Inhibition of Return: underlying mechanisms and contributions of the primary motor cortex (M1)

by

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Abstract

Inhibition of return (IOR) refers to the finding that response times (RTs) to targets are longer when targets are presented at a recently attended-to location relative to targets at new locations. The motor-based component of IOR was explored by investigating the contributions of M1 to IOR. Transcranial magnetic stimulation (TMS) was used to determine if the mechanisms associated with IOR are represented in M1. Participants completed a cue-target task with non-predictive exogenous cues. It was hypothesized that if the mechanisms underlying IOR are represented in M1, then the motor evoked potentials (MEPs) associated with the cued or uncued responses would mirror RTs. TMS of M1 altered RTs, however MEP data did not reveal an effect of cue location on M1 excitability. The data indicate a motor contribution to the IOR effect, but the question of where in the motor system the mechanisms associated with IOR is localized is unanswered.
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Chapter 1

Review of Literature

1.0 Introduction

Given the vast number and complexities of the stimuli in the environment and limited capacity of the human information processing system, it is incredibly difficult for the human brain to bring all the information that the retina receives into consciousness and use effectively to control behaviour (Broadbent, 1958; Neisser, 1967). In addition, much of the information in the world is not directly needed or relevant to the individual. For these reasons, a set of processes, known as attention, has developed through evolution to filter out and prioritize certain sources of information in the environment over others. Stated another way, the human attentional system has developed to assist the perceptual and cognitive systems to select and process the most relevant information while irrelevant information is filtered out and ignored (Broadbent, 1958; Neisser, 1967). Because the environment and goals of the individual are constantly changing, the focus of attention must be shifted and reoriented from stimulus to stimulus. The ability to efficiently orient and reorient attention to different visual events is essential for an individual to adapt to and function in an ever-changing environment. This ability to shift attention to and from different visual events is important for many aspects of daily life, but this ability is particularly important when one is searching for a specific target in the environment; in other words, performing a visual search task.
Whether the individual is trying to find a car in a busy parking lot, a friend in a crowded party, or an apple on a tree, visual search is important in a human beings’ daily living. Because of the importance of visual search to survival, a set of mechanisms has developed to enhance the efficiency of the search. One phenomenon that is thought to reflect the mechanisms that facilitate visual search is the inhibition of return (IOR) effect (Posner & Cohen, 1984; Klein, 2000). The IOR effect refers to the finding that RTs to targets are longer when the targets are presented at a recently attended-to location relative to when the targets appear at a new location. It was speculated that the processes underlying IOR might serve to encourage orienting toward novel objects and events (Posner & Cohen, 1984) and discourage wasteful re-inspections in visual search (Klein, 2000). Although the mechanisms leading to the IOR effect have been the focus of a great deal of research, scientists remain uncertain as to which cognitive mechanisms might be involved in IOR. Initially, these mechanisms were thought to work either at a level of perceptual processing or at the level of attention (e.g., Sereno, Jeter, Pariyadath, & Briand, 2006). However, since the original work on IOR, there have been a number of studies that have challenged this view and have revealed a significant motor component to IOR (Sereno et al., 2006; Klein, 2000). The purpose of the present research project was to investigate the motor component of IOR, and in particular the contributions of the primary motor cortex (M1), to the IOR effect. Before outlining the specific rationale and methods of the present study, a review of the literature on the orienting of attention and the proposed mechanisms of IOR will be presented.
1.1 Attentional Orienting

It is well established that efficient visual orienting is crucial for appropriate interactions with stimuli in the environment. This knowledge led researchers to suggest different attentional mechanisms to accomplish successful orienting and re-orienting. The re-orientation of attention can be performed in two different ways: an endogenous way or an exogenous way (Lupiáñez, Klein, & Bartolomeo, 2006). Endogenous orienting of attention relies on top-down expectancies and is controlled by the observer’s goals or desires (Lupiáñez et al., 2006). In this way, it is thought that the endogenous shifting of attention is mainly under voluntary control. For example, when a person searches for a car in a busy parking lot, they have the knowledge of the characteristics and potential location of that car and shift their attention to certain positions in the visual field in a manner consistent with that knowledge (i.e., looking for a red car in the back left end of the lot). In contrast, exogenous orienting of attention is considered more bottom-up, such that it relies on salient characteristics of the environment causing a relatively automatic or involuntary shift (capture) of attention (Lupiáñez et al., 2006). This exogenous capture of attention typically occurs when there is a sudden dynamic change in the environment. For example, when searching for a car in the lot, the sudden appearance of another car coming toward the individual will capture the person’s attention.

One of the most common methodological approaches used to study the mechanisms of attentional shifts is the precue or cue-target paradigm (Jonides, 1980; Posner, 1980). In this paradigm, participants respond (typically with a key press) to a target (typically a stimulus on a computer screen) presented at one of a number of potential locations. In one exemplar version of this paradigm, Posner and Cohen used an
asterisk inside one of the peripheral boxes as their target stimulus. This target stimulus is preceded by a signalling cue stimulus. Typically this cue is exogenous and is a peripheral, spatially non-informative, stimulus cue that indicates one of the potential target locations. In this version of the task used by Posner and Cohen, the cue stimulus was one of the peripheral boxes suddenly brightening for 50 ms. The key measure or index of the location of attention in these paradigms is the difference between response times (RTs) to targets that are presented at a cued location relative to RTs targets at an uncued location. When RTs to targets at the cued location are shorter than at an uncued location, it is concluded that attention has been shifted to the cued location and facilitates the processing of the target information at that location relative to any other location. When RTs to targets at uncued location are equivalent to or shorter then RTs to targets at cued locations, the conclusion is that either attention was not shifted to the cued location or that some other mechanism is operating at the cued location to hinder processing of the target stimulus.

This cue-target paradigm has been used to study the mechanisms of endogenous and exogenous attention by varying the characteristics of the cue stimulus. The type of cue typically used to study endogenous attention is a symbolic stimulus, such as an arrow or directional word, presented close to the fixation point in central vision. This symbolic central cue is used to study endogenous shifts of attention because the cue must be processed and interpreted by the individual before a shift of attention to a location in space can occur. To study exogenous shifts of attention, the participant is typically presented with a peripheral cue stimulus that is dynamic in nature, such as a flash of light (something that involuntarily captures attention), presented at one of several target
locations. This type of cue is used to study stimulus-driven/exogenous shifts of attention because the spatial location of the cue itself provides all the spatial information necessary to generate the shift of attention (that is, the participant does not need to interpret the stimulus).

In these tasks, two other characteristics of the cue are varied – the timing of the stimuli and predictive value (validity). The timing of the onset of the cue and the target (cue-target onset asynchrony or SOA) is varied to understand the time course of any attentional shifts and facilitatory or inhibitory mechanisms that result from the cue stimulus. With respect to the cues’ predictive value, the cue can be classified as either predictive or non-predictive. In a predictive cuing paradigm, there is a relationship between the location of the cue and the target. More specifically, in a valid or cued target trial, the target appears more often (e.g., 80% of the trials) at the location indicated by the cue than at a location that was not indicated by the cue. The remaining 20% of trials are known as invalid or uncued target trials, where the target appears at the uncued location. In the predictive cuing paradigm, the participant would derive a benefit from shifting attention to the cued location. Accordingly, it is expected that RTs to targets presented at location of cue should be shorter than those at other locations in these predictive paradigms because the participants can voluntarily (endogenous) shift attention to the location of the cue in anticipation of the target. They use the information from the cue to anticipate where the target is going to appear. In a non-predictive cuing paradigm, the cue does not have any relationship to (i.e., is random with respect to) the location of the target so that the participant cannot gain any information from the cue. In this way, there is no advantage for the participant to shift attention to the target location in this non-
predictive cuing paradigm and, as a result, RTs to targets at the cued location should not be any different from those at any uncued location. If RTs to cued targets are different from RTs to uncued targets in this non-predictive cuing task, then it is concluded that a shift of attention did occur and this shift was driven by the cue stimulus (an exogenous shift).

Results from experiments using the predictive cuing method (e.g., Jonides, 1980) have revealed that both central and peripheral cues (related to the visual field) produce similar patterns of facilitation effects (i.e., shorter RTs to targets presented at the cued location than at uncued locations). These facilitation effects arise rapidly (at SOAs of 100 ms) and are long lasting (are present at SOAs of greater than 3000 ms). This pattern of findings suggests that when there is a strategic advantage to using the cue information and that the participant uses both central and peripheral cue information to rapidly shift attention to a location then maintain attention at a cued location. Thus, central and peripheral cues can be used for endogenous (voluntary) shifts of attention when there is an advantage to using the cue.

Research using the non-predictive cuing paradigm, on the other hand, has revealed differences in the patterns of RTs that emerge following central and peripheral cues. When the cue was a non-predictive central symbolic cue (e.g., an arrow at fixation), no facilitation effects were present because RTs for cued targets were not different from RTs for uncued targets. This data suggests that the participants are effectively able to ignore the cue information. Thus, the contrast in the pattern of RTs that emerge following predictive and non-predictive symbolic cues suggest that shifts of attention following these cues are endogenous (voluntary) in nature.
Although it appears that central cues generally do not lead to exogenous shifts of attention, dynamic peripheral cues do seem to generate involuntary shifts in attention. This conclusion is drawn from the patterns of RTs to cued and uncued targets that are presented at different SOAs. When the cue is a non-predictive peripheral cue, a facilitation effect is observed at SOAs as short as 50 ms. The shift of attention here is thought to be involuntary because this facilitation effect occurs even though the cue was not predictive of the target location. This facilitation effect lasts up to about 200 ms.

Considering these facilitation effects occur despite the fact that there is no strategic advantage to shifting attention to the cued location (in fact shifting attention to the cued location causes a cost for targets to uncued locations), it is suggested that the facilitation effects at these short SOAs are the result of an exogenous involuntary orienting of attention to the location of the peripheral visual stimulus (Posner, 1980).

As the SOA increases, an interesting and informative change in the RTs to cued and uncued targets emerges (Posner, 1980; Posner & Cohen, 1984). Specifically, the advantage for cued targets that seem to peak around 100 ms, decreases and is replaced by an RT advantage for targets at uncued relative to targets at the cued location at SOAs of 300 ms and longer. This pattern of RTs is thought to emerge because attention is initially captured and involuntarily drawn to the location of the cue. Because attention is rapidly and involuntarily shifted to the location of the cue, RTs to the target appearing at the cued location of the cue will be shorter than to targets at uncued locations if the target appears in close temporal proximity to the cue (<200 ms). Because the participant knows that the cue does not predict the location of the target, the participant will quickly shift their attention back to the central fixation point so they can effectively respond to targets.
presented at any potential location. The time course of this shift of attention back to the central fixation point is thought to be reflected in the decrease and eventual elimination of the cued target RT advantage over the 200-300 ms SOA period.

To account for the reversed advantage for the uncued over cued targets, it was suggested that the attended-to cued location was tagged with an inhibitory mechanism when attention was shifted back to the central fixation point. This inhibitory mechanism then hindered the return of attention to previously cued (attended to) location. Because the participant has to overcome this inhibition to respond to the target at the cued location, RTs to targets at the cued location are longer than to targets at uncued (not previously attended-to) locations, which do not have this inhibitory coding. Posner and Cohen were the first researchers to report these effects and named these phenomena facilitation associated with an attention shift and inhibition of return (IOR), respectively (Posner & Cohen, 1984; see also Posner, Rafal, Choate, & Vaughan, 1985). Although a large number of studies have been conducted on these phenomena to understand the mechanisms underlying these effects, there is still some debate over the exact nature of these mechanisms. Because the present research is designed to shed new light on these mechanisms, a review of the work in this area will be provided.

1.2 Inhibition of Return

The spatial cue-target paradigm employed by Posner and Cohen (1984) has provided the methodological foundation for most studies of IOR. As described earlier, Posner and Cohen (1984) used a model task in which non-predictive exogenous cues were followed by targets that require simple detection responses (see Figure. 1.1 (A) for
an illustration of the traditional Posner-like cue-target task). More specifically, Posner and Cohen (1984) presented participants with a fixation frame that consisted of two peripheral boxes and a fixation cross. This was followed by a second screen that presented participants with a non-predictive exogenous peripheral cue in one of the peripheral boxes. The cue was the brightening of one of the two peripheral boxes. After varying intervals (cue-target onset asynchronies, CTOAs) from the onset of the cue, a target (displayed as an asterisk) was presented in one of the two peripheral boxes. The observer’s task was to make a quick but accurate detection response (a button press on a keyboard) as soon as the asterisk was detected. Posner and Cohen (1984) used catch trials with cues but no targets to discourage anticipatory responses and measure their frequency in that form of false alarm. Cued targets were represented as targets that appeared in the cued location and uncued targets were represented as targets that appeared in the uncued location. Posner and Cohen (1984) found that within the first 50-150 ms after the cue-appearance, RTs were shorter to targets at previously cued locations than to targets appearing at uncued locations. However, when SOAs exceeded 300 ms, this facilitation effect changed into an inhibition effect, as revealed by longer RTs for targets presented at previously cued locations than to targets at uncued locations (see Figure 1.1 (B) for a graphical illustration of arbitrary behavioral data (RTs) of this phenomenon in a traditional Posner-like cue-target task)
Figure 1.1. (A) Schematic representation of a typical IOR task. First, a fixation frame is displayed and is followed by an exogenous cue (the thickening of one of the two peripheral boxes). After varying intervals (stimulus onset asynchronies, SOAs) from the onset of the cue, a target (which is represented by one of peripheral boxes being completely filled in) is presented at the cued (right) or uncued (left) location. The
observer’s task is to make a speeded detection response as soon as the target appears. (B) Arbitrary behavioural data. Faster responding (having a shorter response time, RT) to cued targets at shorter SOAs (green) represents a facilitation effect of reflexive orienting of attention towards the cue. IOR is reflected in the slower responding (having a longer RT) to targets at the cued location at the longer SOAs (red). Cued trials are represented with black dots and a solid line, while uncued trials use white dots and a dashed line. Adopted from Klein, 2000).

In the paper that first reported the IOR effect, it was suggested that IOR was the result of a mechanism developed to maximize the efficiency of visual search by encouraging the inspection of novel locations. Posner and Cohen (1984) suggested that once the eyes move away from the target location, mechanisms are activated at that location such that it becomes inhibited. This inhibition reduces the effectiveness of a subsequent stimuli at a previously active and attended area of space from triggering attention and, in this way, the mechanisms serves as a basis for searching other areas at which no information had been previously presented.

Klein (1988) expanded on this suggestion and proposed that the mechanisms leading to IOR might operate in visual search to discourage wasteful re-inspection of previously searched locations by biasing orienting responses away from those recently inspected locations. He proposed that there is an initial involuntary orientation of attention to the cued location, and after a delay if the target does not appear in that location, attention is reoriented to fixation, which activates an inhibitory mechanism (see also Taylor & Klein, 1998). This inhibitory mechanism then hinders covert attention and eye movements from orienting to the previously attended-to and inspected location.

Although IOR was first demonstrated in simple detection tasks, many studies have consistently replicated the finding of IOR in discrimination tasks, suggesting that IOR reflects the inhibited return of the mechanisms of attention to the previously cued
location (Chica, Taylor & Lupiáñez, 2010). However, as Taylor and Klein (1998) suggested, it is possible that the inhibitory mechanisms affect the return of covert (i.e., without eye movements) and/or overt (i.e., with eye movements) attention. That is, IOR might result from attentional and/or motor mechanisms. This uncertainty over the contribution of attention and/or motor mechanisms to the IOR effect has inspired an increasing number of studies in the psychology and cognitive neuroscience community, some of which result in conflicting conclusions.

1.2.1 Mechanisms Leading to Inhibition of Return

Despite an accumulation of empirical knowledge, it still remains an open question as to which mechanisms or underlying processes might be involved in the IOR phenomenon. Initially, IOR was suggested to work at a level of perceptual processing or at the level of attention. According to this account, attention automatically shifts away from the cued location approximately 300 ms after the onset of the peripheral cue (Posner & Cohen, 1984). Attention becomes disengaged from that spatial position, after which an inhibitory mechanism starts to operate. As a consequence, the perceptual processing of subsequent stimuli at this cued location is reduced, resulting in a worse (slower and less efficient) performance for targets at the cued location. Reduced performance may be due to a less pronounced sensory representation of the stimuli or slowed perceptual processing (see also Prime & Ward, 2004; Zhou, 2008).

Early support for this perceptual/attentional component in IOR came from Klein (1988) who demonstrated that IOR is only present in search tasks that require attention. Klein (1988) had participants perform one of two different search tasks - an easy parallel
search in which multiple objects can be searched at the same time or a difficult serial
search in which each item must be searched and identified individually. After the visual
search task, participants immediately completed a luminance detection task in which
probes could appear at locations where the item had appeared in the previous search task
(on-item-probes), or at locations where an item had not appeared (off-item-probes). Klein
(1988) predicted that there should be longer detection times for on-item-probes relative to
off-item-probes following the difficult serial search because the participants serially
searched and attended to each item and these previously attended locations would then be
tagged for subsequent inhibition. Conversely, in the parallel search condition, no
difference was expected between on-item-probe and off-item-probe targets because the
presence or absence of the targets could be identified pre-attentively (Klein, 1988).
Because the participants were able to complete the parallel search task without
necessarily attending to any locations, there would be no subsequent inhibition on an on-
location and no differences in the processing of the subsequent target at any location.
Consistent with Klein’s predictions, results from this study revealed that there were
longer RTs to on-item- than off-item-probe targets (IOR) in the serial condition, but no
differences for RTs in on-item and off-item probes in the parallel condition. This pattern
of effects thus provides support for the perceptual/attentional component in IOR.

Further support for the perceptual/attentional component in IOR comes from a
hypothesized that if IOR results from an inhibition of attention, then it should share a
common mechanism with other attentional effects. Specifically, if IOR is attentional then
the magnitude of IOR should be similarly influenced by target modality, target intensity,
and response mode (a motor factor that should not affect attention). To test these hypotheses, Reuter-Lorenz et al. (1996) presented participants with a brightening stimulus to the left or right, brightening at fixation, and a visual or auditory target to the left or right. Results from this study demonstrated that, consistent with the magnitude of attention required to process these stimuli, the magnitude of IOR was greater for low intensity targets than for high intensity targets, greater for visual targets than auditory targets, and was equivalent for manual detection and saccadic responses. These results confirm that the magnitude of attention and the magnitude of IOR were indeed similarly affected by changes in target intensity, target modality and response mode, providing support for an attentional component in IOR.

Although there has been extensive evidence supporting the perceptual/attentional component in IOR, a number of other findings have challenged this view suggesting that central mechanisms other than perceptual/attentional mechanisms are responsible for the IOR effect. One such finding is based on the initial failures to observe IOR in tasks requiring discrimination of non-spatial characteristics, for example, luminance, orientation, form and colour (Terry, Valdes, & Neill, 1994; Taylor & Klein, 1998). Because IOR was present for localization discrimination tasks, but not discrimination tasks that involve non-spatial features, it was proposed that IOR results from a non-perceptual/attentional, perhaps a motor, mechanism and bias. Furthermore, if IOR results from an attentional effect, then it follows that IOR would be expected to influence perceptual judgments such as temporal order judgments (TOJ) or illusory line motion. Although attention is generally shown to have an effect on TOJ and illusions at SOAs less than 300ms, at SOAs greater than 300 ms during which IOR should be expressed, an
IOR effect is not observed for TOJ (Maylor, 1985; Posner et al., 1985) or illusory motion line (Schmidt, 1996). Thus, the absence of IOR-like effects in these two perceptual tasks is not consistent with a perceptual/attentional account of the IOR effect.

Another study from Rafal, Calabresi, Brennan, and Sciolto (1989) provided evidence in favour of a motor component to IOR. In this study, Rafal et al. (1989) presented participants with a central arrow cue to indicate a location (in this way there was no exogenous attentional capture at one location) and then asked participants to prepare a saccade but not execute the saccade to that location. The results of this study revealed that RTs to cued locations were longer than those to uncued locations – an IOR-like effect. Because the cue was central and there was no preceding stimulus at one location, the IOR effect could not have been the result of attentional capture at the cued location. On the other hand, participants were asked to plan and then prevent a motor response (eye movement) to the cued location. Thus, the emergence of the IOR effect in this task (where there was no attentional capture, but a planned and inhibited response) suggests that there is a motor component to IOR. Together with the absence of IOR-like effects in perceptual task such as TOJ and illusionary line motion, these results indicate that IOR does not necessarily reflect an effect of attention and that it might actually depend on a motor bias against responding to stimuli at previously cued locations (Rafal et al., 1989; Taylor & Klein, 1998, 2000). That is, the onset of a peripheral cue automatically activates a saccade plan to the location of the cue, which once executed or suppressed, induces an inhibition effect that hinders the reactivation of subsequent motor responses to targets at or near the cued location approximately 300 ms after the onset of the cue, resulting in IOR.
Additional evidence for a motor component in IOR comes from Welsh and Elliott (2004) who found that goal-directed limb movement trajectories were biased away from the location at which a cue had been presented. Welsh and Elliott (2004) had participants complete rapid aiming movements to targets located to the left or right of fixation following cues at one of the two possible locations. Depending on the block of trials, cues were predictive (80%), nonpredictive (50%) or antipredictive cues (20%). The experiment was designed to investigate how the temporal and kinematic characteristics of the target movement change when the possible target locations are cued informatively or non-informatively. By using goal-directed movements instead of key presses, analyses of kinematic variables such as trajectories can be used to provide additional insight into the influences of cognitive processing on motor system activation and action planning (see Song & Nakayama, 2009 for a review). Particularly, by examining movement trajectories one can gain additional insight into the dynamics of cognitive processing because the direction of reaching movements are represented, in part, by a specialized set of directionally-tuned neurons in the motor system (Georgopoulos, 1995). Of critical relevance to the present work, the results of the Welsh and Elliot (2004) study were that participants responded more quickly to targets at cued locations than to targets at uncued locations when using predictive cues, and more quickly to targets at uncued than to targets at cued locations when using nonpredictive and antipredictive cues. These findings suggest participants prime or preprogram their responses appropriately when they had advance information. Consistent with the idea that preprogramming of responses was represented by a subthreshold increase in activity of the neurons coding for specific characteristics of that response, movement trajectories were altered in the predictive and
antipredictive conditions. Of critical importance to the present study, movement trajectories (the path of movement in space) deviated away from the cued locations in the nonpredictive cue condition. Specifically, movements to the uncued location deviated away from the cued location in the non-predictive condition. Based on these biases in movement trajectories, Welsh and Elliott (2004) proposed that the inhibitory mechanism found in IOR influences the representation of action in motor systems, supporting a motor account for IOR.

More recently, a study by Neyedli and Welsh (2012) examined the temporal and spatial characteristics of aiming movements executed in an exogenous cue-target task with cue-target onset asynchronies (SOAs) of 100, 350, 850, and 1100 ms. They implemented a broader range of SOAs to provide a more comprehensive assessment of the potential expression of attentional and motoric contributions to cueing effects. Neyedli and Welsh (2012) had participants complete aiming movements to targets presented at 100, 350, 850, and 1100 ms following the presentation of a non-predictive cue. RTs and movement trajectory deviations on the axis perpendicular to the primary direction of the movement were analyzed. The authors predicted that if: a) an intrinsic link between attention and action existed (e.g., Tipper, Lortie, & Baylis, 1992), and b) the mechanisms of IOR are represented in the motor system, then movement trajectories should reflect the attentional mechanisms operating at movement onset. Specifically, trajectories should deviate toward the cued location at short SOAs when attention excites the cued response, but should deviate away from the cued location at long SOAs when the cued response is inhibited (Neyedli & Welsh, 2012). Consistent with the author’s predictions, results revealed that the initiation of the response and the kinematics of the
movements were both affected by the non-predictive cue. The critical finding, however, was that there was a divergence in the timing of these effects. RTs revealed no facilitation at the 100ms SOA and a robust inhibition effect at 350, 850, and 1100ms SOAs. Trajectory deviations towards the location of the cue revealed the influence of facilitatory mechanisms at the 100ms SOA, whereas trajectory deviations away from the location of the cue did not emerge until the 850ms SOA. This dissociation between the time course in the emergence of facilitation and inhibition in RTs and trajectories suggests that inhibitory mechanisms acting on the motor system took longer to affect behaviour. Thus, although there is a tight coupling between attention and action, the data suggests that facilitatory and inhibitory mechanisms may operate in attention-dominated systems before cascading to motor centers (see also Welsh, Neyedli & Tremblay, 2013). In the end, the results of this and other studies suggest that there is both a motor and attentional component to IOR (see also Taylor & Klein, 2000; Hunt & Kingstone, 2003; for a review see Klein, 2000).

In sum, most researchers agree that both attentional and motor mechanisms underlie the IOR effect (Taylor & Klein, 2000; Hunt & Kingstone, 2003), however the exact attention and motor contributions to IOR still remains unclear. Where in the brain the mechanism is located and whether it is inhibited attention or it has to do with a bias against responding, it is unknown. This inconsistency creates the space to further investigate the motor component to IOR. Thus, this thesis will attempt to further investigate the motor account of IOR by investigating the contributions of the primary motor cortex (M1) to IOR in manual responses. One technique that has been shown to be especially useful in investigating motor system activation, in particular motor
corticospinal excitability, is the recording of MEPs derived via transcranial magnetic stimulation. Thus, the study reported in the present thesis will examine the magnitude of MEPs that emerge in a cue-target paradigm. However, prior to discussing the experiment, a review of the potential cortical areas involved in IOR will be provided.

1.2.2 Cortical Centres Involved in Inhibition of Return

Before outlining the details of the present study, a brief review of the cortical regions that are potentially involved in the IOR effect will be provided. Although there is distinct evidence that the mechanisms leading to IOR are coded within sub-cortical structures such as superior colliculus that are involved in eye movements (see Doris, Klein, Everling, & Munoz, 2002), the present review will focus on cortical structures because of the evidence that IOR is be coded in the cortical motor systems (e.g., Welsh et al., 2013) and because of the technique employed in the present study (TMS) preferentially interacts with cortical structures.

Based on the findings from previous research examining the RTs and trajectories of aiming movements (e.g., Neyedli & Welsh, 2012), it is suggested that the coding of the facilitatory and inhibitory mechanisms that lead to IOR are represented in M1. It is likely that M1 is not the main or sole contributor to the IOR effect and it is suggested that other cortical structures involved in attention and motor planning, such as the posterior parietal cortex (PPC) and pre-motor cortex (PrM), may be responsible for the mechanisms underlying the IOR effect as well. Indeed, the main premise of the following account is that decision-making centres (e.g., dorsal lateral prefrontal cortex) and attention/motor
areas, such as PPC, PrM and M1 interact in a multi-directional manner and are continually updated by the processing of the other areas (see Cisek, 2007 for a review).

One of the many roles of the PPC is to maintain salience maps of the environment (Welsh, Neyedli, & Tremblay, 2013). The activity in the salience maps can be modulated in two different ways: 1) bottom-up influences from early visual areas; and, 2) top-down influences from the decision-making centers. Once the salience maps are established and maintained, the outputs of the salience maps play two critical roles. First, it could update the set of potential responses by changing the activity in the response selection (PrM) and programming (M1) centers. Second, it could have an influence on the patterns of activity in the salience maps in the decision-making centers which are responsible for initiating the “GO” signal which helps initiate the response to the correct stimulus (the target). This “GO” signal can be an increase of excitation and/or a disinhibition of the motor system to generate the response (see Cisek, 2007 for a review).

It is suggested that, when the cue is presented, there is an initial wave of excitation in the visual system, which flows simultaneously from the visual cortices to the ventral visual areas for identification and to dorsal visual areas in PPC (and then PrM and M1) for response generation (e.g., Goodale and Milner, 1992). This information in dorsal stream areas creates excitation in the salience maps, which helps draw attention to that area of space (Welsh, Neyedli, & Tremblay, 2013.) Once this excitation reaches threshold, the excitation flows to the decision-making center to activate an area of interest where a possible target has been presented and to the PrM and M1 to initiate response-producing activity. Although there is a rapid onset of excitation in the saliences maps of the PPC, there may also be a rapid decay (Welsh, Neyedli, & Tremblay, 2013). This
decay occurs because of the short length of the cue. As a result, the processing of the target at the cued location is facilitated relative to the uncued location and the consequence of this more rapid processing of the target at the cued location leads to the shorter reaction times at cued locations than uncued locations at short SOAs. Due to the tight link between PPC and motor systems, there is an active response code in motor systems at this time too. This active response code at short intervals after the cue is why there are response trajectories that curve to the location of the cue at these short SOAs when there is also a facilitation effect in RT (Welsh, Neyedli, & Tremblay, 2013).

As the SOA increases, however, the ventral stream has sufficient time to identify the cue as a “non-target” and transmit that information forward to the decision-making centers. From here the decision-making centers’ salience maps are updated and the level of excitation is decreased in the cells coding that region of space via inhibition (Welsh, Neyedli, & Tremblay, 2013). This inhibitory process is then relayed back to the PPC to decrease excitability of that region of the salience map so that future capture of attention and processing of information is hindered in the region of space where the cue appeared. The response selection and programming centers of PrM and M1 are possibly more resilient to change since the salience maps update them only indirectly (Welsh, Neyedli, & Tremblay, 2013). Consequently, it takes more time to develop the transition from excitatory to inhibitory coding of the response to the cue in these motor centres. Thus, it appears that 200-300ms is required to develop sufficient inhibition in attention centres, which is consistent with results from Posner and Cohen (1984), but still have trajectory deviations that veer towards the location of the cue at these short SOAs.
Finally, as the SOA increases beyond 300 ms, sufficiently strong inhibition has developed in PPC to have a downstream effect on the related motor centres of PrM and M1 (Welsh, Neyedli, & Tremblay, 2013). This strong inhibitory influence decreases activity in this region of space to below a baseline level. The coupled decrease in activity for the region of space in the salience maps in the PPC and frontal areas then slow the processing of information and the release of the “GO” signal causing a relative increase in RTs for targets at the cued location (Welsh, Neyedli, & Tremblay, 2013). Because the inhibition also grows and affects the coding of the responses in PrM and M1, the response codes initially activated to the cue are reduced to a below base-line level resulting in the trajectory deviations away from the location of the cue at SOAs of 300ms and longer (Posner & Cohen, 1984).

In sum, it is hypothesized that the coding of the facilitatory and inhibitory mechanisms that lead to IOR are represented in M1. However, it may be possible that the mechanisms behind IOR may operate in multiple cortical systems upstream from M1, including the posterior parietal cortex (PPC) or pre-motor cortex (PrM). To address this issue, the current thesis will use transcranial magnetic stimulation (TMS) to probe the excitability of the motor system more specifically M1. To understand why TMS is employed in the present study, a brief outline of the technology and methodology will be provided.

1.3 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a safe, non-invasive technique commonly used for stimulating the cerebral cortex. TMS utilizes the fundamental
physical principles of electromagnetic induction first discovered by Michael Faraday in 1831 (Maeda & Pascual-Leone, 2003). In TMS, a very large electrical charge stored in a capacitor is discharged to a magnetic stimulator (which consists of a copper-wire coil that is connected to the electrical capacitor) (Maeda & Pascual-Leone, 2003). By releasing the electrical current pulse through the induction coil, a magnetic field pulse is generated in the volume surrounding the coil. Once induced, this magnetic field pulse can induce electrical current in any nearby electro-conductive medium. For instance, if the brain is adjacent to the rapidly changing magnetic field, an electrical current can be induced in the extracellular fluid. When the induced current is sufficiently large, depolarization of neuronal membranes occurs causing a generation of action potentials in nearby neurons (Maeda & Pascual-Leone, 2003).

Barker and colleagues (1985) first demonstrated that muscle contractions could be elicited when applying TMS over areas of the motor cortex that corresponds with specific areas of interest in the motor homunculus (Barker, Jalinous, & Freeston, 1985). More specifically, when stimulating the hand area within the primary motor cortex (M1), cortical interneurons become activated which then synapse to the descending pyramidal neurons. Once enough of these neurons become activated, the descending action potentials cause an activation of alpha-motorneurons, which in turn causes a brief muscle contraction. This induced muscle contraction is known as the motor-evoked potential (MEP).

Generally, in TMS experiments of the motor system, stimulation is delivered to the M1 and surface electromyographic (EMG) electrodes are placed on the skin to record the electrical activity in the effector muscles of interest and record the MEPs. Because the
number and activity of cortical interneurons, the descending pyramidal neurons, and alpha-motorneurons activated by the TMS pulse is influenced by the balance of excitation and inhibition at each of the synaptic connections between each set of neurons, the size of the MEP (peak-to-peak amplitude) and the latency from the TMS pulse to the onset of the MEP can then be used as measures of corticospinal excitability. For instance, larger amplitude MEPs for a given level of stimulation are presumed to reflect an increase in corticospinal excitability, whereas smaller amplitude MEPs for a given level of stimulation are presumed to reflect decreased corticospinal excitability or inhibition.

In addition to providing an index of corticospinal excitability, TMS can be used in “temporary lesion” paradigms. Whether it is applied as single pulse appropriately delivered in time or as trains of repetitive stimuli at an appropriate frequency and intensity, TMS can be used to transiently disrupt the function of a given cortical target, creating a temporary virtual brain lesion. In doing this, it allows the researcher to assess the contribution of a given cortical region to a specific behaviour; helping researchers answer questions like “what does it do?” and “when does it do it” (Pascual-Leone, Walsh & Rothwell, 2000). Traditionally, “lesion studies” (in which people with damage to specific areas of the brain perform tasks) have represented the best way of creating a causal link between a brain region and a function/behaviour – the logic being that if a brain area is dedicated to a specific function, then the person with a lesion in a specific area should show a specific dysfunction. However, due to their invasiveness and their dependence on the opportunity and chance occurrence of a given brain injury, “lesion studies” are generally limited to a single or few case studies and cannot be repeatedly tested for confirmation. Thus, TMS provides a novel approach to the scientific study of
regional brain function and behaviour by the possibility of “creating” virtual lesions in the otherwise typically functioning brain (Pascual-Leone, Bartres-Faz, & Keenan, 1999).

With the virtual lesion approach, the TMS pulses create a temporary interference with the neural processing in the stimulated area while the participant is performing a behavioural task. Basically, the TMS pulse generates non-task-related neural noise in the system and/or activates inhibitory neurons in the layers of the cortex. This neural noise effectively shuts the working of the area down for a short time. Thus, effects of TMS on task performance (e.g., RTs) would indicate that the stimulated area is crucially involved in the task.

In sum, although TMS is can be used for diagnostic and therapeutic purposes, TMS has been shown to be a reliable tool for investigating corticospinal excitability and the role of specific cortical areas while participants perform an experimental task. Thus, this current research project will utilize TMS as an investigative tool for understanding the involvement of the M1 in IOR.

1.3.1 Using Transcranial Magnetic Stimulation to Understand the Mechanisms of Inhibition of Return

Although the study reported in the present thesis is the first known study to use TMS to investigate if the mechanisms underlying IOR in hand responses are represented in M1, there has been a previous study that used TMS to investigate the role of a cortical region known as the frontal eye fields (FEF) in the generation of IOR in hand responses movements (Ro, Farne, & Chang, 2003). In this study of IOR in eye movements, FEF was targeted because FEF is a structure primarily involved with generating voluntary eye
movements and is highly interconnected with the superior colliculus (Ro et al., 2003). As noted above, since the discovery of IOR, numerous theoretical and neural accounts of IOR have been proposed. One structure that is mentioned in many accounts is the superior colliculus (Ro et al., 2003; Munoz, 2002). Therefore, considering the heavy connection of FEF with the superior colliculus and the potential involvement in the generation of IOR, Ro et al. hypothesized that stimulating the FEF might reveal the underlying mechanisms in the generation of IOR. That is, if FEF is involved in generating IOR, then TMS might alter the emergence of IOR because of the “temporary lesion” in FEF caused by TMS.

To test this hypothesis, Ro et al. (2003) applied TMS over participants right FEF at a time interval after a visual cue but shortly before the target. Participants completed a choice reaction time task, where they were instructed to press the left button with their index finger of their right hand on a response pad when a left target appeared and the right button with their middle finger of their right hand when a target appeared. Participants were asked to maintain central fixation throughout the study and respond as quickly and as accurately as possible using the hand ipsilateral to the TMS. Half of the participants received TMS over the FEF for the first block and the other half of the participants first received TMS over the control site in the superior parietal lobule (SPL). Results from this study were that when TMS was applied over the right FEF 600ms after the cue and 150ms before the target, IOR was no longer observed in the ipsilateral (right) hemifield. There were two important points to highlight about these findings. First, TMS of SPL did not disrupt the emergence of IOR indicating that the TMS-induced disruption was specific to stimulation of the FEF, and not just a generalized effect associated with
Second, the disruption of IOR only occurred with responses to stimuli in the hemifield ipsilateral to the stimulation (i.e., a hemispheric specific effect) and not with responses to both hemifields. Taken together, due to the cortical region- and hemifield-specific nature of the effect of TMS, the authors suggested that the results indicate that the mechanism of IORs may be located in FEF as opposed to in the superior colliculus as previously suggested (Ro et al., 2003; Munoz, 2002). Instead, they suggested that FEF play a critical role in IOR because attention and associated eye movements are biased away from the cue by the cancelling of the reflexive saccade to the cue and the programming of a voluntary saccade in the opposite direction to the cue (into the space contralateral to the cue). Furthermore, because the superior colliculus is involved with generating reflexive glances to stimuli from different sensory modalities and the FEF is heavily connected to the colliculus, the FEF must also counteract this natural tendency to saccade to the location of the sensory stimulus resulting in IOR (Ro et al. 2003).

Although the Ro et al. (2003) study used TMS to look at the role of FEF-mediated eye movements in IOR, the results demonstrate that attention and eye movements are tightly coupled and that the same human neural structures give rise to both of these behaviours. It also demonstrates that TMS has been effectively used in an IOR paradigm to gain new insights into the neural mechanisms underlying IOR. Therefore, the present work will expand on this study and use TMS to study the mechanisms underlying IOR and whether they are represented in M1.

1.4 Experimental Aims and Predictions
The present experiment was designed to explore the motor-based component of IOR by investigating the contributions of M1 to IOR. More specifically, TMS was used as an investigative tool to determine if the mechanisms associated with IOR are represented in M1. To this end, participants completed a cue-target task with non-predictive exogenous cues. Participants pressed a button with either the left or the right hand when the target (a white square) appeared inside a placeholder location to the left or to the right of a central fixation point. A cue stimulus (brightening of the placeholder box) was presented 100, 300, 600 or 1000 ms prior to the target. TMS was provided to M1 randomly on one-half of the trials immediately prior to target onset. The other half of the trials did not receive TMS. TMS was only provided to right-hemisphere/left-hand system.

TMS was used because it can provide an index of how the mechanisms of facilitation and IOR are represented in M1 in two main ways. First, because the neural noise generated by TMS temporarily disrupts the function of the targeted area (Ro et al., 2003). TMS of M1 might disrupt the expected pattern of RTs to cued and uncued targets (e.g., Ro et al., 2003). Thus, if M1 plays a role in the facilitation and inhibition effects that follow a cue, then the facilitatory effects of the cue at the early SOAs and/or the inhibitory effects of the cue at longer SOAs that are expected to be seen on non-TMS trials (e.g., Posner & Cohen, 1984) will not emerge when TMS is applied to M1. Importantly, it was predicted that a hemisphere/hand specific influence of TMS on IOR should occur in that alterations in the patterns of RTs should only be seen when the left hand is responding. This hemisphere/hand specific influence should occur because TMS was only provided to the right-hemisphere/left-hand system. The patterns of RTs for
targets on the right side of space (requiring a response involving the left-hemisphere/right-hand system) should not be affected (i.e., similar to the RTs for non-TMS trials) because the TMS was not provided to that left-hemisphere/right-hand system. On the other hand, if the mechanisms that lead to facilitation and IOR are not represented in M1 (or at least strictly affect perceptual processes), then TMS of M1 will not disrupt these mechanisms and the same pattern of cued-uncued RT differences will be observed on both non-TMS and TMS trials.

Second, TMS of M1 was used as an indicator of corticospinal excitability while participants performed the cue-target task. Electrical activity was recorded from the first dorsal interosseous (FDI) muscle of the left hand via surface EMG electrodes and the amplitude of the MEPs was assessed. The underlying hypothesis was that if the inhibitory mechanisms influenced the representation of action in M1, then both the pattern of RTs and amplitudes of MEPs in the targeted muscles should be altered in a similar fashion. These two measures should be modulated in the same way because TMS was provided to M1 immediately prior to target onset, and hence at a similar time from the onset of the cue. Based on the evidence presented above by Neyedli and Welsh (2012; see also Welsh et al., 2013) that the facilitation and later inhibitory mechanisms should be represented in M1, the presentation of the cue should affect corticospinal excitability and the size of the muscle contractions that result from TMS provided to M1. Thus, it was predicted that if the mechanisms responsible for the cued-response specific facilitation and inhibition effects are maintained within M1, then MEP amplitudes following the cue on the left side of space should be larger than those following the cue on the right side of space at SOAs less than 200 ms (indicating a facilitation or increase in corticospinal
excitability following the cue on the left side of space relative to following cues on the right side of space). Further, it was predicted that MEPs should be smaller following cues presented on the left side of space than following cues on the right side of space at SOAs greater than 300 ms (indicating an inhibition or decrease in corticospinal excitability). Essentially, the pattern of MEP amplitudes should mirror the pattern of RTs. On the other hand, if the processes of facilitation and inhibition are not coded in M1 and do not affect corticospinal excitability, then MEP amplitudes will not be modulated by the cue and MEP amplitudes following cues on the left side of space will not differ from those on the right side of space across all SOAs.
Chapter 2

Methods

2.0 Participants

Fifteen volunteers from the University of Toronto community were recruited. Due to technical problems, the data from one participant could not be used in the data analysis (incomplete data collection). The data from the remaining fourteen participants (8 female; \( M_{age} = 23.93 \) years, \( SD = 3.41 \)) were included in the final analysis. All participants reported being right-hand dominant and had normal or corrected-to-normal vision. Each participant provided written informed consent prior to participation and received an honorarium of $15 for their time at the end of the study. All procedures were approved by the Ethics Review Office at the University of Toronto and complied with the ethical standards set forth by the 1964 Declaration of Helsinki regarding the treatment of human participants in research.

Prior to their involvement in the study, participants completed a medical history questionnaire (Appendix A) and mental health (Appendix B) to ensure that the use of TMS was not contraindicated. This was to ensure that the person had no conditions or factors that would have caused them harm from using the TMS. These questionnaires provided information on whether the participant (1) has a pacemaker, spinal/bladder stimulator, or acoustic device; (2) has any neurosurgical procedures with craniotomies; (3) has any other intracranial metallic components; (4) has a history of seizure; or (5) are taking any medication that may affect the excitability of their nervous system (i.e., antispastics, anxiolytics, hypnotics, antiepileptics, etc.) (Rossini, Barker, Berardelli,
Caramia, Caruso, Cracco, et al., 1994). Finally, a hand dominance questionnaire was also completed to ensure that everyone participating in the study was right handed.

2.1 Equipment

The TMS system that was used for this experiment was a single-pulse monophasic stimulator MagStim 200 (The MagStim Company, Carmarthenshire UK) containing a figure-8 coil with an internal diameter of 70mm. To locate cortical landmarks and ensure that TMS pulses were delivered to the same location on each trial, an image-guided TMS system (Rogue Research, Montreal, QC; Brainsight 2) was used. EMG data from the left FDI of the index finger was recorded via surface electrodes (Rogue Research, Montreal, QC). A custom E-Prime program was used to control all experimental stimuli and record response data. EMG data was recorded by the Brainsight 2 system at 3000 Hz for a 200 ms interval that began 50 ms prior to the onset of stimulation and ended 150 ms post stimulation. The data was stored for offline analysis using the Brainsight 2 system software.

Participants were seated in a supportive armchair and an adjustable neck brace that cupped the upper neck and base of the skull to hinder unwanted movement. A computer monitor (Dell; REV A00) was placed on a table in front of the participants. All visual stimuli were presented on this monitor. A keyboard was positioned on the table at a distance that was a comfortable arm-reach distance for which participants could provide their responses while resting their elbows on the armrests of the chair. Pillows were placed on top of the armrests under the participant’s arms for extra comfort.
2.2 Procedure

During the experiment, participants were seated comfortably in the TMS chair with a computer monitor placed on a table at eye level approximately 70 cm away. A keyboard was placed in front of them where they rested their palms facing downward. During the experiment, participants had their left index finger positioned resting on the left “shift” key on the keyboard and their right index finger positioned resting on the right “shift” key on the keyboard. These keys were known as the home positions throughout the experiment and participants were asked to return their fingers to these home positions after every response and prior to the next trial. Each session consisted of two different phases; an initial mapping phase and a testing phase.

2.2.1 Mapping Phase

To locate the position of the coil that would maximally stimulate the neurons representing left FDI (aka the motor hotspot), a standard mapping procedure was carried out for each participant. Participants were seated comfortably in the TMS chair with their arms and hands relaxed as much as possible. Surface electrodes were placed on the participants’ left hand to measure EMG activity from the left first dorsal interosseous (FDI) muscle. The head of each participant was registered to the default brain map of the Brainsight 2 system using the following anatomical landmarks: the nasion, the tip of the nose, and the edge of the left and right ear. The Brainsight 2 system was then used to record the participants’ optimal scalp location of the motor cortex that would produce the largest MEP in the left FDI muscle following a TMS pulse to enable accurate re-
positioning of the TMS coil and associated site of stimulation. The following standard procedure was used to locate this motor “hot spot” for the left FDI.

First, a rough location of the hand representation of the left hand in the primary motor cortex of the right cerebral hemisphere was determined using the intersection of the naison-inion line and the interaural line, then moving 6cm laterally on the right side of the scalp and 2cm anteriorly with a measuring tape (Figure 1.2). The rough location was marked with a dot on the participants’ scalp using a washable marker. Next, using this rough estimate of the hand location of the motor cortex as a starting point, the optimal scalp location of the motor cortex for stimulating FDI was determined via an iterative process in which the TMS coil was moved around the scalp in 1cm steps and TMS stimulations of increasing large amplitude until an observable MEP was elicited in the left FDI. In this iterative process, stimulus intensity was initially set at 30% for each participant. If no MEP was observed after the coil position was moved around the scalp, the intensity was increased and the coil was moved around again. Stimulator output was increased in 5% increments and the mapping cycle was repeated until an MEP was observed.

Once a location that led to an MEP was identified, a virtual target on the scalp of the visual brain map was recorded in the Brainsight 2 software. This virtual target then acted as a reference point for the optimal coil location and orientation for stimulation for the duration of the experiment. After the location was identified and recorded, the stimulus intensity was then adjusted up and down in smaller increments until the resting motor threshold (rMT), defined as the minimum stimulus intensity that evoked 5 out of 10 MEPs of at least 50µV (peak-to-peak) from the left FDI, was identified (Rossini et al.,
1994). During testing, the stimulator was set at an intensity of 130% of the individual’s rMT.

**Figure 2.1.** Schematic representation of the vertex of the scalp at the approximate location of the motor hotspot for left FDI in right primary motor cortex (M1).

### 2.2.2 Testing Phase

For the testing phase, participants completed a series of cue-target response trials and TMS was provided to the right-hemisphere on one-half of the trials. Each trial began with the word “READY” appearing in the center of the screen. This signal indicated to the participants to prepare for the upcoming trial and to place their left and right index fingers on the home positions (left and right “shift” keys, respectively) and relax their muscles in both limbs. This preparation period also allowed for the experimenter to properly position the stimulating coil, using the virtual target in Brainsight, over the motor hotspot for left FDI in right M1. Once the participant’s muscles were relaxed, a
second experimenter initiated the trial via a mouse click, which replaced the word “READY” with a blank screen for a 1 s duration. After the 1 s blank screen, a grey central fixation cross and two open grey square target locations (2.5 cm x 2.5 cm) would appear. These peripheral target locations were positioned 10.5 cm to the right and left of the fixation cross. At the end of the fixation phase (1500 ms), one of two peripheral target locations was cued for 50ms using an exogenous non-predictive cue. The cue was the outline of one of the target boxes increasing in thickness. Participants were told that the cue was irrelevant and non-predictive of the target location and, therefore, to ignore it.

At different times (100, 300, 600 and 1000 ms) following the onset of the cue, a target was presented at one of the target locations. The target was a white square that completely filled one of the target boxes. If the target appeared in the left target box, participants were asked to execute a response by lifting their left index finger from the “left shift key”, then abducting it to the “Z” key, and making a button press. If the target appeared in the right target box, participants were asked execute a response by lifting their right index finger from the “right shift key”, then abducting it to the “/?” key and making a button press. Participants were asked to response as quickly and accurately as possible.

On 50% of the trials, TMS was delivered randomly to right hemisphere over the optimal location for stimulating the left FDI. The other 50% of trials received no TMS. There were no sham trials or catch trials used. The TMS pulse was delivered 5 ms prior to the onset of the target. Throughout testing, electrical activity was recorded via surface EMG electrodes from FDI muscle of the left hand. EMG from FDI muscle was recorded at 3000 Hz for 200 ms, 50 ms prior to the onset of the target to 1500 ms after target onset.
Participants completed 11 blocks of 32 trials with rest breaks provided between trials. The first block of trials was a practice block so that participants could familiarize themselves with the task and the TMS. The remaining 10 blocks were analyzed. The 32 trials in each block were randomized and involved a combination of one instance for each category, Cue (left, right), Target (left, right), Cue-Target Onset Asynchrony or SOA (100, 300, 600, 1000 ms) and TMS (TMS, no-TMS). At the beginning and end of each block of trials, two more TMS pulses at 130 % of threshold were administered to the participants. These two pre-block and two post-block MEPs recordings were used as baseline measurements of cortical excitability and were used in later normalization calculations.

2.3 Dependent Variables

Four dependent measures were analyzed; RT, raw peak-to-peak MEP amplitude, normalized peak-to-peak MEP amplitude, and ln peak-to-peak MEP amplitude. RT was defined as the time interval (in ms) between target onset and button press. Raw MEP amplitudes were recorded first as the absolute µV difference between the highest positive and lowest negative voltage recorded. MEP values were then normalized using the mean average peak-to-peak MEP amplitude from the two pre-block and two post-block baseline MEPs as the denominator. This normalization procedure helps to control for any within- and between-block change in corticospinal excitability and/or the slight changes in the placement and orientation of the coil (and associated neural stimulation pattern). The normalization would also help in determining the direction of any changes in corticospinal excitability relative to rest - any MEP values above 1 will indicate increased
corticospinal excitability compared to baseline, and values below 1 will suggest decreased excitability or inhibition relative to baseline. Finally, MEP values were transformed into ln MEPs by taking the natural logarithm of the normalized peak-to-peak MEPs amplitudes.
Chapter 3

Results

3.1 Response Time

RT data was exported from EPrime and put into an Excel file. For each participant, the data was sorted by condition. An average RT and standard deviation value for each condition was calculated. Any trials with RT values larger than two standard deviations from each participant’s mean per condition (outliers) or shorter than 100 ms (anticipations) were removed from the data set. Trials were also deleted if the participant responded using the wrong key. These criteria resulted in the removal of 3% of trials without TMS (range of 1-11% per participant) and 3% of trials with TMS (range of 1-8% per participant). Once these errors and outliers were removed, mean values were calculated for each condition and submitted to the series of analyses outlined below.

For all analyses, Mauchly’s Test of Sphericity was performed to assess sphericity of the data. Some of the data for specific effects violated the assumption of sphericity. A Greenhouse-Geisser correction was applied in these cases. Cases in which the Greenhouse-Geisser correction was applied for violations of sphericity can be recognized by degrees of freedom with decimal places reported for these effects. Post-hoc testing of all significant effects involving more than 2 means was performed using Tukey’s HSD to determine differences between conditions. Alpha was set at 0.05 for all statistical tests. All significant effects are reported.

3.1.1 Omnibus Analysis
RT data was first submitted to a 2 cue (left, right) X 2 target (left, right) X 4 SOA (100, 300, 600, 1000) X 2 TMS (TMS, no-TMS) repeated measures ANOVA. The results of the analysis from the 4-way ANOVA revealed a significant main effect of SOA, $F(3, 39) = 40.06, p < 0.05$. Post-hoc analysis of effect for SOA revealed that RTs were significantly longer for the 100ms SOA condition (459ms) than for all other conditions (300ms SOA = 426ms, 600ms SOA = 422ms, 1000ms SOA = 423ms). The RTs at other SOAs did not significantly differ.

The results of the 4-way ANOVA also revealed a significant TMS by Target Location interaction, $F(1, 13) = 28.56, p < 0.05$. Post-hoc analysis of this interaction revealed that RTs were significantly shorter to right targets when TMS was delivered (414ms) than to all other conditions (left-NoTMS = 438ms, right-noTMS = 440ms, left-TMS = 438ms). No significant differences were revealed between any of the other conditions.

The ANOVA also revealed a significant interaction between TMS, Cue Location and Target Location, $F(1, 13) = 6.94, p < 0.05$. Post-hoc analysis of the interaction revealed no theoretically relevant significant differences. That is, TMS did not significantly affect the patterns of cuing effects - no significant differences were revealed for left or right targets when the cue was on the same side as the target or on the opposite side of the targets or when TMS was delivered or not delivered.

The ANOVA also revealed a significant interaction between TMS, Target Location and SOA, $F(3, 39) = 6.00, p < 0.05$ (see Figure 3.1). Post-hoc analysis revealed that RTs were significantly shorter to right targets when TMS was delivered compared to when TMS was not delivered for all SOA conditions (100ms SOA = 441ms, 300ms SOA
RTs to left targets were significantly shorter when TMS was delivered but only for the 100ms SOA condition. RTs were actually found to be significantly longer to left targets when TMS was applied in the 1000ms SOA condition. No significant differences were found between TMS and no TMS for left targets in the 300ms or 600ms SOA conditions.

Figure 3.1. Mean response time (in ms) as a function of TMS, Target Location and SOA. Standard error of the mean bars are shown.

Importantly, the ANOVA revealed a significant 3-way interaction between Cue Location, Target Location and SOA, \( F(3, 39) = 13.99, p < 0.05 \), that replicated the basic facilitation and IOR effects. Post-hoc analysis revealed that RTs were significantly shorter to left targets when the cue was on the same side as the target (cued target = 454ms) than when the cue was on the opposite side of the target (uncued target = 473ms) in the 100ms SOA condition. RTs were also significantly shorter to right targets when the
cue was on the same side as the target (cued target = 446ms) than to when the cue was on the opposite side as the target (uncued target = 461ms) in the 100ms SOA condition. These findings are consistent with findings from Posner and Cohen (1984) - a short-term facilitation effect. Further post-hoc analysis also revealed that RTs were significantly longer to right targets when the cue was on the same side as the target than when the cue was on the opposite side of the target in the 600ms SOA condition (cued targets = 427ms; uncued targets = 410) and in the 1000ms SOA condition (cued targets = 425ms; uncued targets = 407ms). These findings are consistent with findings from Posner and Cohen (1984), and commonly known as an inhibition of return effect. No significant differences between RTs were revealed for the left target in the 300ms, 600ms or 1000ms SOA conditions.
Figure 3.2. Mean response time (in ms) as a function of Cue Location, Target Location and SOA. Standard error of the mean bars are shown. (A) RTs for trials to left targets. (B) RTs for trials to right targets.

Finally, and most importantly, the ANOVA revealed a significant 4-way interaction between TMS, Cue Location, Target Location and SOA, $F(3, 39) = 6.89, p < 0.05$. To understand this 4-way interaction, the data were separated into non-TMS trials and TMS trials and two 3-way ANOVAs were performed on the data for these conditions.

3.1.2 Analysis of Non-Transcranial Magnetic Stimulation Trials

Regarding the 3-way ANOVA on the non-TMS trials only, the analysis revealed a significant 3-way interaction between Cue Location, Target Location and SOA, $F(3, 39) = 3.62, p < 0.05$. Post-hoc analysis of the interaction revealed that there was a significant IOR effect at the 600ms SOA for both the right (M = -20.49, SD = 23.58) and left (M = -23.11, SD = 21.03) target locations. Facilitation effects at the cued location at the 100 ms
SOA condition (right: $M = -4.43$, $SD = 43.84$; left: $M = -8.79$, $SD = 29.85$) and IOR effects at 300 ms SOA condition (right: $M = -8.21$, $SD = 40.19$; left: $M = -12.75$, $SD = 26.90$) and 1000 ms SOA condition (right: $M = -10.16$, $SD = 26.95$; left: $M = -10.69$, $SD = 24.24$) were in the expected directions, but were not significant. Overall, these findings are generally consistent with the experimental prediction and approximately replicate results from both Posner and Cohen (1984) and Klein (1988).
3.1.3 Analysis of Transcranial Magnetic Stimulation Trials

Regarding the 3-way ANOVA on trials on which TMS was delivered, the analysis revealed a significant 3-way interaction between Cue Location, Target Location and SOA, $F(3, 39) = 20.49, p < 0.05$. Post-hoc analysis of the interaction revealed that there was a significant facilitation effect at the 100ms SOA condition for both the right ($M = 34.79, SD = 25.64$) and left ($M = 28.49, SD = 17.92$) target locations. However, participants demonstrated a significant IOR effect at the 600ms SOA condition ($M = -15.42, SD = 28.07$) and at the 1000ms SOA condition ($M = -26.13, SD = 31.24$) when responding to a right target location. IOR effects at the 300ms SOA condition, for the right target location (right: $M = -2.92, SD = 20.94$) were in the expected direction but were not significant. The cuing effects at all other SOA conditions for responses to the left target were not significant (300ms SOA: left: $M = 11.53, SD = 29.48$; 600ms SOA: $M = 6.15, SD = 27.89$).
left: $M = 0.62, SD = 24.45$; 1000ms SOA: left: $M = -11.61, SD = 24.78$). This result may have emerged due to the extra excitation provided to the left hand via the TMS.

**Figure 3.4.** Mean response time (in ms) for TMS trials as a function of Cue, Target Location and SOA. Standard error of the mean bars are shown. (A) RTs for trials to left targets. (B) RTs for trials to right targets.
Table 3.1. Response Time Data. Mean response times in ms (and standard deviation) values for TMS and non-TMS data.

<table>
<thead>
<tr>
<th>TMS/Non-TMS</th>
<th>Target Side</th>
<th>100 ms</th>
<th>300 ms</th>
<th>600 ms</th>
<th>1000 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-TMS</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cued</td>
<td>469 (42.4)</td>
<td>434 (51.6)</td>
<td>439 (56.3)</td>
<td>438 (74.5)</td>
<td></td>
</tr>
<tr>
<td>Uncued</td>
<td>464 (62.5)</td>
<td>426 (76.2)</td>
<td>419 (61.9)</td>
<td>428 (68.1)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cued</td>
<td>465 (57.9)</td>
<td>439 (53.9)</td>
<td>437 (59.9)</td>
<td>429 (56.5)</td>
<td></td>
</tr>
<tr>
<td>Uncued</td>
<td>474 (53.7)</td>
<td>426 (59.5)</td>
<td>414 (60.9)</td>
<td>418 (61.9)</td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cued</td>
<td>423 (62.2)</td>
<td>412 (54.1)</td>
<td>416 (55.9)</td>
<td>412 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Uncued</td>
<td>458 (67.0)</td>
<td>409 (59.6)</td>
<td>400 (56.6)</td>
<td>385 (65.2)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cued</td>
<td>444 (57.1)</td>
<td>426 (58.2)</td>
<td>426 (60.5)</td>
<td>441 (62.6)</td>
<td></td>
</tr>
<tr>
<td>Uncued</td>
<td>472 (65.5)</td>
<td>438 (65.0)</td>
<td>427 (64.6)</td>
<td>430 (56.2)</td>
<td></td>
</tr>
</tbody>
</table>

3.2 Motor Evoked Potentials

EMG data were exported from Brainsight in text format and integrated with the trial information from EPrime so that the MEPs were matched to the correct trial. Outlier rejection was performed in two different ways. First, the data from the EMG channel was used to calculate the absolute (rectified) average EMG amplitude for the 50ms (-50 to 0ms) window prior to the TMS pulse. To confirm MEP amplitudes were not influenced by pre-existing corticospinal and muscle activity, any trial in which the pre-stimulus average EMG exceeded 3 standard deviations of the total mean for that participant were excluded. Second, for each participant the mean peak-to-peak MEP values were calculated on a by-condition basis. MEPs exceeding 3 standard deviations of the mean
MEP were excluded. Combined, these two outlier rejection criteria resulted in a removal of a total of 4% of the trials and a range of 3-12% per participant. Finally, MEP data were transformed using the normalized value and the natural logarithm to better approximate the normal distribution. MEP values were normalized for each participant by dividing the raw MEP amplitudes by the mean average peak-to-peak MEP amplitude from the two pre-block and two post-block baseline MEPs. Statistical analysis was performed on the raw MEP amplitudes, normalized MEP amplitudes and log transformed MEP amplitudes. MEP data was separated into raw MEP amplitude values, normalized MEP amplitude values and ln MEP amplitude values and submitted to 3 separate 2 cue (left, right) X 2 target (left, right) X 4 stimulus onset asynchrony (SOA) (100, 300, 600, 1000) repeated measures ANOVAs. Although only the results of the analysis of the normalized data will be reported in the present thesis, note that the results of the analyses of the raw and log-transformed data were consistent with these analyses (all ANOVA tables for these analyses are presented in Appendix C).

Contrary to predictions, the analysis of MEP data revealed there were no significant effects ($p > 0.15$) for raw MEP values, normalized MEP values or ln MEP values (see Table 3.2). In other words, the MEP amplitudes elicited during the facilitatory stages at short SOAs following the presentation of the cue (see RT results) did not significantly differ from the MEP amplitudes elicited during inhibitory stages at longer SOAs following the presentation of the cue.
Table 3.2. MEP Data. Mean (and standard deviation) MEP amplitudes for the raw MEP data, normalized MEP data and the ln MEP data.

<table>
<thead>
<tr>
<th>Type of MEP</th>
<th>Target Side</th>
<th>100 ms</th>
<th>300 ms</th>
<th>600 ms</th>
<th>1000 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw MEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cued</td>
<td>691 (383.1)</td>
<td>681 (405.5)</td>
<td>683 (404.0)</td>
<td>671 (400.8)</td>
</tr>
<tr>
<td></td>
<td>Uncued</td>
<td>681 (389.4)</td>
<td>712 (381.7)</td>
<td>663 (385.7)</td>
<td>658 (401.4)</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cued</td>
<td>665 (393.8)</td>
<td>680 (385.1)</td>
<td>666 (404.1)</td>
<td>662 (379.8)</td>
</tr>
<tr>
<td></td>
<td>Uncued</td>
<td>662 (393.5)</td>
<td>682 (383.5)</td>
<td>681 (386.5)</td>
<td>681 (378.9)</td>
</tr>
<tr>
<td>Normalized MEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cued</td>
<td>1.31 (0.25)</td>
<td>1.21 (0.24)</td>
<td>1.21 (0.23)</td>
<td>1.23 (0.40)</td>
</tr>
<tr>
<td></td>
<td>Uncued</td>
<td>1.31 (0.37)</td>
<td>1.40 (0.38)</td>
<td>1.26 (0.29)</td>
<td>1.24 (0.41)</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cued</td>
<td>1.19 (0.17)</td>
<td>1.33 (0.51)</td>
<td>1.21 (0.34)</td>
<td>1.26 (0.37)</td>
</tr>
<tr>
<td></td>
<td>Uncued</td>
<td>1.27 (0.49)</td>
<td>1.29 (0.33)</td>
<td>1.24 (0.37)</td>
<td>1.31 (0.37)</td>
</tr>
<tr>
<td>Ln MEP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cued</td>
<td>0.16 (0.16)</td>
<td>0.086 (0.20)</td>
<td>0.079 (0.23)</td>
<td>0.091 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Uncued</td>
<td>0.15 (0.20)</td>
<td>0.20 (0.25)</td>
<td>0.083 (0.27)</td>
<td>0.082 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cued</td>
<td>0.088 (0.15)</td>
<td>0.13 (0.32)</td>
<td>0.061 (0.31)</td>
<td>0.010 (0.33)</td>
</tr>
<tr>
<td></td>
<td>Uncued</td>
<td>0.096 (0.32)</td>
<td>0.14 (0.24)</td>
<td>0.105 (0.30)</td>
<td>0.13 (0.20)</td>
</tr>
</tbody>
</table>
Chapter 4
Discussion

4.0 Overall Summary

The present study was designed to explore the motor-based component of IOR. To achieve this goal, TMS was used as an investigative tool to determine if the mechanisms associated with IOR are represented in M1. TMS was applied to the M1 of human participants performing an IOR task using a non-predictive exogenous cue and was used: 1) to induce a transient neural disturbance in M1 just prior to the target and response, and 2) to assess corticospinal excitability. It was hypothesized that, if IOR is represented in M1, then both the pattern of RTs should be altered by the TMS and the pattern of the amplitudes of MEPs in the left FDI should be similar to the pattern of RTs on non-TMS trials. It was found that, although TMS of M1 altered RTs, MEP data were not consistent with this predictions based on the notion that the processes of IOR are represented in M1. That is, MEP amplitudes were not significantly different based on cue presentation across SOAs and hence, there was no apparent changes in corticospinal excitability as the time from the cue increased. Thus, the critical finding was revealed in the RT data. Interestingly, the changes in the pattern of RTs were isolated to TMS of the hand being stimulated. This pattern of effects suggests a motor contribution to the IOR effect. Although TMS of M1 had some effect on the IOR mechanism, the fact that IOR was not represented in the MEPs means that it is still a question as to where in the motor system the IOR effect is localized.
Over the following sections of the thesis, the experimental methodology and the findings are discussed with respect to this conclusion. First, the implications and possible explanations for the RT data will be considered. Second, MEP data will be discussed regarding potential complications related to the stimulated cortical hemisphere as well as what might be happening upstream from M1 that could contribute to the RT findings. Finally, limitations and alterations to the current experiment task will be considered.

4.1 Response Time Data

The current methodology was based on the extensive literature on the effects of a non-predictive pre-cue on the processing of responses to targets (e.g., Posner & Cohen, 1984). Based on the findings from that literature, it was predicted that a facilitation effect was expected at short SOAs and an inhibitory effect was expected at longer SOAs on trials on which no TMS was provided. It was hypothesized that, if the mechanisms of IOR are maintained in the motor system, the typical pattern of facilitation and inhibition might be disrupted by TMS of M1 because TMS can disrupt the functioning of the stimulated cortical area.

To address the RT data on non-TMS trials first, although the expected pattern of facilitation effects was in the expected direction, but not significant, the analysis of the RTs revealed a typical pattern of IOR for the left and right target location. Overall, the results for responses to left and right target trails from the non-TMS trials were consistent with the results found by Posner and Cohen (1984). The magnitude of these effects might have been muted because the random delivery of TMS might have affected participant’s arousal, which might have had a general impact on performance. Regarding the RT data
on TMS trials, different patterns of RTs were shown for the left and right targets locations. Critically, the IOR effects observed for right-hand responses were not observed for left-hand responses. The implications of this pattern of results are discussed with respect to the mechanisms underlying the sequence of facilitatory and inhibitory mechanisms that are activated by the cue.

4.1.1 Non-Transcranial Magnetic Stimulation Trials

As reported in the results section, differences were observed in the patterns of RTs on the non-TMS and TMS trials. Regarding the RTs on non-TMS trials, a typical pattern of IOR was demonstrated for responses to both the right and left target locations. Specifically, trends towards facilitation effects were shown at the cued 100ms SOA followed by a significant inhibition effect at the cued 600ms SOA. These results are consistent with the findings from Posner and Cohen (1984). They found that within the first 50-150 ms after the cue-appearance, RTs were shorter to targets at previously cued locations than to targets appearing at uncued locations. However, when SOAs exceeded 300 ms, this facilitation effect changed into an inhibition effect, as revealed by longer RTs for targets presented at previously cued locations than to targets at uncued locations.

As described by Klein (1988; see Klein, 2000 for a review), this facilitation effect at short SOAs is likely due to an initial involuntary orientation of attention to the cued location. Because attention is at the location of the cue, the processing of the target stimulus and the response to the target stimulus at the cued location is more efficient than the target stimulus at the uncued location (which is not attended). After a short delay, however, if the target does not appear in that location, attention is reoriented to central
fixation and this shift of attention back to central fixation is thought to activate an inhibitory coding mechanism at the previously attended (the cued) location. The consequence of this inhibitory coding at the location that was attended is that the processing of the target stimulus and the response to the target stimulus at the cued location is less efficient than the target stimulus at the uncued location.

Considering these results, it is postulated that the IOR effect may have resulted from both an attentional and/or motor mechanism. Specifically, from an attentional view, IOR could have resulted from an initial capture of attention to the cued location and the subsequent inhibition of the re-orienting of attention back to that cued location (Taylor & Klein, 1998). Alternatively, from a motoric view, the sudden onset of the cue in the visual periphery may have generated the IOR pattern not necessarily by virtue of its capture of attention, but maybe by virtue of its activation of an oculomotor programme (Rafal et al., 1989) or motor response to the cue. That is, even if no eye movement is required, the peripheral cue produces an automatic activation of an eye or hand movement that was needed to be inhibited until the target actually appears. This initial inhibition then persisted and hindered the reactivation of that response at longer SOAs - generating IOR. Most authors agree that both attentional and motor mechanisms underlie the IOR effect and the data from the non-TMS trials do not address this debate in any meaningful way.

4.1.2 Transcranial Magnetic Stimulation Trials

Regarding the RTs on TMS trials, interesting differences were observed for the responses to the right and left target locations. Similar to what was observed on the non-
TMS trials, RTs for the right target location showed a typical pattern of facilitation and IOR. Specifically, participants demonstrated a significant facilitation effect at the cued 100ms SOA and significant inhibition effects at the cued 600ms and 1000ms SOAs. Once again, these results are consistent with the findings demonstrated by Posner and Cohen (1984). In particular, at short SOAs (less than 150ms) RTs were shorter to targets that appeared at the same location as the cue; at long SOAs (greater than 300ms), this trend reversed and RTs were longer to targets that appeared at the same location as the cue. Posner and Cohen (1984) suggested that the facilitation effect reflects an exogenous capture of attention by the visual transient cue. Thus, early facilitation replaced by a later inhibition is dependent on the withdrawal of attention back to fixation following an initial exogenous capture by the peripheral cue. Because the RTs for the right target location demonstrated a typical pattern of IOR, these findings suggest that the TMS of the M1 in the right hemisphere did not cause interference with the responses being coded in the left hemisphere. Interestingly, there was a slightly exaggerated facilitation effect at cued 100ms SOA. It is possible that the exaggerated facilitation effect may have resulted from an alerting or startling effect caused by the auditory and/or somatosensory stimulation associated with the TMS pulse. This alerting or startling effect could have enhanced the participants’ performance by preparing them for an upcoming response.

Interestingly, and of greater novelty, the pattern of RTs differed for the TMS trials for the left target location. Although a significant facilitation effect at the cued 100ms SOA was maintained, an inhibition-like effect looked like it was emerging at the 1000ms SOA, but was not significant. Thus, TMS of M1 seemed to disrupt the expected pattern of IOR. Possible explanations for these results might be that the TMS may be interfering
with the establishment of the inhibitory mechanisms. It might also be possible that TMS may have activated the motor cortex and may be working against the inhibitory mechanism by creating a facilitation effect. Finally, TMS may have caused neural noise or static which, in turn, could have delayed responses making it more difficult (and longer) for the inhibition effect to emerge. Regardless, because the changes in the pattern of RTs were isolated to TMS of the hand being stimulated, this pattern of effects points to a motor component to the IOR effect. Interestingly, Ro et al. (2003) found a similar lateralized effect from TMS on FEF and IOR. Results from this study showed that when TMS was applied over the right FEF 600ms after the cue and 150ms before the target, IOR was no longer measured in the ipsilateral hemifield; a hemi-spatial effect was found which is consistent with our hemisphere/hand specific effect. Although it is hypothesized that the mechanisms underlying IOR are represented in M1, it may be possible that the mechanisms behind IOR may operate in cortical systems upstream from M1, such as in the posterior parietal cortex (PPC) or pre-motor cortex (PrM). Thus, to get a better idea as to where the IOR effect is localized, the results of the analysis of the MEP data will be discussed.

4.2 Corticospinal Excitability

Most researchers agree that motor system mechanisms contribute to the IOR effect. However, what remains uncertain is where in the motor system the IOR effect is localized. Although there is distinct evidence that the mechanisms leading to the IOR effect are coded within sub-cortical structures, such as superior colliculus (Posner et al., 1985; Sapir et al., 1999), the current methodology was based on the literature that
suggests that the mechanism leading to the IOR effect are coded within cortical structures (Ro et al., 2003; Welsh et al., 2013). Based on the findings from that research, it was predicted that if the mechanisms responsible for the cued-response specific facilitation and inhibition effects are maintained within M1, then MEP amplitudes for the cued responses should be larger than those for uncued responses at SOAs less than 200 ms (indicating a facilitation or increase in corticospinal excitability) and should be smaller for cued responses than uncued responses at SOAs greater than 300 ms (indicating an inhibition or decrease in corticospinal excitability). Analyses of the MEP data did not confirm this hypothesis. Specifically, MEP amplitudes were not affected in a meaningful way by the cue-target asynchrony in that there were no apparent changes in corticospinal excitability as the time from the cue increased. MEP data will be discussed regarding potential complications related to the stimulated cortical hemisphere as well as what might be happening upstream from M1 that could contribute to the findings above.

As reported in the results section, analysis of the MEP data did not reveal a statistically significant effect of the cue stimulus on raw MEP values, normalized MEP values or ln MEP values for the left or right target locations. That is, the MEP amplitudes elicited during periods in which facilitatory effects in RTs did not significantly differ from the MEP amplitudes elicited during inhibitory effects in RT for the left or right target locations. Overall, these data suggest that, although the RT data indicate there was some influence from the TMS on the mechanisms leading to the cuing effects, the cue did not significantly influence corticospinal excitability. Though the MEP data did not support the hypothesis that the mechanisms underlying the IOR effect are represented in M1, it did not necessarily contradict the evidence of a motoric view of IOR. It might just
suggest that the mechanisms underlying the IOR effect are coded in the motor system perhaps upstream from M1 – a discussion I turn to next.

4.3 Cortical Structures Involved in Inhibition of Return

Based on the findings from previous research, it was anticipated that M1 would play a role in coding the facilitatory and inhibitory mechanisms that lead to IOR and, as such, the pattern of MEP amplitudes would mirror the pattern of RTs; this was not the case. Although these data indicate that M1 may play a minimal role in IOR, it is suggested that other cortical structures involved in attention and motor planning such as the posterior parietal cortex (PPC) and pre-motor cortex (PrM) may be responsible for the mechanism underlying the IOR effect (Welsh et al., 2013). For instance, the PPC plays an important role in spatial attention (via salience maps) and producing planned movement (see Cisek, 2007, for a review). However, before an effective movement is initiated, salience maps of the environment must be maintained. These salience maps can be established and maintained in two ways: 1) bottom-up influences from early visual areas; and 2) top-down influences from the decision-making centers. Once the salience maps are established and maintained, they may play two important roles. First, they may be used to update the set of potential responses by changing the activity in response selection (PrM) and programming (M1) centers. Second, the salience maps may influence the activity in the decision-making centers (such as dorsolateral prefrontal cortex DLPFC), which are responsible for ensuring that, the individual responses to the correct stimulus (target) by initiating the “GO” signal (via excitation or disinhibition of the motor system) (Cisek, 2007).
In the context of the present cue-target task, the following series of events have been proposed (Welsh et al., 2013). When a cue is presented, it produces a wave of excitation that travels simultaneously from the visual cortices to ventral visual areas for identification and then to the PPC for response generation. Once this occurs, the PPC generates excitation in salience maps from the information from visual areas, indicating a potential area of interest to “draw attention” to that area of space. First, there is a rapid increase in excitation and, when a threshold is surpassed, the excitation flows to the decision-making center to activate an area of interest where a possible target has been presented and to the PrM and M1 to initiate response-producing activity. If the target subsequently appears at the cued location during this excitatory stage, then the processing of that stimulus will be efficient and a cued-target advantage will be observed in both RT and trajectories.

However, just as there is a rapid onset of excitation in the salience maps of PPC, there may also be a rapid decay (Welsh et al., 2013). This rapid decay may be a result of the level of excitation in the salience maps diminishing due to the short duration of the cue. Hence, salience maps in the PPC are returning or have already returned to baseline when the time from cue onset to target presentation increases. As a consequence, the processing of the target at the cued location is not facilitated by the uncued location and no cued-target RT emerges. On the other hand, the decay of response codes in the motor system is less rapid. Thus, due to the slower decay of the response codes, the response to the cue is still active and now co-exists with the newly activated target response at the moment of response initiation. Therefore, when aiming movements are required, these
response codes may actually cause movements to deviate towards the cued location on uncued target trials at short and medium cue-target intervals (Welsh et al., 2013).

With respect to IOR, as the SOA increases, there is adequate time for the ventral system to classify the cue as a “non-target” and transmit that information to the decision-making centers. From here the decision-making center updates its own salience map, which then decreases the level of excitation in the cells coding that region of space. This inhibitory process is then transmitted to the PPC so it can decrease the excitability of that region on the salience map and hinder future captures or shifting of attention and the processing of information from the region of space where the cue is presented. This inhibitory influence is received in the PPC and decreases the activity in this region of space to below a baseline level. Together, these decreases in activity for the regions of space in the salience maps in the PPC and frontal areas subsequently, slow the processing of information and the release of the “GO” signal resulting in an inhibition effect at targets at the cued location at SOA of 300ms and longer (Posner & Cohen, 1984).

The response selection and programming centers of PrM and M1 may be more resilient to change since the salience maps in PPC update them. Consequently, it takes more time to develop the transition from excitatory to inhibitory coding of the response to the cue. Thus, it appears that 200-300ms is required to develop sufficient inhibition in attention-dominated centres, which is consistent with results from Posner and Cohen (1984), but takes more time to influence response coding in motor-dominated systems of PrM and M1.

Recall the hypothesis that, if the IOR effect was clearly represented in M1, then both the pattern of RTs and amplitudes of MEPs in the left FDI should have been altered
in a similar fashion. Although, there were no meaningful changes in the excitability of M1 from the cue as revealed by the MEP data, there were changes in the RT as a result of the TMS. More specifically, there was a hemisphere/hand specific RT difference in which the facilitation was preserved and the inhibition delayed by the TMS. It is likely that these influences emerged, not because of coding in M1, but because of transmissions of the neural noise from the stimulated area in M1 to other areas such as PPC and PrM via reciprocal (“upstream”) connections. It is important to note here that the hemisphere/hand specific nature of the effect (only RTs to left targets and responses by the left hand were affected by the TMS) indicates the alteration in RTs was not a generalized effect due to TMS, but was localized to the hemisphere that was stimulated. Given the hemisphere-specific influence from the TMS in the RT data, it is suggested here that the mechanisms underlying the IOR effect are coded in the motor system but perhaps upstream from M1, such as PrM or PPC. Therefore, it may have been the case that the MEP data did not reflect the facilitation and IOR effect, but TMS of M1 affected the emergence of facilitation and IOR, because the stimulated area and associated corticospinal tracts were downstream of the cortical areas that are critically responsible for the IOR effect.

4.4 Limitations and Future Direction

Although the results of the current thesis present novel information regarding the mechanisms of facilitation and IOR, certain limitations to the current experiment should be addressed in future studies. One possible limitation and possible explanation for the absence of a significant reflection of the IOR effect on MEPs may have to do with the
stimulated hemisphere/hand system. In the present experiment, the right-hemisphere/left-hand system was stimulated to isolate the effect of TMS on M1. Due to the fact that the cortical structures in the left hemisphere have been reported to play a role in movement planning of both limbs (Frey, 2008; Johnson-Frey et al., 2004), we chose to stimulate the right hemisphere to adopt a more conservative approach. That is, if the left hemisphere is involved in coding movements for both the right and the left hand, then TMS may have interrupted movement planning of both hands and a hand/hemisphere specific effect could not have been distinguished from a generalized interference effect of TMS alone. However, it might be possible that our approach may have been too conservative. Because the role of the right hemisphere in movement planning in right-handed people is more limited than the left hemisphere, its level of activation may have not been adequate to bring about an observable difference in the MEP data. Although it is not certain that this is the reason no differences were present in the MEP data, it is recommended that future studies stimulate the left hemisphere/right-hand system to perhaps provide a more sensitive testing of the role of motor programming areas (M1) in IOR.

Another limitation that should be considered is the lack of a sham manipulation. A valid sham should simulate similar characteristics of TMS (acoustic artifact, scalp muscle stimulation, daily experimenter contact, expectations about efficacy and side effects), but not result in cortical stimulation (Lisanby, Gutman, Luber, Schroeder & Sackiem, 2001). Sham TMS is typically administered by tilting the coil 45-90° off the scalp, with the tips of one or two wings of the coil touching the scalp. Lisanby et al. (2001) recommend tilting the coil 90° from tangential rather than the 45° sham to minimize cortical effects by the outer boundaries of the magnetic pulse. Introducing a
sham condition would help to validate that TMS actually had an effect on RT and that the RT effects were not caused from an alerting or startling effect caused by the auditory and/or somatosensory stimulation associated with the TMS pulse. Thus, future work should include a 90° sham condition to confirm that results are reflective of a TMS effect and not simply an effect of the somatosensory experience associated with the TMS pulse.

Another possibility for the lack of neurophysiological evidence for the coding of the mechanisms of IOR in M1 may stem from task-related limitations. Recall that before the test even began, the TMS needed to be calibrated and the target motor hotspot mapped in an attempt to ensure that the same area of the cortex was stimulated on every trial. During this calibration and mapping, the participant was to remain as still as possible. Once the calibration and mapping was finished, the coordinates of the participant’s head (via the location of a rigid body marker on a headpiece worn by the participant) and the stimulating coil were used throughout the entire experiment to ensure accurate replacement of the coil and associated magnetic pulse. During the experiment, participants were instructed to mind the tracker on their headpiece and try to prevent unwanted movement of headpiece. However, it may have been the case that movement of the headband occurred during the experiment and allotted breaks, which may have caused the calibration to become offset. As a result, the optimal location of M1 may have been lost without the experimenter’s knowledge and a non-optimal location in M1 was being stimulated during testing. Thus, it is recommended that future studies standardize the task and employ re-calibrations at several points during testing to ensure the site of stimulation is consistent and accurate.
Lastly, there may have been issues with the task itself. Recall that participants were asked to abduct and then flex their index fingers to make a response. Participants were asked to respond in this way so that the activity of the FDI muscle (which is an abductor and flexor of the index finger) could be more effectively isolated in the response task. Because this is a more complicated and relatively non-standard movement (relative to a simple flexion-only keypress responses typically employed), the response may have challenged the motor system a little too much and affected the isolation of the neural processes that were of interest in the present study. Therefore, it is recommended that future studies utilize a different response technique that still isolates the FDI, such as a simple finger flexion, but that is less challenging for the motor system.

4.5 Conclusion

Many previous studies have focused on distinguishing sensory, attentional, and motor-based components of IOR. For the present study, a typical IOR task was adapted by including TMS over primary motor cortex to focus on and test motor accounts of IOR. Specifically, TMS was applied to the M1 of human participants and was used: 1) to induce a transient neural disturbance in M1 just prior to the target and response, and 2) as an indicator of corticospinal excitability while participants performed an IOR task using a non-predictive exogenous cue. It was hypothesized that, if IOR is represented in M1, then both the pattern of RTs and amplitudes of MEPs in the FDI should be altered in a similar fashion. It was found that, although TMS of M1 altered RTs, MEP data were not affected by the cue. The pattern of results indicated that MEP amplitudes were not significantly different across SOAs and hence, there was no apparent changes in corticospinal
excitability as the time from the cue increased. The critical finding was in the RT data where IOR was not present following TMS. Because the changes in the pattern of RTs were isolated to TMS of the hand being stimulated, this pattern of effects suggests a motor system contribution to the IOR effect. What remains in question is where exactly in the motor system the IOR effect is localized. Therefore, future research is necessary to determine where in the motor system the IOR effect is localized. It is recommended that future studies take into consideration the limitations outlined in this thesis (the stimulated hemisphere/hand system, sham manipulation and calibration and task-related limitations) and correct for them. Overall, the present research suggests a motor contribution to the IOR effect, but that further work is needed to clarify where in the motor system the mechanisms are operating.
References


Appendices

APPENDIX A: MEDICAL HISTORY QUESTIONNAIRE
FOR VOLUNTEERS PARTICIPATING IN STUDIES INVOLVING
TRANSCRANIAL MAGNETIC STIMULATION

SURNAME:............................ GIVEN NAMES:............................
DATE OF BIRTH:............................ SEX:.....................
ADDRESS:..............................................................................................
HOME PHONE:............................ WORK PHONE:............................

1. When was the last time you had a physical examination?

2. If you are allergic to any medications, foods or other substances, please name them.

3. If you have been told that you have any chronic or serious illnesses, please name them.

4. Have you been hospitalized in the past three years? Please give details.

5. During the past twelve months: Has a physician prescribed any form of medication for you? Y/N Have you experienced any faintness, light-headedness, blackouts? Y/N Have you occasionally had trouble sleeping? Y/N Have you had any severe headaches? Y/N Have you experienced unusual heartbeats such as skipped beats or palpitations? Y/N Have you experienced periods in which your heartbeat felt as though it were racing for no apparent reason? Y/N

6. At present: Do you experience shortness of breath or loss of breath while walking? Y/N Do you experience sudden tingling numbness or loss of feeling in your arms, hands, legs, feet or face? Y/N Do you get pains or cramps in your legs? Y/N Do you experience pain or discomfort in your chest? Y/N Do you experience any pressure of heaviness in your chest? Y/N Do you have diabetes? Y/N If yes, how is it controlled (please circle one)? Dietary means... insulin injector... oral medication... uncontrolled...

7. Have you ever been told that your blood pressure was abnormal? Y/N
8. How often would you characterize your stress level as being high (please circle one)? never...occasionally... frequently... constantly...

9. Have you ever undergone electro-convulsive-therapy (ECT)? Y/N

10. If you are female, are you or is there a chance you might be pregnant? Y/N

11. Have you ever experienced seizures or fainting spells? Y/N

12. Have you ever been told that you have any of the following illnesses? (please circle all that apply) myocardial infarction... arteriosclerosis... heart disease... heart block... coronary thrombosis... rheumatic heart... heart attack... aneurism... coronary occlusion... angina... heart failure... heart murmur...

13. Has any member of your immediate family been treated for or suspected of having any of the following conditions? Please identify their relationship to you (e.g., father, mother, etc.) (a) Epilepsy- (b) Stroke- (c) Diabetes- (d) Heart disease- (e) High blood pressure- (f) Memory loss- (g) Dementia-

14. Please list all operations or surgical procedures of any kind performed in the last 15 years. 1. 2. 3. 4. 5. 6

15. Have you ever been injured by any metallic foreign body (e.g., nail, bullet, shrapnel, etc.)? Y/N

16. Have you ever engaged in metal grinding? Y/N If yes, could metal fragments be present near your eyes? Y/N

17. Is there any history of head trauma with loss of consciousness? Y/N

18. Please indicate if you have any of the following: Cardiac pacemaker Y/N Aneurysm clips Y/N Implanted cardiac defibrillator Y/N Any type of biostimulator Y/N Any type of internal electrodes (e.g., cochlear implant) Y/N Insulin pump Y/N Any type of electronic, mechanical or magnetic implant Y/N Hearing aid Y/N Any type of intravascular coil filter or stent (e.g., IVC filter) Y/N Artificial heart valve prosthesis Y/N Orbital/eye prosthesis Y/N Any type of surgical clip or staple Y/N Intraventricular shunt Y/N Artificial limb or joint Y/N Dentures Y/N Any implanted orthopaedic item (e.g. pins, rods, screws, nails, clips, plates, wire) Y/N Any other implanted item Y/N
I certify that the above information is correct to the best of my knowledge. I have read and understand the entire contents of this form and I have had the opportunity to ask questions regarding the information on this form.

Volunteer's name

______________________________________

Volunteer's signature

______________________________________ Date: _____________________

Witness's name

______________________________________

Witness's signature

______________________________________ Date: _____________________
Appendix B: Participant and Testing Session Information

Date: __________________ Participant Number: __________ Age: __________

Gender (circle one): Female / Male

Vision (circle one): Normal / Corrected-to-normal

Do you wear corrective lenses of any kind?

If so, please wear them when you participate in the study.

Assessment of Mental Health

1) With a “yes” or “no” answer, please tell me if you have any pre-existing mental illnesses or disorders of the central nervous system. If your answer is “yes”, please do not provide any details.

2) With a “yes” or “no” answer, please tell me if you have had a concussion or other closed-head injury within the last 3 months. If your answer is “yes”, please do not provide any details.

Note: Potential participants must answer “no” to both of these questions in order to be allowed to enter into the study. When they arrive for the testing session, they will also be required to complete a more thorough Health Questionnaire.

Determination of Hand Dominance

Please answer these questions using the following scale:

Always the left hand - Mostly the left hand - Either hand – Mostly the right hand – Always the right hand

1) Which hand do you use to write with when you are writing with a pen?

2) Which hand do you use to throw a ball?
3) Which hand do you use to eat soup with a spoon?

4) Which hand do you use to brush your teeth?

5) Which hand do you use to hold a hammer when hammering a nail into a wall?

**Stimulation and Recording Details**

EMG Channel 1: Muscle__________ Estimate MEP P2P amplitude at rMT:______µV

EMG Channel 2: Muscle__________ Estimate MEP P2P amplitude at rMT:______µV

Resting motor threshold: _______% Number of MEPs >100 µV P2P: ________/10

Testing level (130% rMT): _______%
Appendix C: ANOVA Tables

Table 1
Test of Within-Subject Effects for a 2 Cue (left, right) X 2 Target (left, right) X 4 SOA (100, 300, 600, 1000 ms) X 2 TMS (TMS, no-TMS) Repeated Measures ANOVA using Response Time Data.

<table>
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<th>Source</th>
<th>df</th>
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<th>F</th>
<th>p</th>
<th>ηp²</th>
</tr>
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<td>.198</td>
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<tr>
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<td></td>
<td></td>
</tr>
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<td>.138</td>
<td>.161</td>
</tr>
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*df*, degrees of freedom; *MS*, mean square; *F*, F-Ratio; *p*, probability; *η²*, partial eta squared.

*, p ≤ 0.05; **, p ≤ 0.001.
Table 2
Test of Within-Subject Effects for a 2 Cue (left, right) X 2 Target (left, right) X 4 SOA (100, 300, 600, 1000ms) Repeated Measures ANOVA using only TMS Trials of Response Time Data.

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</table>

*df*, degrees of freedom; *MS*, mean square; *F*, F-Ratio; *p*, probability; *ηp²*, partial eta squared.
* *p*≤ 0.05; ** *p*≤ 0.001.
Table 3

Test of Within-Subject Effects for a 2 Cue (left, right) X 2 Target (left, right) X 4 SOA (100, 300, 600, 1000ms) Repeated Measures ANOVA using only non-TMS Trials of Response Time Data.

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<th>MS</th>
<th>F</th>
<th>p</th>
<th>ηp²</th>
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<td>.814</td>
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<tr>
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<tr>
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<td>24.850</td>
<td>.000**</td>
<td>.657</td>
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<tr>
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<td>6.437</td>
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<td>.331</td>
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<tr>
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<td>.540</td>
<td>.658</td>
<td>.040</td>
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</tbody>
</table>

*df*, degrees of freedom; *MS*, mean square; *F*, F-Ratio; *p*, probability; *ηp²*, partial eta squared.

*, *p* ≤ 0.05; **, *p* ≤ 0.001.
Table 4

Test of Within-Subject Effects for a 2 Cue (left, right) X 2 Target (left, right) X 4 SOA (100, 300, 600, 1000ms) Repeated Measures ANOVA using Actual MEP Data.

<table>
<thead>
<tr>
<th>Source</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>p</th>
<th>ηp²</th>
</tr>
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<tbody>
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<td>Source</td>
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<tr>
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<td>.035</td>
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<tr>
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<tr>
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<td>SOA</td>
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<td>.541</td>
<td>.053</td>
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<td></td>
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<td>.739</td>
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<td>.054</td>
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<td>.600</td>
<td>.619</td>
<td>.044</td>
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<tr>
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<tr>
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</tr>
</tbody>
</table>

*df*, degrees of freedom; *MS*, mean square; *F*, F-Ratio; *p*, probability; *ηp²*, partial eta squared.

*, *p* ≤ 0.05; **, *p* ≤ 0.001.
Table 5
Test of Within-Subject Effects for a 2 Cue (left, right) X 2 Target (left, right) X 4 SOA (100, 300, 600, 1000ms) Repeated Measures ANOVA using Normalized MEP data

<table>
<thead>
<tr>
<th>Source</th>
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<th>MS</th>
<th>F</th>
<th>p</th>
<th>ηp²</th>
</tr>
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<td>.797</td>
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<tr>
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<td>.096</td>
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<tr>
<td>Error(SOA)</td>
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<td>.044</td>
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<td></td>
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<tr>
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<td>.055</td>
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<td>Cue Location*SOA</td>
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<td>1.590</td>
<td>.207</td>
<td>.109</td>
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<tr>
<td>Error(Target Location*SOA)</td>
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<td>.043</td>
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</tbody>
</table>

*df*, degrees of freedom; *MS*, mean square; *F*, F-Ratio; *p*, probability; *ηp²*, partial eta squared.
* *, *p* ≤ 0.05; **, *p* ≤ 0.001.
<table>
<thead>
<tr>
<th>Source</th>
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<th>F</th>
<th>p</th>
<th>η²</th>
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<tr>
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<td>0.019</td>
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<td></td>
</tr>
</tbody>
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*df*, degrees of freedom; *MS*, mean square; *F*, F-Ratio; *p*, probability; *η²*, partial eta squared.

*, *p* ≤ 0.05; **, *p* ≤ 0.001.