not featured in the task. Other aspects of the procedure were the same as for the Simple Verbal task.

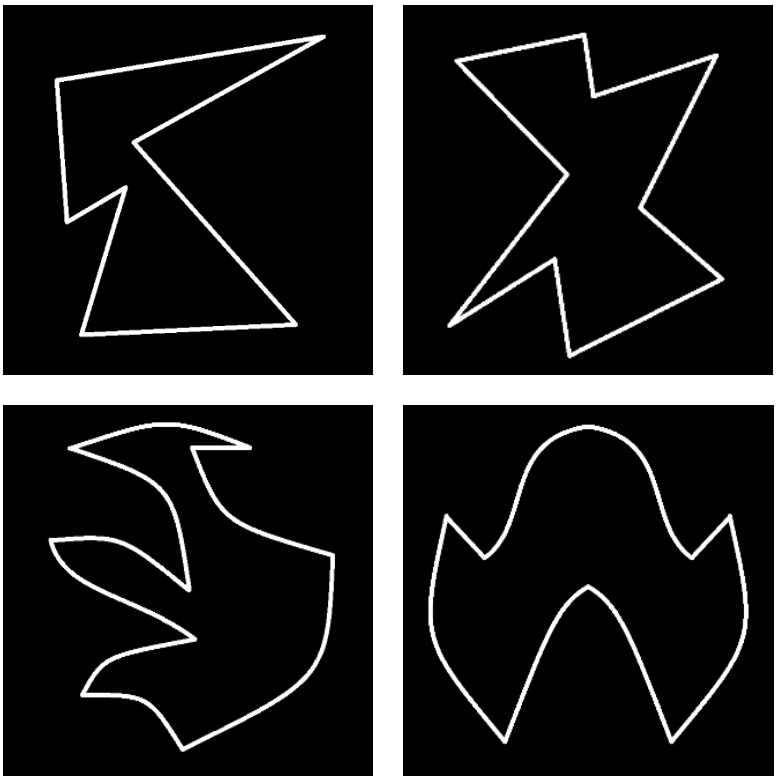

Figure 2. *Examples of Stimulus for the Spatial Tasks. The top two shapes are like those used in the simple task, the bottom two like those used in the complex task. The two right most shapes represent no-go stimuli. In the simple task this shape would have been prespecified.*

Counterbalancing. Two versions of each task were created which featured different targets, and for the complex tasks, entirely different stimuli sets. In each session, the simple tasks were always presented prior to the complex ones. However, the order of the two task domains was counterbalanced, with spatial preceding language in half of all trials, and language preceding spatial on the other half. Finally, the assignment of TMS condition to sessions was also counterbalanced across participants. A summary of the counterbalancing of the major stimulus manipulations is shown in Table 1. Full lists of the stimuli used in each task version are presented in Tables 12, 13, and 14 of the appendix.

Participant	Session 1	Session 2	Session 3
1	Sham version 1	Left version 2	Right version 1
2	Sham version 2	Left version 1	Right version 2
3	Left version 1	Right version 2	Sham, version 1
4	Left version 2	Right version 1	Sham version 2
5	Right version 1	Sham, version 2	Left version 1
6	Right version 2	Sham version 1	Left version 2
7	Sham, version 1	Left version 2	Right version 1
8	Sham version 2	Left version 1	Right version 2
9	Left version 1	Right version 2	Sham, version 1
10	Left version 2	Right version 1	Sham version 2
11	Right version 1	Sham, version 2	Left version 1
12	Right version 2	Sham version 1	Left version 2
13	Sham, version 1	Left version 2	Right version 1
14	Sham version 2	Left version 1	Right version 2
15	Left version 1	Right version 2	Sham, version 1
16	Left version 2	Right version 1	Sham version 2
17	Right version 1	Sham version 2	Left version 1
18	Right version 2	Sham version 1	Left version 2

Table 1. *Counterbalancing of stimulation site and task version.*

TMS.

Hardware. The TMS machine used was a *Magstim Rapid 2* (Jali-Medical, 2016), with a handheld butterfly coil, and guided by a *Polaris Vicra Position Sensor* (Northern-Digital, 2016). A handheld coil was used as it produced greater accuracy during trial sessions. This coil was recalibrated at least once on every day that a session was run to optimize accuracy.

Localisation of TMS targets. Sack et al. (2009) compared methods of TMS target localization and found that with the exception of individual fMRI guided targeting, an option not available for the current study, the most accurate and reliable method was the use of individual MRI scans. This was the method used in the current study. Location of the TMS targets on the surface of the brain was achieved using *BrainSight* software (v. 2.2.15). This software constructs a map of each individual participant's brain in stereotactic space from their MRI scan, which is then used to align the location of the coils onto physical space through the use of infrared reflective markers placed on both the TMS coil and the participant's head (Rogue-Research, 2015).

In order to localize the infrared marker on the participant's head, location information was input using an infrared pointer that denoted the tip of the nose, the nasion, as well as the left and right ears. The mapping of this model on to the physical head was then validated by running the marker across the scalp of the participant and ensuring that it was also tracking the line of the scalp on the computer model. If the model did not line up with physical space in this way, registration was repeated until it did.

Placement of target locations on the computer model was based on a combination of anatomical landmarks and MNI co-ordinates, whereby the outcome of an initial co-ordinate guided placement was adjusted based on the experimenter's visual assessment. This was done to

in order to adjust for individual neuroanatomical variation, and to avoid placement of a target area in a sulcus. This decision was also supported by the findings of Sack et al. (2009), who found that using anatomical guidance to place targets produced greater efficacy than placement based on group norms alone. The intended angle of the TMS coil handle is also a component of these target vectors, and for consistency this was always placed parallel to the approximate line of the lateral sulci. Average MNI coordinates for the pIFG, defined as in this study as the dorsal midpoint of the pars opercularis, were sourced from Chambers et al. (2007), and the average MNI coordinates in the current study are compared to these in Table 2. MNI coordinates for individual participant target locations can be found in Table 13 within the appendix. Sham stimulation involved the turning of the coil at 90º so that no actual stimulation was delivered, with the coil placed on the top of the head, at the approximate midpoint between the two experimental sites. Participants were told that as this site has less muscles they would not experience quite the same sensation as the other sites.

Location of the focal point of stimulation upon the surface of the model brain relative to the target location was intended to be sampled every 2000ms during all non-sham TMS in order to check accuracy. However, due to procedural error, some sessions had samples taken more frequently (every 200ms), and in two sessions samples were not recorded. Based on all samples available mean targeting error was .96mm (SD=.79mm). Angular error relative to the target vector was also sampled, producing a mean of .79º (SD=1.49º). We deemed this accuracy to be sufficient.

	Anatomical Location	X	Y	Z
Chambers et al. (2007)	Left IFG	-66 *(2.6)*	20 *(5)*	13 *(3.1)*
	Right IFG	63 *(2.6)*	21 *(3.5)*	13 *(4.1)*
Current Study	Left IFG	57.7 *(3.1)*	17.3 *(5.6)*	15.7 *(4.8)*
	Right IFG	58.8 *(2.6)*	18.4 *(4.0)*	14.2 *(4.0)*

Table 2. *Mean MNI coordinates (mm) for each anatomical target, and comparison to norms sourced from Chambers et al. (2007). Values in parentheses are standard deviations.*

Stimulation Parameters. While the stimulation intensity was not altered across participants in this study due to the output limitations of the machine available, thresholds were taken as part of good TMS practice (Sandrini et al., 2011). This measure is defined as the percentage power output required to produce a visible twitch in the right hand, in response to 50% of single pulse stimulations of the motor cortex in the left hemisphere. These measurements were taken at the end of each participant's second session, and are presented in Table 3.

Stimulation frequency parameters were similar to the continuous 'Theta burst' parameters described by Huang, Edwards, Rounis, Bhatia, and Rothwell (2006). However, reduced power output of 45% maximum output, from the standard 60%, as well as reduction of within-burst frequency from 50 Hz to 30 Hz, were necessary due to the limitations of the machine available. Repeated bursts of 3 pulses at 30 Hz were delivered at a rate of 5 Hz, for approximately 41 seconds, making for a total number 600 individual pulses. These parameters were chosen as continuous theta burst allows for a reasonable effective suppression time (approx. 60 minutes), while also minimizing the time required for stimulation in comparison to single pulse parameters, which is of benefit for participant comfort (Huang et al., 2006). Stimulation was not performed on consecutive days.

Participant (1-9)	Motor Threshold	Participant (9-10)	Motor Threshold
1	58%	10	60%
2	52%	11	45%
3	56%	12	65%
4	59%	13	60%
5	62%	14	43%
6	63%	15	60%
7	52%	16	63%
8	69%+	17	57%
9	60%	18	62%

Table 3. *Participant Motor Thresholds. Note: Stimulation of participant 8 did not produce a motor response 50% of the time when output was at 69%. Given ethical limitations against using output of 70% or higher motor threshold was recorded as 69%+.*

Procedure. In order to saturate practice effects each session involved the participant completing a practice version of all four tasks. This was followed by TMS set up and stimulation, with this occurring in a reclining chair for the left and right IFG stimulation sessions, and in a separate chair for the sham session. This was done in order to reduce the participant's awareness that the TMS coil was on its side. Participants then immediately returned to the computer and completed the four tasks. Tasks took around 20 minutes, well beneath the estimated theta burst suppression time (Huang et al., 2006). A head rest was used to keep the distance between participant and screen stable (approx. 60cm). In addition to this standard procedure, motor threshold was taken at the end of the second session.

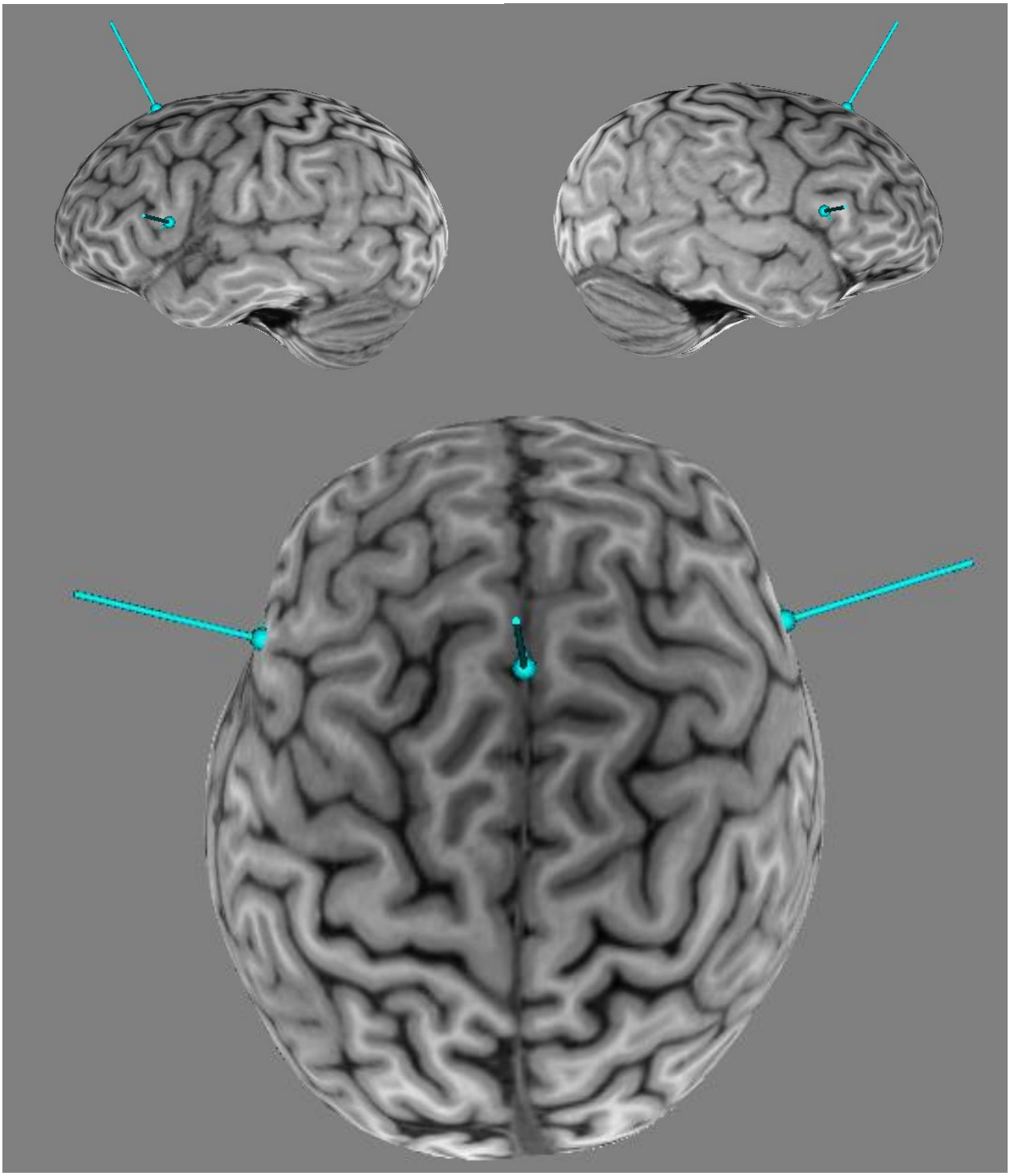

Figure 3. *Lateral and Superior Views Exampling Target Locations in the Current Study. Markers indicate the Left pIFG, Right pIFG, and the sham site (for which the coil was turned 90°). Thank you to Emma Ashcroft, for use of her beautiful brain.*

Chapter 4: Results

Inhibitory Error Rates

'Proportion error' was defined as the proportion of no-go trials on which each participant pressed the 'L' key within the 1500ms window. In this way, it was specifically a measure of inhibitory error. Table 4 presents means and standard deviations for this measure as a function of task and stimulation site. Figures 4 and 5 show the same data plotted graphically for the simple tasks and the complex tasks respectively.

	Stimulation Site		
Task	Left	Sham	Right
Simple Spatial	0.36 *(0.20)*	0.35 *(0.19)*	0.37 *(0.22)*
Complex Spatial	0.39 *(0.16)*	0.40 *(0.19)*	0.44 *(0.17)*
Simple Language	0.47 *(0.18)*	0.46 *(0.17)*	0.45 *(0.20)*
Complex Language	0.42 *(0.19)*	0.42 *(0.16)*	0.47 *(0.17)*

Table 4. *Mean proportion error by Task and Stimulation site. Values in parentheses are standard deviations.*

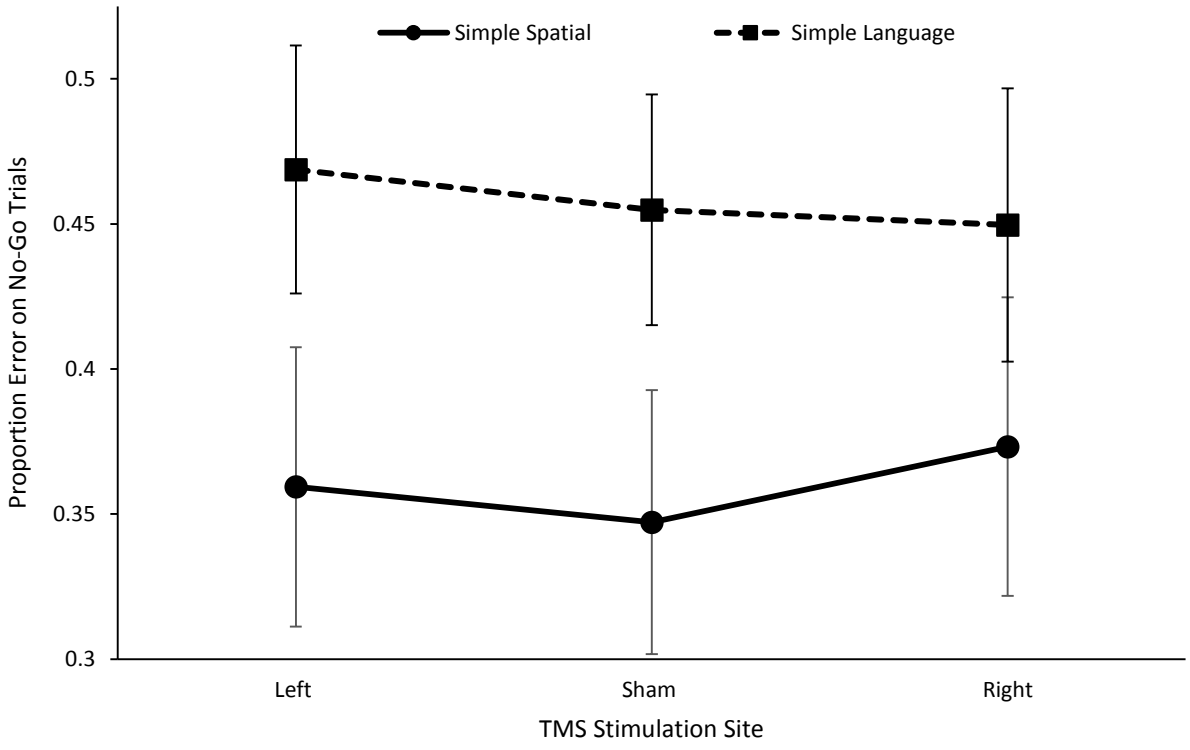

Figure 4. *Mean proportion error for both simple tasks across each TMS condition. Error bars represent standard error of the mean.*

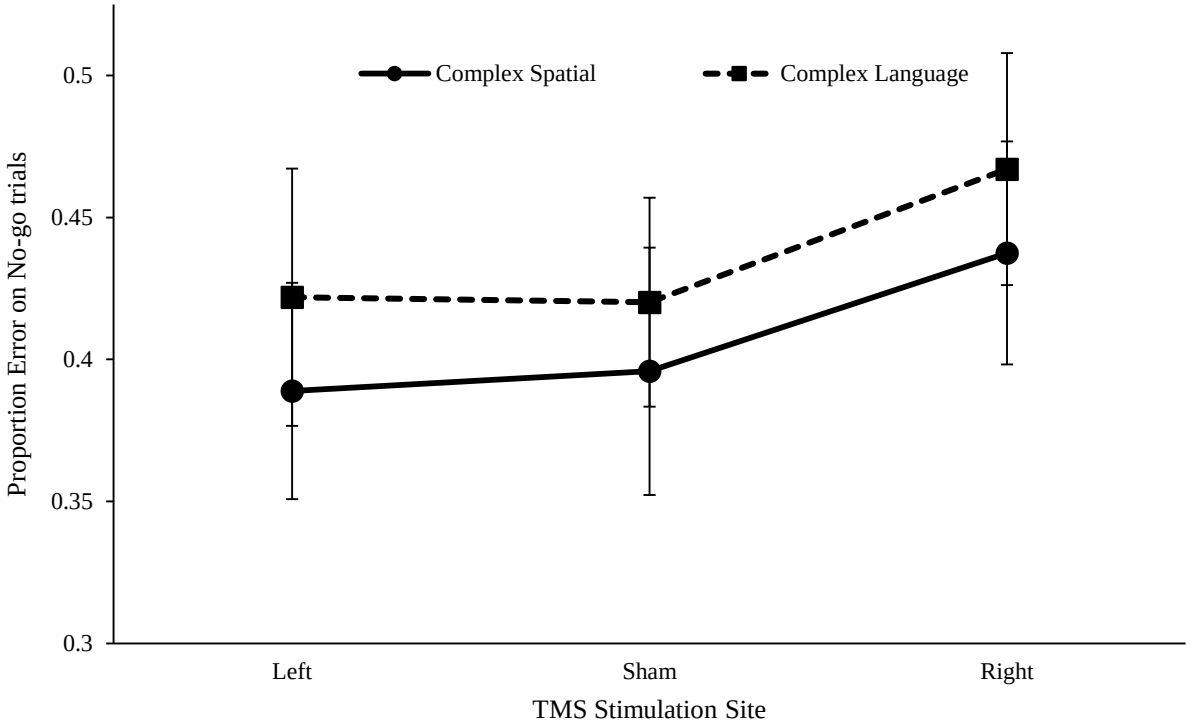

Figure 5. *Mean proportion error for both complex tasks across each TMS condition. Error bars represent standard error of the mean.*

To investigate the effects of TMS site (Left, Sham, Right), and task (Simple Spatial, Complex Spatial, Simple Language, Complex Language), proportion error outcomes were submitted to a 3x4 repeated measures ANOVA. This analysis revealed a significant effect of task ($F(3,51)=10.89$, $p<.001$), with the effect of TMS site being non-significant ($F(2,34)=.52$, $p=.599$). Mauchly's test of sphericity was significant for the interaction term ($p=.030$), and hence a Greenhouse-Geisser correction was applied, with this interaction also being non-significant ($F(3.79,64.40)=.55$, $p=.689$). Inhibitory error outcomes then, did not support the hypothesis.

Response Time

'Response time' [RT] was defined as the time taken in milliseconds to press the 'L' key on go trials. In this way, it is not a direct measure of any inhibitory processing, but is an indication of how challenging the participant was finding the task. Prior to analysis, response time data were winsorized and outliers, defined as response times greater than three standard deviations from an individual's mean performance on each task, were removed.

The individual response time data for each item and each individual were then submitted to a Linear Mixed Model analysis using the R lme4 package (Bates & Sarkar, 2007). The fixed effects included in the model were Task and TMS site, and the Task by Site interaction. Session number was not included in this analysis for reasons of simplicity. The model also included two crossed, random effects: participant and item identity (Baayen, Davidson, & Bates, 2008)). Intercepts were specified for each random effect. F values reported are the Type 3 hypothesis tests for each of the fixed effects, using the Satterthwaite approximation for the calculation of the degrees of freedom, as provided in the R package lmerTest (ANOVA function), and rounded to the nearest integer.

The least squares means resulting from the model are presented in Table 5. There was a significant main effect of task ($F(3,32)=57.26$, $p<.001$), TMS site ($F(2,17792)=18.71$, $p<.001$), and a significant interaction between task and TMS site ($F(6,17695)=3.68$, $p=.001$). In order to localize the interaction, we performed post-hoc contrasts for each individual task, comparing each stimulation site (Left or Right) to the Sham baseline. The results are shown in Table 6, and displayed graphically in Figures 6, 7, and 8. After correction for multiple comparisons, the only tasks that yielded significant comparisons between TMS and sham were the complex and simple language tasks. In both tasks, there was a small but statistically reliable decrease in response time following right stimulation, when compared to sham.

	Stimulation Site		
Task	Left	Sham	Right
Simple Spatial	327.83 *[309, 347]*	327.01 *[308, 346]*	324.45 *[305, 344]*
Complex Spatial	367.77 *[349, 386]*	371.77 *[353, 390]*	364.88 *[346, 384]*
Simple Language	333.84 *[314, 353]*	335.29 *[316, 355]*	325.44 *[306, 345]*
Complex Language	427.91 *[403, 453]*	422.52 *[398, 448]*	406.34 *[381, 431]*

Table 5. *Estimates of the Least Squares Means for RT on go trials in milliseconds [95% CI]*.

Task	Comparison	*t* value	*p* value
Simple Spatial	Left vs. Sham	0.26	.794
	Right vs. Sham	0.79	.428
Complex Spatial	Left vs. Sham	1.26	.206
	Right vs. Sham	2.12	.034
Simple Language	Left vs. Sham	0.45	.654
	Right vs. Sham	2.92	.004*
Complex Language	Left vs. Sham	1.67	.095
	Right vs. Sham	4.79	<.001*

Table 6. *Summary of pairwise comparisons of response time for each task and stimulation site. In these comparisons, the Left and Right TMS stimulation sites were each compared with the relevant sham baseline for the same task. * indicates statistical significance after Bonferroni correction for multiple comparisons (p<.00625).*

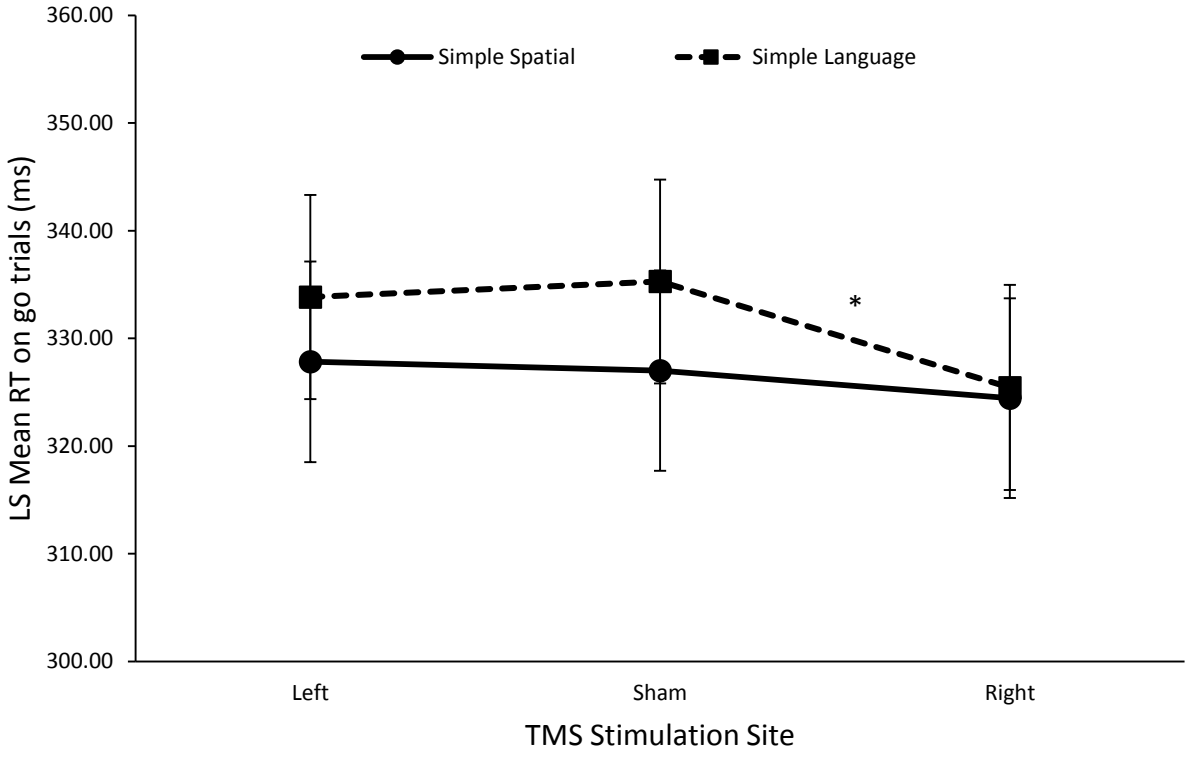

Figure 6. *Mean RT on go trials for both simple tasks across each TMS condition. Error bars represent standard error of the mean. * indicates statistical significance after Bonferroni correction for multiple comparisons (p<.00625).*

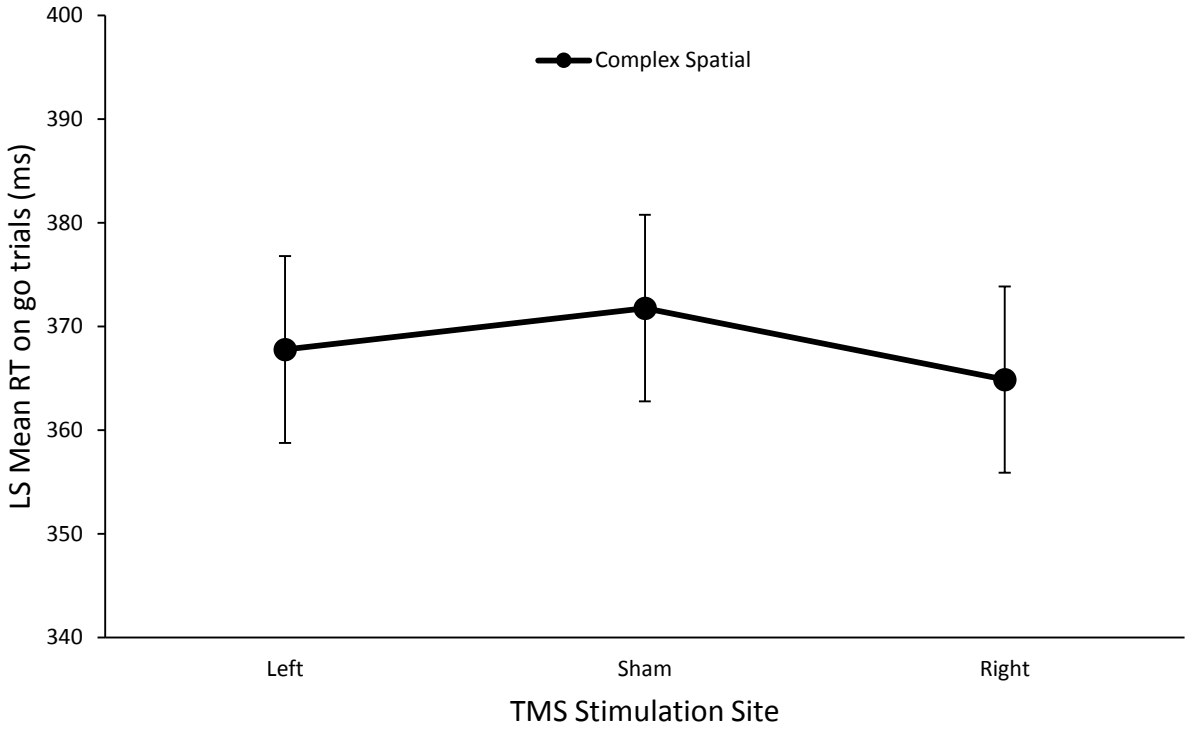

Figure 7. *Least Squares Mean RT on go trials for the complex spatial task across each TMS condition. Error bars represent standard error of the mean. * indicates statistical significance after Bonferroni correction for multiple comparisons (p<.00625).*

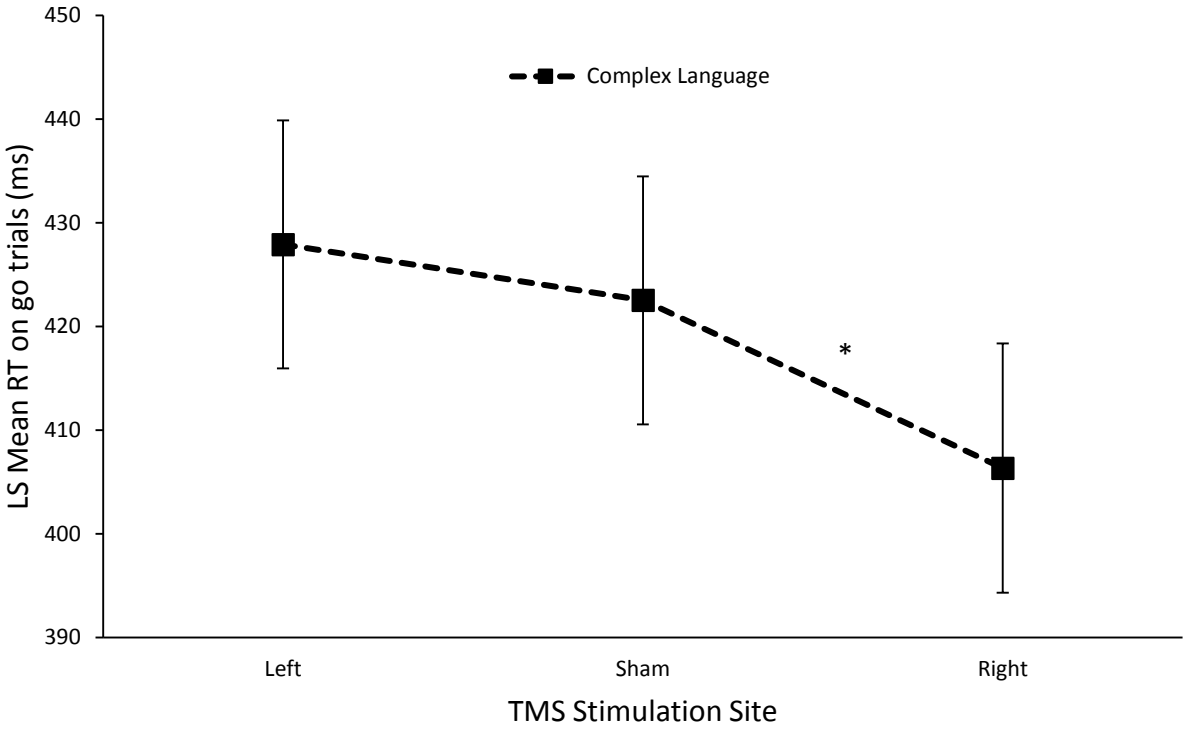

Figure 8. *Least Squares Mean RT on go trials for the complex language task across each TMS condition. Error bars represent standard error of the mean. * indicates statistical significance after Bonferroni correction for multiple comparisons (p<.00625).*

Exploratory Analysis

Weighted proportion error. Conceivably, an inhibitory error made when performing the tasks at a slow speed is more indicative of difficulties with inhibitory processing than is an inhibitory error made when performing the tasks quickly. In the same vein, if TMS stimulation makes a certain task more challenging, participants may slow down rather than simply make more errors. 'Weighted proportion error' was a variable developed in an attempt to account for these speed accuracy trade-offs. This was calculated by taking the average RT for each individual on each task, dividing it by the individual's average RT across tasks, and multiplying this figure by the original error rate. This produced a weighted error rate that is smaller if a participant was going particularly fast during a session (relative to their normal speed), and larger if they were going slower. Means and standard deviations of this measure are presented in Table 7.

	Stimulation Site		
	Left	Sham	Right
Simple Spatial	0.34 *(.20)*	0.32 *(.18)*	0.34 *(.20)*
Complex Spatial	0.40 *(.18)*	0.39 *(.17)*	0.44 *(.17)*
Simple Language	0.43 *(.15)*	0.42 *(.14)*	0.40 *(.15)*
Complex Language	0.50 *(.24)*	0.49 *(.17)*	0.51 *(.18)*

Table 7. *Mean weighted error by task and stimulation site. Values in parentheses are standard deviations.*

Weighted proportion error outcomes were submitted to a 3x4 repeated measures ANOVA to investigate the effects of TMS site (Left, Sham, Right) and Task (Simple Spatial, Complex Spatial, Simple Language, Complex Language) respectively. Mauchly's test of sphericity was not significant for all factors and therefore sphericity was assumed. This analysis revealed a significant

effect of task ($F(3,51)=27.80$, $p<.001$), with the effect of TMS site being non-significant ($F(2,34)=.42$, $p=.660$). The interaction term was also non-significant ($F(6,102)=.48$, $p=.819$). This analysis of weighted proportion error then, did not support the hypothesis.

Analysis of error by session. A manual examination of the data across sessions revealed that the effects of TMS seemed to be strongest within the first session and much weaker in later sessions, particularly within the complex tasks. For example, within the complex non-verbal task on the first session, mean proportion error on no-go tasks was 14% higher following stimulation of the right posterior IFG than when following sham TMS, and 5% higher than sham following left posterior IFG stimulation. In the third session however, all TMS conditions produced mean proportion error within 1% of each other on this task. This trend was apparent in all tasks aside from the simple language task, as can be observed in table 8. Alongside this trend there also appeared to be a possible main effect of session whereby error rate increased in later sessions, together these trends are possibly indicative of a mechanism such as boredom or decreased motivation within the participants as sessions go on, washing out the effects of TMS. Alternatively, this may be due to increased automatization of the tasks with practice, producing less demand for executive override.

		Stimulation Site		
Task	Session	Left	Sham	Right
Simple Spatial	1	0.34 *(.26)*	0.27 *(.10)*	0.36 *(.23)*
	2	0.35 *(.15)*	0.35 *(.21)*	0.39 *(.26)*
	3	0.39 *(.23)*	0.42 *(.25)*	0.36 *(.20)*
Complex Spatial	1	0.36 *(.21)*	0.31 *(.12)*	0.45 *(.12)*
	2	0.41 *(.67)*	0.47 *(.18)*	0.45 *(.21)*
	3	0.40 *(.12)*	0.41 *(.23)*	0.41 *(.19)*
Simple Language	1	0.41 *(.18)*	0.40 *(.09)*	0.38 *(.15)*
	2	0.46 *(.18)*	0.48 *(.18)*	0.48 *(.25)*
	3	0.53 *(.20)*	0.48 *(.23)*	0.49 *(.21)*
Complex Language	1	0.39 *(.19)*	0.35 *(.08)*	0.45 *(.15)*
	2	0.37 *(.16)*	0.44 *(.14)*	0.42 *(.22)*
	3	0.51 *(.22)*	0.47 *(.22)*	0.53 *(.15)*

Table 8. *Mean proportion error on no-go trials for each task under each TMS condition, broken down by session. Values in parentheses are standard deviations.*

In order to investigate these trends, proportion error data was subject to a Linear Mixed Effects Model ANOVA that incorporated session number as a factor, alongside the previously included factors of TMS site and task. The first model incorporated all factors and possible interactions, and revealed one significant effect, that of session number ($F(1,175.14)=18.18$, $p<.001$), with all other terms being insignificant. In the next model the three-way interaction was removed, producing the same result with all terms but session number having insignificant effects. Each of the two way interactions were then removed, with similar results at both stages.

Once all interaction terms were removed, the factor of task was seen to be significant ($F(3,192)=8.55$, $p<.001$), alongside the originally significant factor of session number ($F(1,192)=19.00$, $p<.001$), with the factor of TMS stimulation site being insignificant ($p=.264$). In sum, this analysis did support the observed trend of increased proportion error in latter sessions, however, the observed trend of decreasing effects of TMS across sessions was not found to be significant. Results of this analysis are presented in full in Table 14 in the appendix.

Given that a significant effect of session number on proportion error was observed in the Linear Mixed Effects Model ANOVA, it was decided to study the outcomes from the first session in isolation, as this seemed to be the purest point before participants were repeatedly exposed to the tasks. At this point in the experiment, not all participants had completed all TMS conditions, making this a 4x3 mixed measures design. Linear mixed model ANOVA was performed, but revealed no significant effects with or without the interaction term incorporated. Results are presented in Table 9.

	Terms	DF(Satterthwaite approximation)	F. value	p. value
First Model	Task	3,45	2.29	.091
	TMS	2,15	0.47	.634
	Task x TMS	6,45	0.96	.466
Second Model	Task	3,51	2.30	.088
	TMS	2,15	0.47	.634

Table 9. *Results of a linear mixed model ANOVA, modeling the effect of 'task', and 'TMS stimulation site', on proportion error for no-go trials, during each participant's first session only.*

** indicates statistical significance (p<.05).*

Chapter 5: Discussion and Conclusions

In the reported experiment, participants completed four different go/no-go tasks following three different conditions of TMS stimulation. The three conditions were: stimulation of the right pIFG, a site that has been associated with a right lateralized inhibition network; stimulation of the left pIFG, a site associated with language processing, particularly semantic selection; and sham stimulation. The four tasks were designed so that the decision to inhibit was rooted in either a language or spatial domain, with simple and complex versions of each. On the basis of the theory of Mostofsky and Simmonds (2008), as well as an observed bias in the relevant literature towards the use of spatial stimuli, it was theorized that the apparent right lateralized inhibitory network often observed in go/no-go tasks may reflect the nonverbal nature of the materials, rather than anything intrinsically right lateralized about this type of response inhibition. It was therefore predicted that left pIFG stimulation would produce a greater inhibitory error rate (inappropriate responses on "no-go" trials) in the language tasks than right pIFG stimulation, and right pIFG stimulation would produce greater inhibitory error rate in the spatial tasks than left pIFG stimulation. In line with Mostofsky and Simmonds (2008), it was also predicted that this increase in error rate would be most apparent within the complex tasks, and minimal within the simple tasks.

Error Data Findings

The error results do not support these predictions. There was no significant overall effect of TMS on measures of inhibitory error, nor any interaction between TMS and task. When we weighted the error measure according to the participant's average response time on go trials, in an attempt to account for speed-accuracy trade-off, this overall result did not change. These findings are not in line with previous research explored in Chapter Two which indicates that at

the very least we could have expected an effect of right pIFG stimulation. Considering this, it is possible that our study was underpowered. We chose, inhibitory error as our dependent measure because we considered it the best indicator of impaired inhibitory processing, however, one drawback of this approach is that this measure relies on a low frequency event – errors – rather than a continuous measure like response time. In order to effectively use an error-based measure as the primary dependent variable, it may be necessary to increase participant numbers significantly. However, a lack of power cannot be the only reason for our null results; power issues notwithstanding, even the trends in our data are not consistent with the domain specific hypothesis.

More specifically, a trend was observed towards increased inhibitory errors following rightward stimulation on both complex tasks; a similar trend was not observed in the simple tasks. If this pattern were borne out in future studies, then it would be of great interest. Such findings would not support domain lateralization within response inhibition. They would however support a right lateralized inhibitory network that is causally engaged when the decision to inhibit is a complex one, but not when the decision is simple or well-practiced. This would be in line with the theory and supporting meta-analysis of Mostofsky, Simmonds and colleagues (Mostofsky & Simmonds, 2008; Simmonds et al., 2008), who hold that response inhibition itself is essentially occurring within the pre-SMA, but that the cognitive processes used to *inform* this inhibition recruit frontal and parietal areas when the decision to inhibit is a complex one. Such findings would also support the observation of rightward lateralization (Buchsbaum et al., 2005; Chambers et al., 2009; Chikazoe, 2010). It must be remembered however, that these observed trends were not statistically significant in the current study, and therefore further study with greater power is required to test whether these trends are indeed robust.

Putting aside the issue of statistical power, there are four possible reasons for the null outcome. The first possibility is that neither the left nor the right pIFG is crucial for effective inhibitory control in this setting. However, this account seems unlikely given the strong evidence presented in the literature for pIFG involvement, including the support of earlier TMS studies, as reviewed in Chapter Two (and for further reviews see; Chambers, Garavan, & Bellgrove, 2009; Chikazoe, 2010). Second, it is possible that our TMS stimulation was not sufficiently intense. As noted in Chapter 3, standard TMS output is 60% of maximum, but due to the limitations of the single-capacitor machine available the current study used a reduced output of 45%, further, within-burst frequency was dropped from 50 Hz to 30 Hz for the same reason. This may have reduced the efficacy of the experimental manipulation resulting in smaller and less reliable effects. One way to address this problem in future studies is to use a dual-capacitor machine (if available).

A third possibility is that the specific localization of stimulation did not consistently target the precise region of the pIFG that is crucial to successful inhibition in this setting. If we were not stimulating in the correct location consistently enough, then we would not expect significant results even if the pIFG is playing a causal role in response inhibition. That said, coordinates used in this study were sourced from Chambers et al. (2007) who demonstrated that TMS of the right pIFG produced difficulties with response inhibition. It does not seem likely then, at least for our rightward site, that our intended target was not in the correct location. There is still the question of how constantly we were placing and stimulating on these targets, and such sources of error will be discussed later in the further limitations section of this discussion.

The fourth possible reason for the lack of expected effect of TMS to the pIFG is that our tasks may not have been challenging enough to tap into the inhibitory control processes

associated with the pIFG. The study used a repeated measures design, in which participants completed all tasks under all stimulation conditions, with practice tasks completed at the start of every session in an attempt to saturate practice effects. Therefore, it is likely that participants' task competency increased substantially over the course of the experiment. Despite this, there were significant increases in error rate across sessions. It is possible that this increase could reflect factors other than task competency – for example, continued exposure to the tasks, plus decreased novelty of the experimental setting, may have produced a reduction in motivation to do well and monitor for errors. Both of these factors – increased competency and reduced efforts - could have combined to increase the automaticity of participants responses, reducing the need for pIFG engagement (Mostofsky & Simmonds, 2008). In order to address this, future studies should consider using between-subjects or mixed measures designs with much larger sample sizes. Single session, between-subjects designs may be better suited for the study of executive function skills, in which novelty plays a core role. If within-subjects repeated session designs are used, efforts should be taken to reduce practice and maintain motivation across sessions.

RT Findings

Inhibitory errors would seem to be the most transparent measure of response inhibition in a go/no-go task. However, RT data has the potential to shed some further light on the processes engaged during the tasks. Specifically, we found that on both the simple and the complex language tasks, RTs were faster following stimulation of the right pIFG than following sham stimulation.

In interpreting this finding, it is vital to first consider what RT actually measures within the current design. Intuitively, it seems a measure of how challenging the participant is finding each task: we might expect participants to slow their responses in order to avoid inhibitory

errors. This can be broken down into two component parts; firstly, how difficult the task actually was, and secondly the participants' assessment of and response to this difficulty. This latter component fits under the rubric of monitoring, a capacity defined in the Chapter One as the monitoring of one's own activity and external circumstances so as to ensure behaviors are successfully meeting goals within a changing context. There is considerable evidence to suggest that monitoring behaviors rely heavily on right lateralized networks (Stuss, 2011; Stuss et al., 2005).

However, our RT findings were not entirely consistent with a monitoring account. Monitoring is usually conceptualized as a domain-general ability (Stuss, 2011; Stuss et al., 2005). In contrast, the RT effects we observed here were domain-specific (they were only observed on language tasks). Also, and more importantly, the effects observed following TMS stimulation were facilitatory in this case: right pIFG stimulation *decreased* RTs relative to sham. Previous TMS studies have reported facilitatory effect of stimulation to sites contralateral to the region believed to be crucial to task performance, and such phenomena have been attributed to decreased interhemispheric inhibition (Blankenburg et al., 2008; Seyal, Ro, & Rafal, 1995). Very tentatively then, we could speculate a possible explanatory mechanism whereby disruption of the right pIFG made the language tasks easier by reducing competing input from the stimulated site; this would allow the left pIFG, which as discussed earlier is likely specialized for language processing, to perform its task more effectively. This does raise the question however of why such an effect was not observed on the spatial tasks following stimulation of the left pIFG. One possibility is that the right pIFG may be less specialized for spatial processing than the left pIFG is for language based processing, thereby reducing the expression of the contralateral

disinhibition effect within the spatial domain. However, since the primary predicted effects were not confirmed, we can only speculate here.

Further Limitations

Aside from the issues already highlighted, there are other factors that limit the accuracy or generalizability of these results, and these should be also be borne in mind.

The first limitation concerns the accuracy of TMS localization. Although TMS localization was sampled and indicated sufficient accuracy, this kind of sampling provides a measure of the stimulation vector relative to the target vector in the model only. In fact, there are other sources of error within the TMS process. Aside from the potential error associated with the initial choice of stereotaxic coordinates to target for TMS (an issue discussed above), error is also introduced in the placement of these normalized coordinates onto the model of each individual participant's brain, and the generation of the model in the first place. Further error is present in the mapping of these individualized models onto physical space, in the calibration of the coil with its infrared marker, and in the placement of the coil in line with the target vector. Our accuracy measure only measures this last kind of error. Most significant of these is the error associated with mapping the stereotactic model onto each participant's head in physical space, a caveat of TMS studies in general. As described in the Chapter Three, standard efforts were taken to minimize this error, specifically by validating the fit of the model by running a pointer over the participant's scalp and assuring this follows the line of the skull upon the computer model. However, this reliance on visual assessment may have introduced a few millimeters of extra error into the accuracy of the stimulation vector onto the actual brain. This error is likely to be small in comparison to the overall diameter of the area stimulated during TMS, but it nonetheless should be recognized.

Another of the error sources mentioned above, that is worthy of some discussion, is the placement of individual targets. Looking at the coordinates for these (available in Table 13 of the Appendix), there is quite a bit of variability. This is because, as described in Chapter Three, placement of these targets was not based on co-ordinates alone, but rather, placement was adjusted in accordance with anatomical landmarks. Sack et al. (2009) found that this produces greater functional accuracy than localization based on normed coordinates. Presumably then, while some of this variability surely represents error, some of it is also likely accounting for individual anatomical variability and the mapping of normalized brain coordinates onto this diversity.

Efforts were taken to minimize the other sources of targeting error also. For example, the TMS coil's relation to its infrared marker was recalibrated frequently. One error source that was not addressed however, was the accuracy of the MRI generated stereotactic models; consequently the accuracy of these models, the associated 'BrainSight' software, and the MRI scans themselves is a base assumption that underlies the current findings (Rogue-Research, 2015). While the error introduced from each of these separate error sources is likely very small, the cumulative effect of these different sources of error should be considered as a limitation, and also given more attention within TMS studies in general.

Moving away from targeting error, a further limitation relates to the mentioned use of reduced power output and within-burst frequency of our stimulation parameters. As well as reducing the magnitude of disruption, it is conceivable that this may have reduced the period during which TMS was having a disruptive effect. In an attempt to account for this, the lag between stimulation and task completion was minimal, and task duration kept short. In order to investigate this was sufficient, one possibility considered was to check whether the frequency of

errors dropped systematically over the course of the tasks. Considering that frequency of errors could have reasonably been expected to decrease with growing task proficiency anyway, this would have required comparison across the different TMS conditions. However, given that the effect of TMS did not meet significance over the relatively short task period, the likelihood of this investigation finding significant results was deemed low. Furthermore, continued speculation did not warrant the increased risk of type one error. For these reasons this investigation was not performed. Another related concern was individual variation in factors such as skull thickness that may have influenced susceptibility to TMS. One possibility was to incorporate our measure of motor threshold into our models, or to check whether this measure correlated with any dependent variables. These investigations were not undertaken given that our within-subjects design should have accounted for this anyway, as well as concerns over the validity of using the motor threshold measure for this purpose. Nevertheless, this remains an interesting consideration for future studies.

Finally, in regard to the simple language task, should future studies use a similar design then modification of this task is suggested. The use of letters in this study was chosen as it seemed prima facie more simple. In retrospect, use of word stimuli, with a particular word serving as the no-go target would still have fit the definition of a simple task as defined in Simmonds et al. (2008) in that the no-go stimulus would be constant, but would have also been more language oriented and thereby better suited to the question of domain specificity. Such a construction would also have been more analogous to the simple spatial task.

Summary and Conclusions

While the ability to inhibit inappropriate responses can be pragmatically conceptualized as a single capacity, we must remember that in different situations with different requirements,

performance of this capacity with engage different neural networks. Accordingly, response inhibition can be studied in many different ways. In this study, we examined one specific type of response inhibition: the ability to inhibit a prepotent inclination to respond under certain stimulus conditions. To measure this type of response inhibition, we used a series of go/no-go tasks. Specifically, we hypothesized that during complex tasks the pre-frontal neural networks informing this type of response inhibition are lateralized in a domain specific fashion – that is, processing is primarily occurring in different hemispheres depending upon the nature of the decision cued by the stimulus materials. We tested this hypothesis by comparing and contrasting different go/no-go tasks that varied as to their stimulus domain and complexity (specifically whether the stimuli were verbal or spatial, simple or complex), and varying the locus of TMS stimulation (right pIFG, left pIFG, sham). Our hypothesis - that disruption of processing within the right pIFG would increase the number of inhibitory errors during a complex spatially oriented task, while disruption of processing within the left pIFG would do the same but for a complex language based task, was not confirmed. It seems likely that our design – which utilized inhibitory errors as the dependent measure – may have been underpowered. However, even the trends in the data were not consistent with our hypothesis; rather, they were more suggestive of a consistently right lateralized inhibitory network that is engaged under conditions of increased complexity as described by Mostofsky and Simmonds (2008). Ultimately, there does not appear to be any evidence from this study for the domain specific lateralization hypothesis. Future research in this area that improves on the current study by reducing participant exposure to practice, using between or mixed measures designs, utilizing a larger sample size, and a TMS machine capable of standard theta burst parameters, is suggested. The possibility of domain

specific lateralization thus remains a fascinating one. If you wish to ponder on it, we only ask that you take care while crossing the street.

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Appendix

Simple Language Task	Complex Language Task	Simple Spatial Task	Complex Spatial Task
A	**nurse**		
B	**acrobat**		
C	**politician**		
D	**architect**		
E	**chef**		
F	**parent**		
G	**musician**		
H	**vet**		
H	kettle		
H	menu		
H	arson		
I	wine		
J	sweater		
K	rainbow		
L	hemisphere		
M	diploma		
N	wrist		
O	tarantula		

P	feather		
Q	mouse		
R	guillotine		
S	studio		
T	eagle		
U	universe		
V	vehicle		
W	arson		
X	receipt		
Y	summit		
Y	cabaret		
Y	syrup		
Y	sewage		
Z	traffic		

Table 10. *Stimuli for version 1 of all tasks, no-go stimuli are bold and shaded.*

Simple Language Task	Complex Language Task	Simple Spatial Task	Complex Spatial Task
A	**pilot**		
B	**referee**		
C	**librarian**		
D	**clown**		
D	**monk**		
D	**poet**		
D	**mechanic**		
E	**apprentice**		
F	furnace		
G	fruit		
H	cradle		
I	smudge		
J	microscope		
K	bean		
K	tube		
K	battleship		
K	meal		
L	satellite		
M	bulb		

N	pelican		
O	horoscope		
P	rooster		
Q	skull		
R	chocolate		
S	jaguar		
T	cradle		
U	brooch		
V	package		
W	venom		
X	blueberry		
Y	pigeon		
Z	juice		

Table 11. *Stimuli for version 2 of all tasks*, *no-go stimuli are bold and shaded.*

Simple Language Task	Complex Language Task	Simple Spatial Task	Complex Spatial Task
A	**judge**		
B	**minister**		
C	**president**		
D	**officer**		
E	**doctor**		
F	**teacher**		
G	**mayor**		
G	**captain**		
G	scissors		
G	window		
H	spoon		
I	coffee		
J	love		
K	drain		
L	bottle		
M	elephant		
N	shoe		
O	river		
P	cosmos		

Q	storm		
R	bird		
S	plane		
T	orange		
U	computer		
V	wire		
W	brain		
X	water		
X	poster		
X	chicken		
X	cake		
Y	bark		
Z	kitten		

Table 12. *Stimuli for practice version of all tasks, completed at the start of each session. No-go stimuli are bold and shaded.*

		MNI Coordinates		
Participant	Target	X	Y	Z
1	Left	-53	16	10
	Right	53	23	20
2	Left	-54	24	17
	Right	60	19	11
3	Left	-59	22	10
	Right	63	21	13
4	Left	-56	18	10
	Right	59	15	17
5	Left	-60	13	12
	Right	62	9	8
6	Left	-53	31	19
	Right	59	20	16
7	Left	-56	15	14
	Right	58	22	9
8	Left	-61	17	16
	Right	63	21	13
9	Left	-59	12	16
	Right	55	24	11
10	Left	-60	20	12
	Right	59	20	15
11	Left	-58	5	24

	Right	58	17	12
12	Left	-60	19	14
	Right	59	15	14
13	Left	-56	18	25
	Right	59	16	15
14	Left	-56	14	26
	Right	57	18	21
15	Left	-66	20	13
	Right	60	22	11
16	Left	-56	17	13
	Right	56	21	16
17	Left	-58	19	18
	Right	59	18	14
18	Left	-60	9	14
	Right	58	11	22

Table 13. *MNI coordinates denoting the target locations (left pIFG, right pIFG) for each participant.*

Model	Terms	DF(Satterthwaite approximation)	F. value	p. value
First Model	Task	3,175.14	0.78	.509
	TMS	2,186.32	0.37	.694
	Session	1,175.14	18.18	<.001*
	Task x TMS	6,175.14	0.64	.702
	Task x Session	3,175.14	0.92	.432
	TMS x Session	2,187.05	0.20	.822
	Task x TMS x Session	6,175.14	0.50	.807
Second Model	Task	3,181.14	0.79	.502
	TMS	2,192.46	0.37	.690
	Session	1,181.14	18.49	<.001*
	Task x TMS	6,181.14	0.42	.862
	Task x Session	3,181.14	0.94	.424
	TMS x Session	2,193.19	0.20	.819
Third Model	Task	3,187.14	0.80	.493
	TMS	2,198.57	0.38	.686
	Session	1,187.14	18.83	<.001*
	Task x Session	3,187.14	0.96	.415
	TMS x Session	2,199.30	0.20	.816
Fourth Model	Task	3,189	0.81	.490
	TMS	2,189	1.34	.264
	Session	1,189	18.99	<.001*

	Task x Session	3,189	0.96	.411
Fifth Model	Task	3,192	8.55	<.001*
	TMS	2,192	1.34	.269
	Session	1,192	19.00	<.001*

Table 14. *Results of a linear mixed model ANOVA, modeling the effect of 'task', 'TMS stimulation site', and 'session number' on proportion error for no-go trials.*