TRANSCRANIAL MAGNETIC STIMULATION OF EARLY VISUAL CORTEX DURING TRANS-SACCADIC INTEGRATION OF OBJECT FEATURES

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A THESIS SUBMITTED TO
THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTERS OF SCIENCE

GRADUATE PROGRAM IN BIOLOGY
YORK UNIVERSITY
TORONTO, ONTARIO

March 2014

ABSTRACT

Visual information is integrated across saccades to maintain a continuous spatiotemporal representation of the world. This study investigated the role of early visual cortex (EVC) in trans-saccadic integration using functional magnetic resonance imaging guided repetitive transcranial magnetic stimulation (rTMS) protocol. Triple-pulse rTMS was applied over left and right EVC during the *fixation task* (participants maintained gaze), and *saccade task* (participants made an eye movement that either maintained or reversed the visual quadrant of the test stimulus). rTMS had no effect when 1) fixation was maintained, 2) saccades kept the stimulus in the same visual quadrant, or 3) quadrant corresponding to the first Gabor patch was stimulated. However, rTMS affected performance (relative to opposite EVC rTMS) when saccades brought the remembered visual stimulus into the magnetically stimulated quadrant. This effect increased with saccade amplitude. These results show that EVC is involved in the memory and 'remapping' of visual features across saccades.

ACKNOWLEDGEMENTS

Sincere thanks to Dr. J. Douglas Crawford for accepting me as a graduate student in his research laboratory and giving me an opportunity to be a member of his research team. He also provided me with continued support and feedback on my work.

A special thanks to Dr. Joost C. Dessing for providing me with the essential hands-on training with laboratory equipment, generous support, advise, feedback and assistance in developing and executing my projects. Thanks to Dr. Keith A. Schneider for providing the functional localizer stimulus program code. Thanks to Saihong Sun for technical assistance and programming of the TMS/Psychophysics stimulus.

I would also like to thank all members of the Crawford lab for their support. This project was funded by the Natural Science and Engineering Research Council of Canada (NSERC) DISCOVERY grant.

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CHAPTER 1

GENERAL INTRODUCTION

1.1 Overview

In the natural world, visual information is distributed over a large spatial range and in order to process this information, we make eye movements from one object of interest to another. This allows objects of interest to be projected on the fovea. In fact, during natural viewing, our eyes are never still (Melcher and Colby 2008). Humans make 3-5 rapid eye movements, known as saccades per second (Rayner 1978; Rayner 1998; Ibbotson and Krekelberg 2011; Prime et al. 2011; Ahissar and Arieli 2012). This means that we process the visual world in chunks of approximately 200-300 millisecond (ms) fixations (Rayner 1978; Rayner 1998). Furthermore, this causes the image of the world to change its position on the retina as one moves his/her eyes from one point in the visual scene to another (Merriam et al. 2007). Regardless of such change in position of retinal images, we continue to perceive the world in a coherent and stable manner. This phenomenon is known as *spatial constancy* or *visual remapping* during which stable representations of the visual world acquired during moments of brief fixations in between eye movements are combined to lead to a coherent and stable visual perception (Irwin 1996; Colby and Goldberg 1999; Merriam et al. 2007). It allows us to integrate information across distinct fixations and used information predictably to avoid processing delays.

The process of *trans-saccadic perception* (TSP) consists of two steps: 1) *Trans-saccadic memory* during which visual information acquired during the brief moments of fixation is stored in memory, and 2) *Trans-saccadic integration* (TSI) during which visual information from trans-saccadic memory is fused together. As such, a combination of these two steps leads to an undisrupted, continuous perception of the world (Prime et

al. 2008; Prime et al. 2011). Recent research in humans has provided further evidence of a role of the striate cortex in the process of visual remapping and that the extrastriate visual areas have access to the remapped spatial information (Merriam et al. 2007). A handful of studies have investigated the role of the early visual cortex (EVC) in visual perception and memory representations using transcranial magnetic stimulation (TMS) in healthy human participants (De Weerd et al. 2012; van de Ven et al. 2012; van de Ven and Sack 2013), and have found a key role of EVC in memory representations, especially with higher memory loads (3 targets) during fixation in comparison to a low memory load (1 target) condition (van de Ven et al. 2012). As such, EVC has been shown to be involved in short term memory of object feature information. However, no one has yet shown how the EVC contributes to the process of spatial remapping of visual features, by using a saccade task paradigm.

1.2 Visual Input and Processing Pathways

The visual system plays a key role in generating an internal representation of the world where one assigns meaning and significance to the external world. This ability is often referred to as *perception* (Milner and Goodale 1995). Perception is possible via processing of visual information which takes place at different parts of the brain (Figure 1.1; Page 9). Overall, visual processing occurs in various stages including encoding of visual information, manipulation or transformation of visual information and guiding actions (Milner and Goodale 1995; Kalat 2008). Light from the environment is projected onto the retina that consists of unevenly distributed photoreceptors (rods and cones) on its interior surface (Milner and Goodale 1995; Kalat 2008). Photoreceptors (cones) that are

specialized for colour vision and high visual resolution are mainly concentrated in the fovea (Kalat 2008). This allows for computations of various visual signals to take place within the retina before this information is transformed into action potentials that make their way to the brain (Milner and Goodale 1995). Additionally, this processed information is passed onto the brain via various types of cells in a heterogeneous manner (Milner and Goodale 1995; Ibbotson and Krekelberg 2011). Axons of some ganglion cells carry information regarding spatial distribution of light whereas other axons carry information on temporal dynamics (Milner and Goodale 1995). This information is then projected to the lateral geniculate nucleus (LGN) which functions as a relay centre. The LGN consists of six layers (three from the right eye and three from the left eye) that can be further divided into magnocellular and parvocellular pathways (Milner and Goodale 1995). The magnocellular system is colour blind, relatively fast, has high contrast sensitivity, low spatial resolution and receives input from parasol ganglion cells whereas, the parvocellular system is colour sensitive, relatively slow, has low contrast sensitivity, high spatial resolution and receives information from midget ganglion cells. These two systems stay separate as they progress towards the EVC (Milner and Goodale 1995).

Early visual cortex is a crucial brain region where the earliest visual processing takes place. Moreover, it can be further broken down into various subregions including visual area 1 (V1) which is specialized for detecting orientation and edges (Hubel and Wiesel 1959; Hubel and Wiesel 1968; De Valois et al. 1979); visual area 2 (V2) which is specialized for processing of colour, binocular cues and form (Livingstone and Hubel 1988); visual area 3 (V3) which is responsible for the processing of global motion (Braddick and O'Brian 2001); visual area 4 (V4) which is specialized for the processing

of colour and task (De Valois et al. 1993), and visual area 5 (V5) which is specialized for the processing of motion (Kreiter and Singer 1996). One of the earliest neurophysiology studies related to early visual cortex was conducted by Hubel and Weisel (1959) where the receptive fields of the striate cortex in cats was stimulated to study the excitatory and inhibitory areas. Another study by Hubel and Weisel (1968) obtained single unit recordings from cat striate cortex and revealed evidence of activation in response to specific spatial location and orientation. Overall, these results established the role of area V1 in orientation discrimination and provided evidence of neuronal specialization. Another neurophysiology study revealed that damage to visual cortical areas via bilateral removal in cats resulted in long-lasting deficits in performance on tasks related to pattern and form discrimination (Spear and Baumann 1979). However, certain abilities that are initially lost due to damage of visual areas can be recovered via retraining (Spear and Baumann 1979).

The overall visual input pathway can be separated into two distinct pathways: 1) *ventral pathway* (what) functions in object identification and projects information from the visual cortex to the temporal cortex for object perception (Figure 1.1; Page 9), and 2) *dorsal pathway* (where; how) functions in spatial localization and projects visual information to posterior parietal cortex (PPC) for spatial perception and visuomotor actions (Figure 1.1; Page 9) (Goodale and Milner 1992; Milner and Goodale 1995; Prime et al. 2011). As such, the dorsal pathway is thought to feed into PPC and the ventral pathway is thought to feed into the inferotemporal cortex (Milner and Goodale 1995). It is also believed that the reason for the two distinct pathways is that each transforms incoming visual information for different purposes (Milner and Goodale 1995).

At present, there are two main hypotheses regarding the integration of information from the ventral and dorsal pathways. First, based on the traditional view of the visual system, it was believed that processing of visual information occurred via *bottom-up, feedforward connections,* allowing the ventral and dorsal pathways to function independently as visual information was projected from the retina to higher cortical areas (Figure 1.2; Page 10; Lamme and Roelfsema 2000; Bullier 2001; Hochstein and Ahissar 2002; Ro et al. 2003; Prime et al. 2008; Prime et al. 2010; Prime et al. 2011; de Graaf et al. 2012). Second, recent research has provided concrete evidence of the contributions of *top-down, re-entrant feedback connections* allowing for the integration of visual feature information from the ventral stream and spatial remapping signals from the dorsal stream as visual information is projected from higher cortical areas to EVC for visual perception (Figure 1.2; Page 10; Beckers and Homberg 1992; Cowey and Walsh 2000; Pascaul-Leone and Walsh 2001; Ro et al. 2003; Silvanto et al. 2005; de Graaf et al. 2012). Several TMS studies have provided evidence for early TMS effects (Corthout et al. 1999; Paulus et al. 1999; Kammer et al. 2003; Laycock et al. 2007; de Graff et al. 2012) and late TMS effects (Heinen et al. 2005; Camprodon et al. 2010; de Graff et al. 2012) over the EVC has been shown to have a masking effect on performance during various visual tasks involving low level visual feature perception. As such, the distinction between feedback and feedforward streams of visual information matches the notion of two potential TMS masking dips, however the specific timings of these effects still remains unclear (de Graaf et al. 2012).

These models have been seen in the anatomical connections of the primate brain where the two streams project signals via parallel pathways converging in pre-frontal regions as well as lateral connections between the temporal and parietal cortices (Petrides

and Panday 1984; Goldman-Rakic 1988; Baizer et al. 1991; Felleman and Van Essen 1991; Webster et al. 1994; Prime et al. 2011). In addition, visual cortex is seen as the initial and lowest stage of feedforward visual hierarchy due to its small receptive fields, simple nature of response properties and early timings of response to visual input (Hubel and Wiesel 1977; Bullier 2001; Juan and Walsh 2003). In contrast, feedback pathways from secondary visual areas to V1 have been shown to engage in complex interactions. According to the reverse hierarchy theory, feedback connections to V1 have been proposed (Ahissar and Hochstein 2000). The theory proposes that higher visual areas carry out preliminary analysis of visual attributes and V1 provides detailed analysis of fine structure and spatial localizations (Juan and Walsh 2003).

Similarly, previous TMS studies have shown that back projections from V5 to V1 play an important role in awareness (Cowey and Walsh 2000; Pascual-Leone and Walsh 2001; Juan and Walsh 2003; Ro et al. 2003). Cowey and Walsh (2000) tested the role of area V5 in the absence of area V1 in conscious visual impressions of moving stimuli. Six fully sighted subjects and three peripherally blind subjects were tested using a moving stimulus in a phosphene localized TMS experiment. Area V5 is essential for normal perception of visual motion. However, in the absence of major inputs from V1, activity in area V5 alone, induced by TMS was found to be insufficient to generate a visual percept of movement in the contralateral field defect (Cowey and Walsh 2000).

Top-down processing relies on memory and knowledge stores. In this case, understanding is based on a general context and previous knowledge and experience with the world is used to fill in the gaps to form a clear perception (Goldstein 2010). Alternatively, *bottom-up processing* relies on information from sensory receptors and

uses incoming information as a starting point for perception. Therefore, bottom-up processing plays a crucial role in perception and top-down processing may follow once sensory receptors are activated via bottom-up processing. For example, when a patient presents a doctor's prescription to a pharmacist (which may appear as unreadable squiggles to an ordinary person), the pharmacist uses sensory visual information from the retina (bottom-up processing) in combination with his/her knowledge of the drugs and previous experience with this doctor's handwriting (top-down processing) to understand the squiggles (Goldstein 2010).

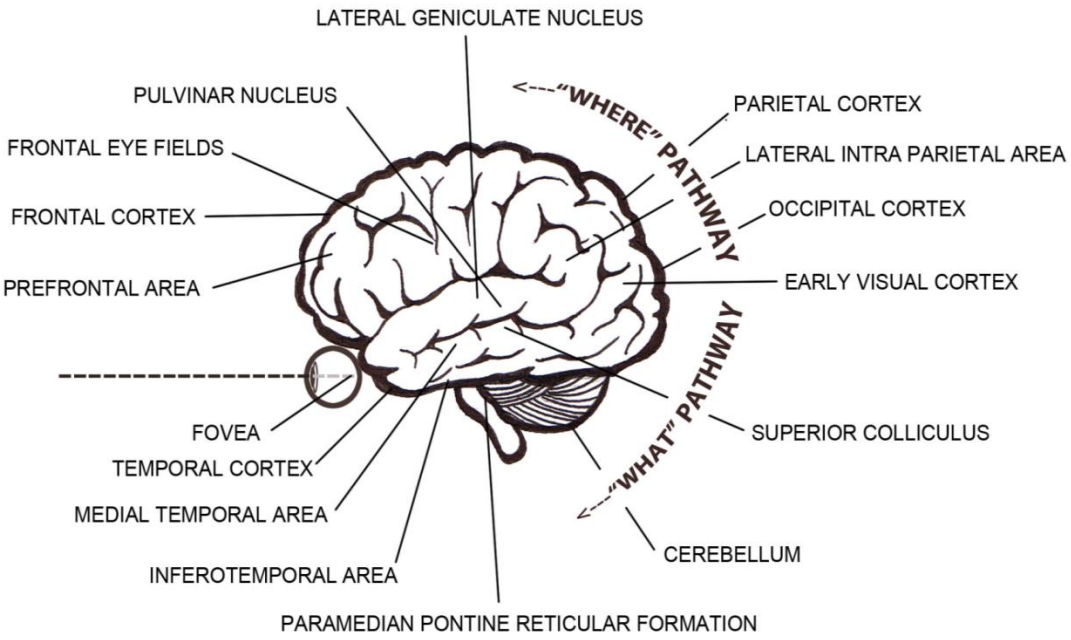


Figure 1.1: Major brain areas involved in visual input and processing pathways.

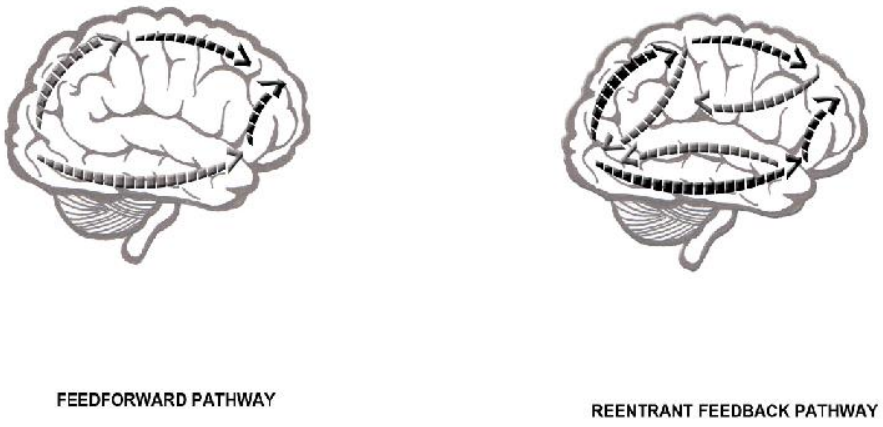


Figure 1.2: Illustration of the flow of visual information via **a)** feed-forward pathway and **b)** re-entrant feedback pathway.

1.3 Visual Short Term Memory (VSTM)

Visual short term memory (VSTM) is an active system that temporarily saves and updates visual information for a period of a few seconds (Jackson et al. 2008; Silvanto and Cattaneo 2010). Information about the world is maintained in VSTM to enable a coherent perception of the world (Jackson et al. 2008). In fact, VSTM allows for sensory information to be translated into a more durable representation that is longer than the physical availability of the visual input by a few seconds (Silvanto and Cattaneo 2010). Serences et al. (2009) showed that activation patterns in V1 during the delay period in a short term working memory task greatly depends on the visual features that subjects are asked to maintain. For instance, high levels of activation were seen when subjects were asked to remember stimulus orientation in comparison to when they were asked to remember stimulus colour. This confirmed that low level visual areas such as area V1 can retain specific visual feature information in working memory for periods of a few seconds, even when the stimulus is no longer physically present during the memory intervals (Pearson et al. 2009; Harrison and Tong 2009; Serences et al. 2009). Furthermore, research has shown that TMS can preferentially activate neurons involved in VSTM maintenance of static stimulus (Cattaneo et al. 2009; Silvanto and Cattaneo 2010), whereas several other studies have shown that TMS tends to have disruptive effects on VSTM of visual motion priming paradigms (Campana et al. 2002; Campana et al. 2006). In a fMRI study by Soto et al. (2007), increased levels of activation of occipital areas were seen upon reappearance of stimulus being held in VSTM.

The concept of working memory was introduced by Baddeley and Hitch (1974) who proposed that it consists of a central executive system that allots limited attention

resources to maintain and manipulate information in two memory buffers. The first one consists of a phonological loop for maintaining verbal information and the second consists of a visuo-spatial sketchpad for maintaining visual information (Baddeley and Hitch 1974). The capacity of VSTM is debatable as it depends on various factors including duration of maintenance, stimulus complexity and attention resources (Cowan 2001; Vogel et al. 2001; Stevanovski and Jolicoeur 2007; Bays and Husain 2007; Sligte et al. 2008; Silvanto and Cattaneo 2010). However, recent research has shown that VSTM has a limited capacity of about four to five items for simple features (Olson and Chun 2000; Olson and Jiang 2002; Prime et al. 2008). It is also believed that the active maintenance of visual stimuli in short term memory storage is possible due to activation of cortical regions that also encode input (Silvanto and Cattaneo 2010). Most importantly, VSTM acts as a bridge between immediate encoding and appropriate behavioural actions. Additionally, studies have shown that it could be greatly influenced by emotions (Mikels et al. 2005; Perlstein et al. 2005; Jackson et al. 2008) and is poor for unattended information (Olson and Chun 2000).

At present, there are two main theories related to VSTM known as 1) *Object-based theory* which suggests that conjoining multiple features of a single object into a single chunk allows for greater features to be attended without additional costs or interference; and 2) *Multiple resources theory* suggests that VSTM works with separate pools of information for remembering different features. Furthermore, there are three main hypotheses regarding VSTM capacity limits: 1) *Strong object hypothesis* suggests that VSTM capacity limits are on the basis of the number of objects; 2) *Strong feature hypothesis* suggests that VSTM capacity limits are based on the number of features; and 3) *Weak object hypothesis* suggests that VSTM capacity limits are based on the number

of features but such features can be conjoined into larger chunks to allow for an overall greater number of features to be stored in VSTM (Olson and Jiang 2002). In contrast to the notion of VSTM, O'Regan (1992) suggested that people do not need to store detailed visual representations of the world in a memory store since they can always refer back to the outside world as an external information store.

Additionally, it is important to note that the terms VSTM and trans-saccadic memory refer to different forms of memory stores which may be used in the process of TSI. Trans-saccadic memory consists of a short lived, high capacity memory store related to sensory processes, whereas VSTM is a limited capacity store where information can be held for upto a few seconds which is related to cognitive processes (Kerzel and Zieglar 2005). Trans-saccadic memory refers to the process by which visual system maintains spatial location and visual features of objects across eye movements (Irwin 1991). A summation of images stored in trans-saccadic memory during discrete periods of fixations allows us to experience stable visual world (Irwin 1991). This distinction will be maintained throughout the writing of this thesis and an emphasis will be placed on trans-saccadic memory, as one of the steps in the process of trans-saccadic perception.

van de Ven et al. (2012) conducted a TMS experiment with a fixation task using a shape discrimination paradigm with low (1 stimuli) and high (3 stimuli) memory loads. Results showed that TMS induced memory-consolidation interference at 200 ms, further implicating a role of EVC in short-term memory consolidation of sensory visual information. However, to our knowledge, no previous study has investigated the functional role of EVC in spatial remapping and trans-saccadic perception using a *saccade task* paradigm that requires the subjects to make an eye movement. Moreover,

previous studies that have attempted to investigate the role of EVC using a TMS paradigm made use of varying TMS coil positioning techniques. In such studies, TMS coil was placed over the EVC relative to the inion or via generation of phosphenes at a certain position of the visual field (Pascaul-Leone and Walsh 2001; Boyer et al. 2005; Silvanto et al. 2005). Even though such studies show robust effects of post-saccadic TMS on visual perception (Amassian et al. 1989; Prime et al. 2008; Prime et al. 2010; Thielscher et al. 2010; de Graaf et al. 2012), precise conclusions about the targeted cortical structures is still unclear. As such, consistent with recent findings that EVC is involved in short-term visual memory (Harrison and Tong 2009; van de Ven et al. 2012) and remapping of visual targets during saccades (Merriam et al. 2007), I have proposed that EVC is also involved in TSI of visual features such as orientation (Prime et al. 2008; Prime et al. 2010). The aim of this thesis was to test this hypothesis with the use of a combined fMRI-TMS protocol and provide further support regarding whether EVC plays a functional role in TSI.

VSTM can be broken down into 3 phases, namely encoding, maintenance and retrieval (Todd and Marios 2004). The storage capacity of the VSTM is thought to be limited. Todd and Marios (2004) scanned 17 subjects to investigate the neural basis of VSTM storage capacity limits. Participant's accuracy in VSTM task declined as the number of stimuli decreased. Activation was seen in the intraparietal sulcus, posterior parietal cortex, anterior cingulate cortex, and ventro-occipital cortex. Similar patterns of activation were also reported in previous functional magnetic resonance imaging studies (Harrison and Tong 2009; Serences et al. 2009; Riggall and Postle 2012). Serences et al. (2009) demonstrated higher activation in area V1 during the delay periods in an

orientation discrimination task. These fMRI results further suggested that human early visual areas can retain visual feature information in working memory for a period of few seconds after the disappearance of the stimulus (Serences et al. 2009). Furthermore, a TMS study by Silvanto and Cattaneo (2010) investigated whether TMS has influence over VSTM. TMS was found to activate neurons engaged in VSTM in V5/MT+, suggesting that TMS could transfer information from VSTM to conscious perception and visual awareness (Silvanto and Cattaneo 2010).

1.4 Saccades

Previous research has shown that eye movements are not random but are rather strategically made to areas of interest within a visual scene (Walker-Smith 1977; Underwood 1998). Eye movements serve two important functions: 1) stabilize images on the retina, and 2) shift gaze on an object of interest (Müri et al. 2002). Saccadic eye movements are used for visual exploration and allows for the alignment of new objects onto the fovea as one moves his/her eyes from one object to another (Müri et al. 2002;). Saccades are often known as ballistic eye movements since their trajectory and velocity is pre-programmed and cannot be altered once a saccade has begun (Purves et al. 2001). Such eye movements are rapid and can vary greatly in size (Purves et al. 2001). Furthermore, it takes about 200 milliseconds (ms) for an eye movement to begin, known as *saccade latency* since this time is required for the position of the target with respect to the fovea to be computed in order to determine how far the eye has to move (Purves et al. 2001).

Visual information from the retina is relayed to the lateral geniculate nucleus (LGN), followed by the early visual cortex (V1-V3), where preprocessing of the visual information takes places (Figure 1.1; Page 9). In the primary visual cortex, activity is dependent on the location of the visual stimulus presentation, relative to gaze. The superior colliculus (SC) is thought to play an important role in saccade initiation (Sparks et al. 2000). Neurophysiology studies in rhesus monkeys confirmed neuronal coupling between high-frequency pre-saccadic burst of collicular neurons and saccade onset (Sparks 1978; Sparks et al. 2000). Frontal eye fields (FEF) is also seen to have high bursts of neuronal activity, similar to SC (Dias and Bruce 1994; Sparks et al. 2000). Activity in the lateral intraparietal area (LIP), a subdivision of the parietal cortex has been seen in response to the attention to specific locations in visual space and intention to make saccadic eye movements.

1.5 Spatial Updating and Remapping

The position of stationary objects on the retina changes with each eye movement, yet we are able to perceive the world as stable. This is possible due to the phenomenon of spatial updating or remapping, a neural mechanism that compensates for shifts in the retinal image caused by voluntary eye movement (Merriam et al. 2007; Ryan et al. 2007). The brain constructs a stable representation of the visual world by combining information about voluntary eye movements with sensory information from the visual system (Merriam et al. 2007; Ryan et al. 2007). There are three primary functions of spatial remapping including providing support for action control, sensorimotor adaptation and spatial memory (Bays and Husain 2007).

Early studies in monkey parietal cortex revealed neuronal activity related to spatial updating across eye movements. Additionally, neuronal activity was also seen in the lateral intraparietal area (LIP), a region in the dorsal visual pathway. Duhamel et al. (1992) conducted a study to test whether this region might also be involved in remapping object locations across saccades. LIP neurons are known to have receptive fields which are tied to retinal coordinates, similar to classic receptive fields (Bays and Husain 2007). Duhamel et al. (1992) found that visual receptive field for some LIP neurons shifted just before a saccade, from their normal retinal location to the location that the receptive field would occupy after a saccade.

Recent neuroimaging research in humans has provided further evidence of a role of the striate cortex in the process of visual remapping and that the extrastriate visual areas have access to the remapped spatial information (Merriam et al. 2007). Additionally, single-unit recording studies have also indicated a key role of the neurons in monkey lateral intraparietal cortex (LIP) for the process of visual remapping (Goldberg et al. 1990; Duhamel et al. 1992; Gottlieb et al. 1998; Kusunoki et al. 2000; Heiser et al. 2005; Merriam et al. 2007). A majority of LIP neurons were found to have a burst in activity during visual remapping tasks and reversible inactivation of LIP had detrimental effects on performance on tasks that required updated spatial information (Li and Anderson 2001). Remapping has also been observed in the FEF and superior culliculus (Merriam et al. 2007). In the past, remapping has been extensively studied in cortical areas involved in eye movements and attention (Merriam et al. 2007). However, more recently, it has been hypothesized that if remapping is important for perceptual stability, then updated spatial information should reach spatial areas that are involved in the

process of visual perception (Merriam et al. 2007). Merriam et al. (2007) conducted a fMRI study with humans to test the hypothesis regarding the ability of the extrastriate visual areas in humans to access remapped spatial information. Subjects were required to perform a single-step saccade task similar to the ones seen in various neurophysiology studies (Nakamura and Colby 2002) and two control tasks including stimulus only fixation task and saccade only task (Merriam et al. 2007). A strong evidence for remapping in the striate cortex and all of the examined extrastriate visual areas including a strong pattern of activation in areas V3A and V4 and a comparatively lower level of activation in areas V3, V2 and V1 was found (Merriam et al. 2007). These findings were similar to the observations of previous neurophysiology studies (Nakamura and Colby 2002). As such, these results provided further evidence that updated visual representations are present in cortical areas linked to visual perception (Merriam et al. 2007). Furthermore, remapping in the visual cortex is believed to be due to extensive interconnections between LIP and extrastriate visual cortex (Anderson et al. 1990; Blatt et al. 1990; Morel and Builler 1990; Baizer et al. 1991; Merriam et al. 2007). Remapping is also found to be more robust in higher order visual areas such as V3A and V4 in comparison to the lower level visual areas including V1, V2 and V3 (Merriam et al. 2007).

Thalamic and frontoparietal lesions in humans have found to result in deficits on a double-step saccade task, leading to impairments in remapping of the location of the second target after the first saccade has been executed (Colby and Goldberg 1999; Bellebaum et al. 2005). Findings from neuroimaging studies point to a role of dorsal parietal region, homologous to monkey area LIP in spatial remapping. Such studies

found evidence of remapping of remembered spatial locations across the hemispheres, from one parietal region to the other when a saccade reverses the location of a remembered location relative to fixation (Medendorp et al. 2003; Merriam et al. 2003).

1.6 Trans-saccadic Memory and Integration

Visual information is acquired during the brief moments of fixation and is stored in *trans-saccadic memory* (Figure 1.3b; Page 22). These discrete bits of visual information are fused together during a process of *trans-saccadic integration* (Figure 1.3c; Page 22). A combination of these two steps leads to an undisrupted, continuous perception of the world, known as *trans-saccadic perception* (Figure 1.3a; Page 22; Prime et al. 2008; Prime et al. 2011). Real world perception and daily activities including face-to-face interaction with others, walking and reading all requires this complex process to integrate spatially and temporally discontinuous visual sensory input (Melcher and Colby 2008). As a result of research over the last few decades, three main theoretical points have been concluded: 1) perception across eye movements does not rely on fusion of patterns across saccades, especially when the position and orientation changes over time relative to the viewer (Jonides et al. 1982; Bridgeman and Mayer 1983; Pollatsek et al. 1990; Irwin 1991; Melcher and Colby 2008) 2) rather than any special saccade related mechanisms, trans-saccadic perception relies on a visual short term memory that is also thought to have a capacity of around 3-4 complete object, however this value is debatable as it depends on the complexity of object details (Irwin 1991; Magnussen 2000; Alvarez and Cavanagh 2004; Melcher and Merrone 2007; Melcher and Colby 2008), and 3) a final group of theories state that little or no information is maintained across saccades,

such as that seen in the studies of change detection with complex scenes (Rensink 2000; O'Regan and Noe 2001; Melcher and Colby 2008).

There are three main theories on how the brain does TSI and integrates visual information across eye movements. First, it is thought that perception across eye movements is similar to superimposing different patterns from separate fixations (Jonides et al.; 1982; Pollatsek et al. 1990; Melcher and Colby 2008). However, it is now known that visual information is not fused across saccades (Bridgeman and Mayer 1983; Irwin 1991), especially in conditions that result in changes in the position and/or orientation of the object (Melcher and Colby 2008). Second, it is believed that visual information obtained from distinct fixations is temporarily stored in visual short term memory. Several studies have been done to determine the capacity of this working memory, by measuring our ability to detect changes in different patterns separated by a blank delay of a few seconds (Irwin 1991). In fact, studies conducted in our lab have provided evidence that the capacity of the visual working memory is 3-4 objects (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011). As the memory load increases beyond this point, subject's ability to retain visual feature information depreciates (Magnussen 2000; Alvarez and Cavanagh 2004; Melcher and Morrone 2007; Prime et al. 2008; Prime et al. 2010; Prime et al. 2011). Third, it may be possible that little or no visual information is maintained across saccades (Rensink 2000; O'Regan and Noe 2001). Studies involving change detection with complex scenes during the time of a saccade provide evidence for these theories (Melcher and Colby 2008). Given the existing framework of such theories of TSI, Melcher and Colby (2008) proposed that the visual system combines predictive and useful visual information across saccades.

Furthermore, during visual processing, spatial selectivity and stimulus of the receptive fields are thought to be constant (Melcher and Colby 2008). During trans-saccadic perception, neurons whose receptive fields cover a given stimulus location respond to it. During a saccadic eye movement, a corollary discharge of the eye movement command results in a transfer of the stored stimulus information to neuron whose receptive fields encode for the new location of the stimulus following the eye movement (Melcher and Colby 2008). This process is known as remapping and emphasizes a shift of visual information from the coordinates of initial eye position to those of the final eye position (Melcher and Colby 2008). As such, activity is seen in neurons that were not part of the classical receptive field. However, the neural mechanisms underlying the process of remapping are not yet fully understood. Recent research has revealed a role of the lateral intraparietal sulcus (Goldberg and Bruce 1990; Umeno and Goldberg 1997; Melcher and Colby 2008), FEF (Goldberg and Bruce 1990; Umeno and Goldberg 1997; Melcher and Colby 2008), EVC (Nakamura and Colby 2002; Melcher and Colby 2008), and SC (Walker et al. 1995; Melcher and Colby 2008). SC is the believed to a source of the corollary discharge is then relayed to FEF via the thalamus. The role of the parietal and visual cortex is still under investigation (Melcher and Colby 2008). Additionally, remapping can take place for saccades in any direction and magnitude, meaning that neurons have potential action to visual information anywhere in the visual field (Melcher and Colby 2002). Future research is needed to study the connectivity and mechanisms of the receptive fields (Melcher and Colby 2008).

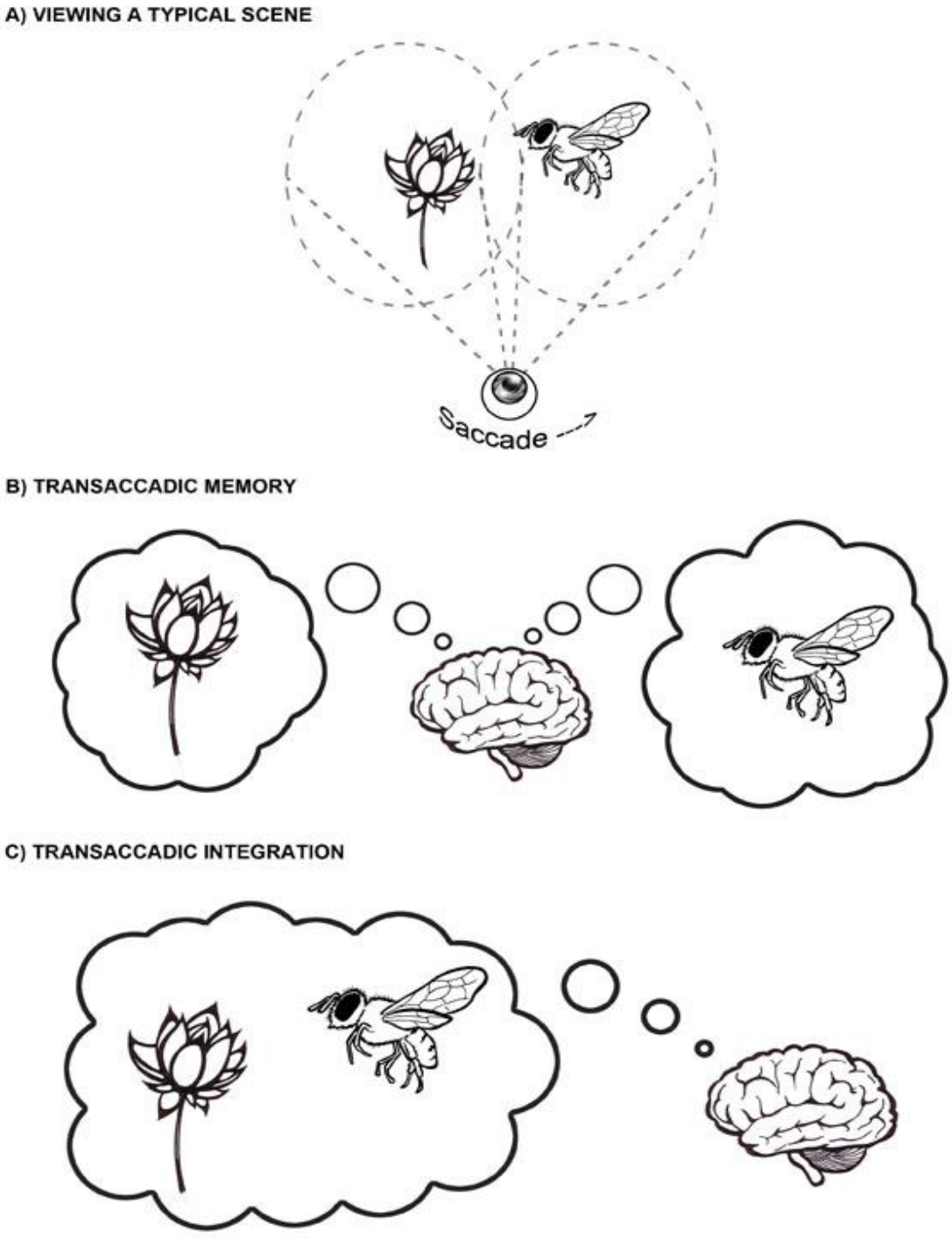


Figure 1.3: Illustration of the process of trans-saccadic perception (TSP): **a)** an example of a typical scene, **b)** trans-saccadic memory where distinct visual information is stored temporarily, and **c)** trans-saccadic integration of the distinct visual information which leads to a coherent and continuous perception of visual world.

1.7 Purpose of current thesis

In this thesis, I investigated the functional role of the human EVC in spatial remapping using a fMRI guided TMS protocol. I hypothesized that if EVC plays an important role in integrating visual feature information to help maintain spatial constancy, TMS over this region would alter participant's abilities to perform a visual feature (i.e. orientation) discrimination task. The saccade and fixation conditions used for this experiment allowed for a rigorous investigation of the functional role of EVC (and/or its network connections). The data collected for this experiment allowed us to answer the following questions: 1) Are there hemifield-specific effects of TMS on the ability of the subjects to remember and integrate low-level visual feature information when presented at a low memory load?; 2) Are TMS effects dependent on saccade size and/or target eccentricities? The answers to these questions will allow us to provide further support for either the feedforward or the re-entrant feedback pathways and provide causal evidence for a role of human EVC during trans-saccadic perception.

Previous research conducted in our lab showed that subjects made significantly greater errors during saccade and fixation tasks when TMS was administered over the right parietal eye fields as well as right and left frontal eye fields (FEF) (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011), further suggesting that TSI requires integrating information from the dorsal and ventral visual streams. Other research has also shown evidence for a masking effect of TMS at 100 ms post stimulus (Amassian et al. 1989; Prime et al. 2008; Prime et al. 2010; Thielscher et al. 2010; de Graaf et al. 2012), providing support for the re-entrant feedback activity from higher areas (Amassian

et al. 1989; Thielscher et al. 2010). However, this hypothesis is still under debate and many argue a special role for EVC, especially area V1 in visual awareness (Thielscher et al. 2010; de Graaf et al. 2012).

Here, I investigated the functional role of the human EVC in spatial remapping using TMS. I hypothesized that if EVC plays an important role in integrating visual feature information to help maintain spatial constancy, TMS over this region would alter participant's abilities to perform a trans-saccadic visual feature discrimination task. In this study, participants saw a visual stimulus in either the bottom-right or bottom-left quadrant of the visual field (VF), relative to gaze and had to report whether a subsequent probe had rotated in the clockwise or counterclockwise direction, in comparison to the previously presented target stimulus. I administered triple-pulse repetitive TMS (rTMS) to the right EVC and left EVC which allowed us to directly test the functional role of EVC in spatial remapping. Based on previous TMS studies (van de Ven et al. 2012), I predicted that TMS would not influence performance during the *fixation task* where the location of the stimulus is maintained within the same hemifield and there is no need for spatial remapping. Similarly, I predicted that during the *saccade task* when subjects made eye movements that did not cross mid-line, maintaining the stimulus within the same hemifield, TMS would not have an influence on subject's performance as remapping is required within hemifield only. However, during the *saccade task* when subjects made eye movements that crossed mid-line, requiring visual information to be remapped across hemifield, TMS would have an influence on subject's performance.

CHAPTER 2

GENERAL METHODOLOGY

2.1 Functional Magnetic Resonance Imaging (fMRI): Overview

fMRI is a commonly used technique by a growing number of scientists for measuring brain activity underlying psychological phenomenon (Arthurs and Boniface 2002; Aue et al. 2009). It detects changes in haemodynamics (i.e. blood oxygenation and flow) to specific brain regions, in response to brain activity, known as BOLD (blood oxygenation level dependent) (Arthurs and Boniface 2002). It is based on the notion that more active brain areas demand a higher blood flow. As such, fMRI can be used to produce activation maps involved in various mental processes. It is a non-invasive, relatively safe technique, has excellent spatial (ability to distinguish different locations in the image; Huettel et al. 2004) and temporal (ability to distinguish changes in the image over time; Heuttel et al. 2004) resolutions, improved signal to noise ratio, allows for continuous collection of data (great for tracing ongoing processes) and relatively easy to use (Huettel et al. 2004; Aue et al. 2009; Cacioppo and Decety 2009).

2.2 fMRI Localizer

A bifield alternating checkerboard wedge stimulus was used in this experiment. Localizer stimulus was provided by Dr. Keith Schneider and consisted of high contrast bifield checkerboard wedges. Localizer data was analyzed using BrainVoyager QX 2.10 (Brain Innovation Inc.). Motion correction was performed to account for any possible movement of the subject's head in the scanner, thereby preventing misalignment of voxels (space corresponding to a tiny cube in the brain of a specified dimension) to the respective brain areas. Functional data (from the 4 runs) was averaged and overlayed onto the anatomical scan. Activation threshold was increased in order to determine the voxel with peak activation corresponding to a given quadrant of the visual field. This

information was later used to navigate the TMS coil using the Brainsight 2 neuronavigation system (Rogue Research Inc. 2011; Figure 2.1; Page 29) during the TMS sessions.

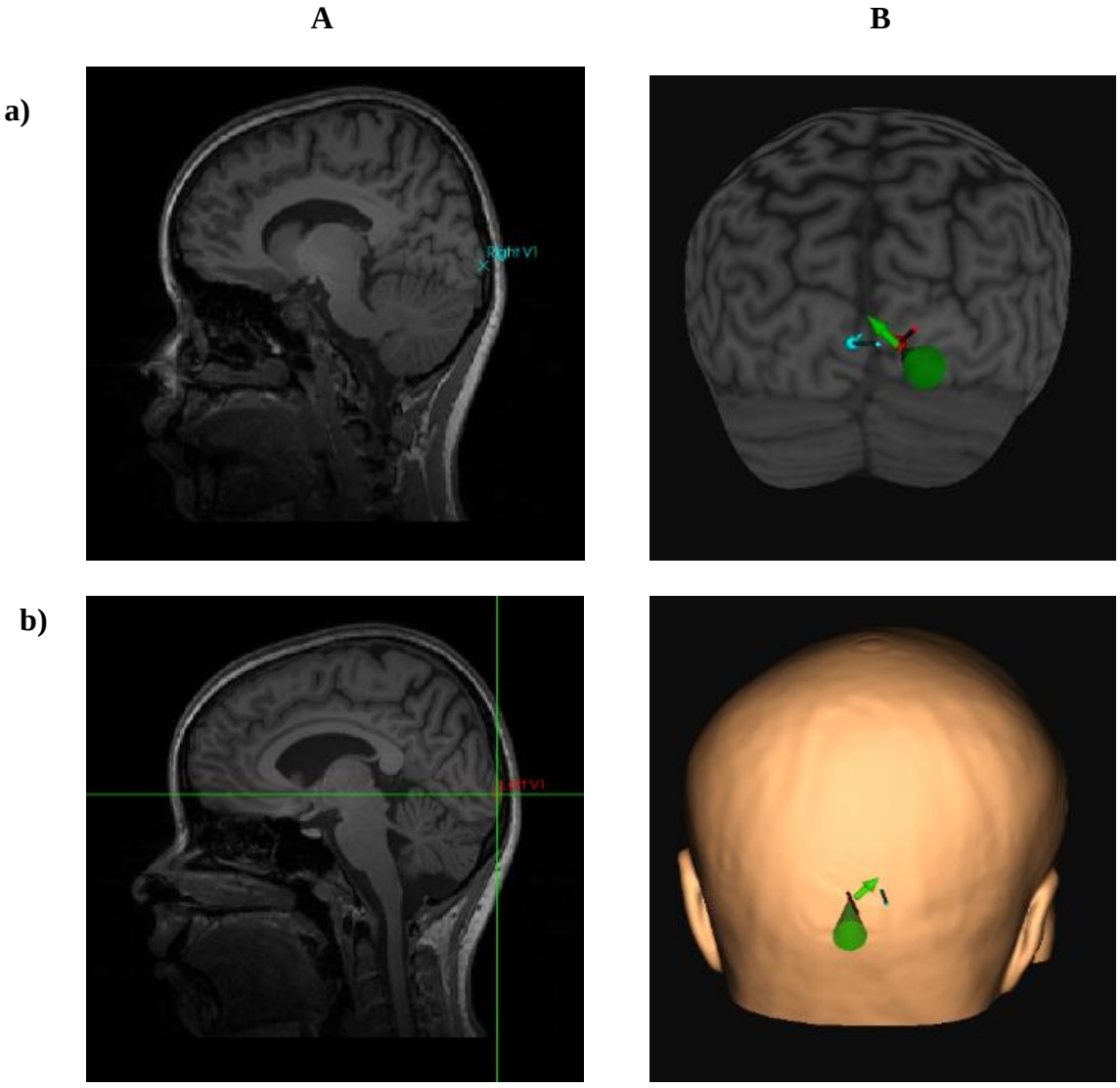


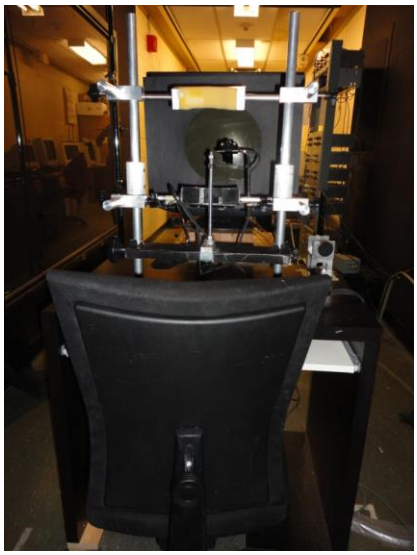
Figure 2.1: Location of the target sites on one representative subject. The target sites **a)** right EVC and **b)** left EVC are marked with the green spikes on the curvilinear brain or skin overlay (Panel B). TMS coil was placed tangentially to the skull at an angle of 45° and was mirrored on the right and left hemispheres.

2.3 Psychophysics

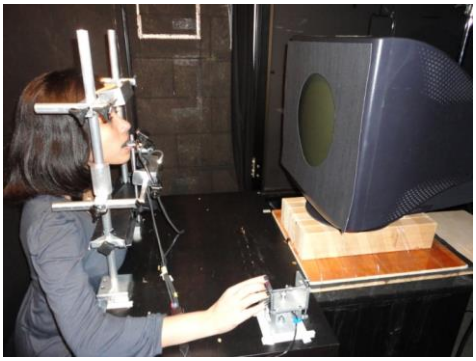
Psychophysics refers to behavioural assessment of subject's performance on various sensory and motor tasks. This experiment was conducted in a dimly lit room, where subjects were seated approximately 51cm from the centre of the monitor (Figure 2.2; Page 31). Subject's head was stabilized using a dental impression bar and head rest (Figure 2.2; Page 31). Subjects were asked to compare the orientation of a test stimulus (probe) with the previously presented stimulus (target). Subjects were required to rotate a mechanical knob in the direction of the perceived orientation change (Figure 2.2; Page 31).

In this experiment, a preliminary psychophysics assessment was conducted with all subjects in order to determine their ability to perform an orientation discrimination task. Individual subject data was fitted using a logistic regression psychometric function. A psychometric analysis was conducted to determine individual baseline thresholds, based on a desired 75-85% accuracy range on the *fixation* and *saccade tasks* (Figure 2.3; Page 32; Table 2.1; Page 33). I chose the 75-85% accuracy range because a two-alternative forced choice task was used in this experiment where the minimum performance is 50% and maximum performance is 100%. As such, an accuracy window of 75-85% would make it possible to see facilitative or suppressive effects of rTMS. Further, based on initial piloting, it was determined that the subjects found the *saccade task* to be more difficult that the *fixation task.* As such, I chose the window of 75-85% accuracy level. This also served as an exclusion criterion.

a)



b)



c)

Figure 2.2: Pictures of **a)** the laboratory setup showing the circular aperture placed over the stimulus presentation monitor; mechanical knob for the subjects to make a two-alternative forced choice response; head rest and bite bar used to stabilize the subjects' head; **b)** experimental setup with a model subject, and **c)** mechanical knob for subjects to rotate in the clockwise or counterclockwise direction to make a two-alternate forced choice in order to indicate the direction of perceived orientation change of the probe in comparison to the previously presented target.

Average = 5.1°

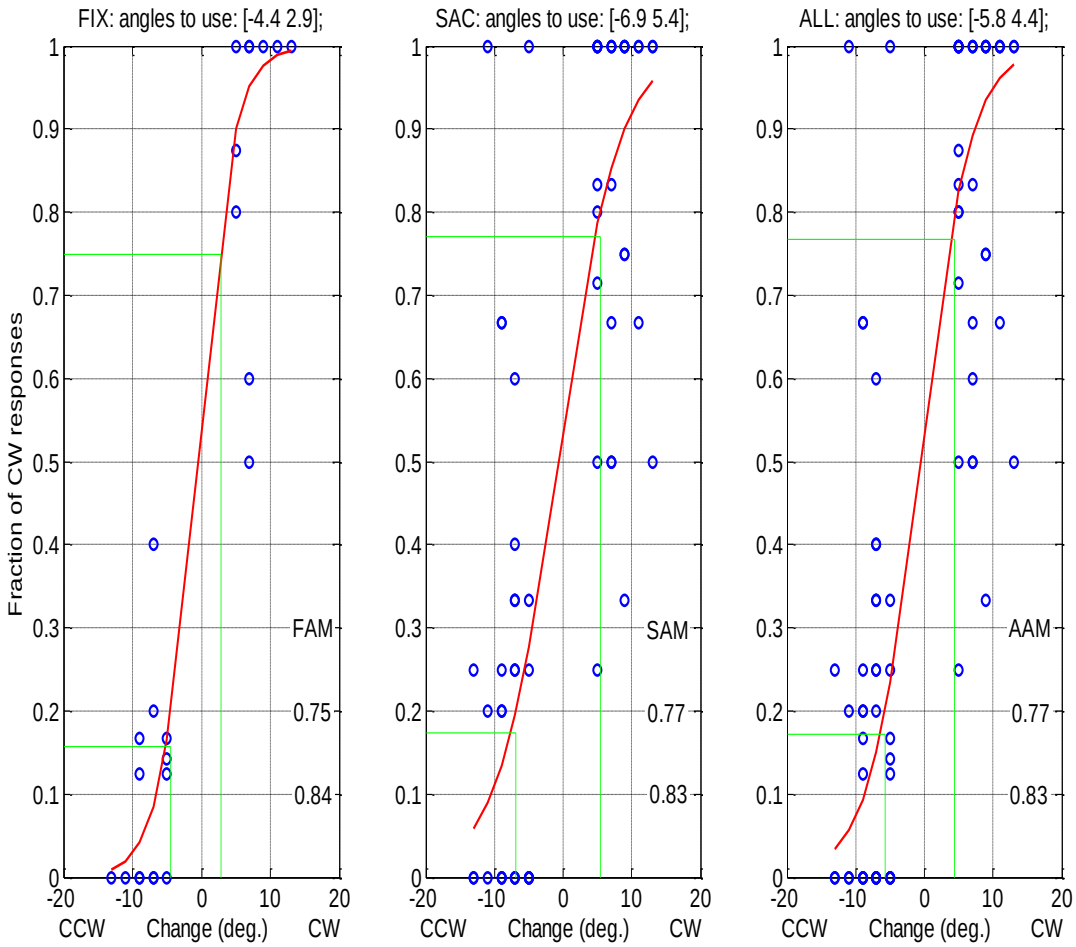


Figure 2.3: Behavioural threshold data illustrating the baseline angles (degrees) for orientation change detection for fixation and saccade tasks for a representative subject obtained via a psychophysics assessment. Performance on all trials was averaged to determine a baseline angle for orientation change at which subjects are able to achieve an accuracy level within 75-85% range. This angle was later used during all trials in the TMS sessions.

Table 2.1: Behavioural threshold angles (degrees) for orientation change detection within 75-85% accuracy range for subjects who were able to achieve this level of accuracy during the psychophysical assessment sessions.

SUBJECT ID	THRESHOLD FOR ORIENTATION CHANGE DETECTION (BASELINE ANGLE DETERMINED VIA PSYCHOPHYSICS ASSESSMENT; DEGREES)
1	3.5
2	6.7
3	7
4	8
5	7
6	5.1
7	5.9
8	6.9

2.4 Transcranial Magnetic Stimulation (TMS)

2.41 Overview

One of the early approaches to study brain-behaviour relationships in humans was to intracranially stimulate the sensory cortex in patients undergoing brain surgeries. Such invasive methods limit the number of subjects available for a study since it only provides access to specific patient populations with a great variability in brain damage or other neuropsychological disorders (van de Ven and Sack 2013). In the past, electrical stimulation was a commonly used technique for the study of brain functions. However, at present, magnetic stimulation has increased in popularity. Magnetic stimulation uses a pulse of magnetic field, resulting in a current flow through the tissue. At the cellular level, both mechanisms of stimulation lead to similar outcomes (Barker 2002). In both techniques, a charge flows into an excitable cell membrane, resulting in a transmembrane potential, which further leads to depolarization of the cell membrane and initiation of an action potential which then propagates via nerve conduction pathways (Barker 2002). One of the major differences in the two techniques is that the magnetic stimulator as opposed to the electrical one is not in direct contact with the tissue. However, magnetic stimulation when used at frequencies for the purpose of altering brain activity is not affected by the electrical properties of the body and can easily pass through bone, soft tissue, clothing and air (Barker 2002). Furthermore, a magnetic field pulse induces an electric field in the tissue and causes flow of an ionic current. Given an optimal amplitude, spatial characteristics and duration of the induced current, it can result in depolarization of the cell membrane and hence, an action potential (Barker 2002; Lemon

2002). It can also result in indirect effects from synaptic actions of excited neurons (Lemon 2002). Magnetic stimulation has a set of advantages and disadvantages. Equipment required for magnetic stimulation is relatively costly and bulky. Fast repetition rates are harder to achieve and the site of stimulation is less accurately known in comparison to electrical stimulation. However, magnetic stimulation allows for brain stimulation with little discomfort, makes routine stimulation for patients and healthy volunteers possible and allows for access to deep peripheral nerves and facial nerves that were previously only accessible with needle electrodes (Barker 2002). Therefore, techniques such as TMS are useful alternatives for the study of localized brain regions in healthy subject populations (van de Ven and Sack 2013).

More specifically, during TMS, a biphasic current flows through one or more coils of wires to generate a magnetic pulse. This further allows for localized brain stimulation of specific brain regions of interest. Positioning the coil over the subjects' scalp allows for delivery of the magnetic pulse to the cortical tissue immediately underneath, locally altering electrical current flow in the neural tissue. TMS pulses can be applied singly or repetitively, known as a repetitive TMS (rTMS) pulse train. Although research has shown that TMS can alter brain activity, whether it always leads to inhibitory or excitatory effects when administered at given frequencies and over given brain regions has not yet been confirmed (Caparelli et al. 2012). Caparelli et al. (2012) conducted a simultaneous TMS-fMRI study in healthy subjects using varying frequencies of stimulation and their results indicated a great variability in the patterns of brain activity in all participants. Similar variability in the results were reported for participants who were able to see phosphenes (flashing lights seen by the subjects) in comparison to those

who were not. Such variability in fMRI activation, as seen via BOLD signals may result from metabolic needs (oxygen requirements) of inhibitory neurons.

In addition, researchers often measure a stimulation threshold when administering TMS with the intent of manipulating brain activity. Threshold refers to the minimal level of stimulus required to provoke a given response (Reid et al. 2002). Resting motor threshold (RMT) is the measure of cortical excitability and represents the lowest TMS intensity at which a motor evoked potential (MEP) of a given size can be recorded (Reid et al. 2002). In order to record the resting motor threshold, hand area of M1 is stimulated using single pulse to determine the lowest possible intensity at which a MEP can be seen. MEP represents the firing of a fraction of spinal motoneurons projecting on the hand muscle. It can be achieved only when stimulation produces a volley of impulses of sufficient size in the corticospinal tract, causing the spinal motoneurons to reach their firing thresholds (Wassermann 2002). Such a technique was used during this experiment to record RMT values from the M1 area of the left hemisphere in all subjects.

TMS was developed by Dr. Barker and colleagues at the Royal Hallamshire Hospital and the University of Sheffield in 1985 with an aim to stimulate the corticospinal motor system (Barker 2002; Wassermann 2002). It has since gained tremendous popularity for use in therapeutic and research settings. Furthermore, it is a reasonably safe and non-invasive technique that can be used to manipulate brain activity with relative spatial and temporal accuracy in humans (Amassian et al. 1989; Kastner et al. 1998; Pascual-Leone et al. 2000; Wassermann 2002; Sack et al. 2009; Theilscher et al. 2010; Dugué et al. 2011). Over the last few decades, TMS has become an important tool

in the study of motor output maps, neuroplasticity and perception (Rossi et al. 2009; Grafman 2002). It has been applied to the sensory cortex and other higher order regions including the lateral prefrontal and PPC to study perception and memory functions (van de Ven and Sack 2013). However, the role of the sensory cortex in memory is still not known. Overall, the use of TMS has improved our understanding of the human brain, especially the human motor control system. Research using TMS on humans has depended on knowledge gained from animal experiments and findings of such human studies have in turn helped to further that knowledge base. Furthermore, effects of TMS are rather complex, including both direct and indirect effects on brain activity and they depend on a large variety of cortical elements. As such, interpretation of such effects is not an easy task (Lemon 2002).

2.42 Safety

Safety regarding the use of TMS on healthy volunteers as well as patient populations is an important concern. Recent meta-analyses have confirmed that the administration of TMS at low to moderate intensities (approximately 30-60%) for shorter durations is relatively safe (Machii et al. 2006; Janicak et al. 2008; Loo et al. 2008). It is important to note that such conclusions are being made on the basis of limited experience and data from the use of TMS over the last 20 years. Several potential side effects of TMS include seizure induction, headache, local pain on scalp, neck pain, toothache, paresthesia, synscope (anxiety and psycho-physical discomfort), transient acute hypomania induction, transient hearing changes, endocrine after effects, effects on neurotransmitters, effects on the immune system and undesired long lasting cognitive and

neuropsychological changes (Rossi et al. 2009). In addition, other potential safety concerns include brain tissue heating, induced voltages in nearby wires and electronic devices, attractive forces on ferromagnetic objects and repulsive forces on non-ferromagnetic objects as well as magnetization resulting from the magnetic field pulse generated by the TMS coil (Rossi et al. 2009). Magnetic field exposure for subjects and operators may also pose a potential health risk. At present, there is a consensus that single sessions of TMS or rTMS do not pose a significant health risk due to relatively short durations of exposure however, negative health effects due to long term exposure to low intensity stimulation are still unclear (Rossi et al. 2009). Moreover, given a variety of factors such as stimulus intensities, pulse repetition rate, pulse length, inter-burst intervals, stimulator waveform, coil geometry, coil position and orientation against the scalp, variability in neuroanatomy and family history of neuropsychiatric disorders, it is difficult to predict the likelihood of seizures and an accurate safe upper limit for stimulation protocols (Barker 2002). Although all current TMS research is conducted under the guidelines of a set of ethical considerations established by various academic, research or medical institutions, it is essential to continuously work on updating recommendations of practice, safety guidelines and ethical considerations (Rossi et al. 2009).

2.43 Positioning the coil over visual cortex

Geometry of the coil is an important factor in addition to other factors including nerve geometry and tissue conductivity which determines the amplitude and spatial distribution of activation (Barker 2002). The first magnetic stimulator coils were circular

since such geometry was easy to construct and easy to position over various regions of the scalp. However, it posed a relative uncertainty regarding the exact site of stimulation. The area underneath the centre of the circular coil was commonly misunderstood as the site of stimulation (Barker 2002). As such, in order to maximize the certainty regarding the site of stimulation, the figure-of eight coil geometry was proposed by Ueno and colleagues in 1988. At present, this coil configuration is most widely used in research and clinical settings. The figure-of-eight coil consists of two circular coils placed side by side and connected such that the current flow in one coil rotates in the opposite direction in comparison to the other coil (Barker 2002). Such geometry ensures that the electric fields and current at the point at which the two circular coils are connected with each other are greatest than that found elsewhere under the coil (Barker 2002).

Furthermore, the depth of penetration and the size of the stimulated area are also key factors. The depth of penetration depends on individual variability in brain anatomy, the size and geometry of the coil and the intensity of the applied stimulus (Barker 2002). Nerves at a depth of approximately 11.5 mm are known to be stimulated by a figure-of-eight coil (Barker 2002). Moreover, magnetic fields decrease rapidly (to the fourth power of distance below the coil) as the distance to deeper brain structures increases (Lemon 2002). As such, deeper brain structures including the basal ganglia and thalamus are impossible to stimulate directly (Lemon 2002). This was also the reason that this study only focused on the regions of the early visual cortex that correspond to the bottom-right and bottom-left quadrants of the visual field, relative to the subjects' fixation.

Additionally, only a handful of studies investigating the role of the EVC in VSTM, visual learning and visual perception using TMS in healthy human participants have been published in the recent years (De Weerd et al. 2012; van de Ven et al. 2012;

van de Ven and Sack 2013). These studies have used different techniques for positioning the TMS coil over the subjects' scalp. Positioning of the TMS coil is an important factor in the probability of finding an effect of TMS on behavior (Sack et al. 2009; Graaf et al. 2011; van de Ven and Sack 2013). There are three main ways in which coil placements are used. First, coil placements may be anatomically determined by placing the coil a few centimeters above the inion. However, this ignores the inter-individual variability in occipital cortical morphology and functional anatomical mapping (Rademacher et al. 1993; van de Ven and Sack 2013). Second, coil placement may also be determined via phosphene localizations. During this method, TMS is applied over the visual cortex to induce phosphenes (flashing lights seen by the subject) at different positions over the scalp to identify an optimal coil placement position. It is important to note that the probability of reliably seeing phosphenes is quite low and greatly relies on subjective reporting by the subjects. As such, this method also leads to a great inter-individual variability (Romei et al. 2008; Sack et al. 2009; van de Ven et al. 2012; van de Ven and Sack 2013). Third, functional localizations using fMRI is a new method that is rapidly gaining popularity. In this method, specific stimulus can be displayed for the subjects while they are in the MRI scanner and brain activity can be recorded. TMS coil can be navigated using the coordinates of the peak activation voxels in Briansight 2.0 Neuronavigation system. This technique takes individual variability in brain morphology and functional activity into account, thereby making it one of the more accurate techniques for determining coil positions (Sack et al. 2009; van de Ven ad Sack 2013).

2.44 Current Study

During the experiment discussed in this thesis, rTMS was applied unilaterally with the aim of stimulating the extra striate visual areas, mainly EVC to modify transmission of visual input. The TMS coil was positioned based on retinotopically-defined quadrants using fMRI (Figure 2.1; Page 29). TMS coil was held at an angle of 45° over the subject's scalp and the position was mirrored for right EVC and left EVC (Figure 2.4; Page 42; Figure 2.5; Page 43).

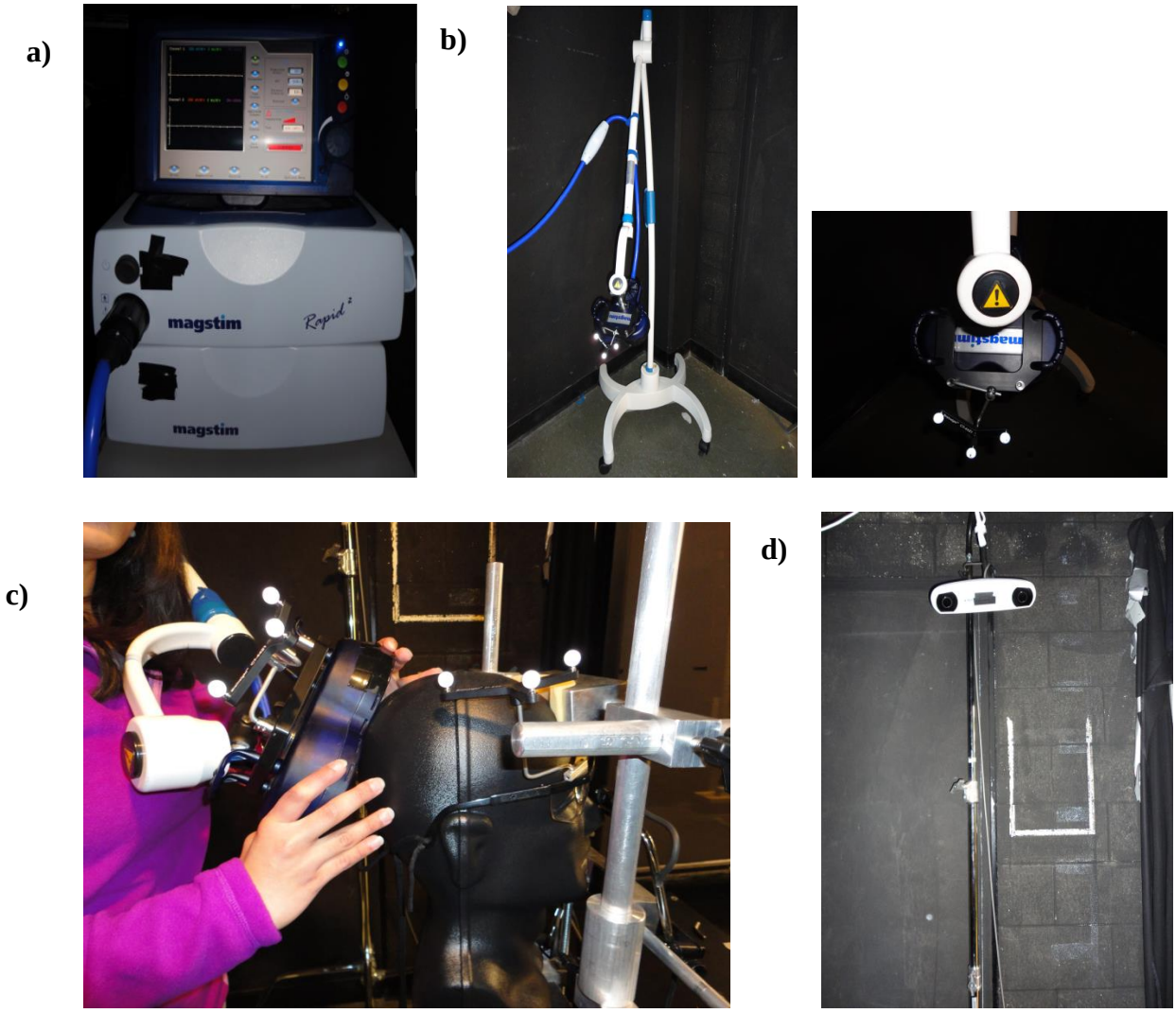


Figure 2.4: Transcranial magnetic stimulation apparatus **a)** Magstim 200 Rapid 2 magnetic stimulator consisting of the charging unit and control panel that triggers an electrical pulse to the stimulator coil; **b)** a 70mm figure-of-eight coil inside the Magstim plastic encasing that receives that the electrical discharge from the charging unit and produces a brief magnetic pulse; **c)** stimulator coil held against a phantom head to illustrate its relative position. A magnetic field passes through the subject's skull and interferes with neural activity in the targeted region; and d**)** Polaris Vicra camera system used to track the position of the stimulator coil and the subject's head in space in order to assist with coil neuronavigation during the experiment.

Figure 2.5: Illustration of positioning of the TMS coil over the subject's scalp.

2.5 Eye Position Recording

Eye position was monitored during each TMS session using an EyeLink 2.0 desktop-mounted eye tracker (SR Research Ltd. 2002; Figure 2.2b; Page 31). A nine-point grid of fixation points was used to calibrate the camera before the start of each session for all subjects (Figure 2.6; Page 45). Stability of the eye position during fixation and saccade trials was evaluated using a custom programming code written using Matlab 7.0.0 (The Math Works Inc. 2004). During the fixation task, eye data was evaluated on the basis of maintaining relatively stable eye position throughout the trial with eye movement of 1° or less. Furthermore, during the saccade task, eye data was evaluated based on 1) saccades made at the appropriate time in comparison to the onset of the second fixation point, and b) saccades made were of appropriate size in comparison to the saccade size required for a given trial (discrepancy of 1.5° or less was considered acceptable). If such criteria were not met during any given trial, the data from such trial was discarded and was not used for the purpose of any analyses. Data from one subject was omitted due to poor eye movement recordings.

Eye movement signal during a saccade trial for one representative subject is shown in Figure 2.7 (Page 46). Horizontal (magenta line) and vertical (green line) components of the eye position were evaluated. Since subjects were only required to make saccades in the horizontal plane, eye position in the vertical plane was expected to remain stable throughout any given trial.

Figure 2.6: Illustration of the nine-point grid of fixation points used during the calibration routine at the beginning of each experimental session for all subjects.

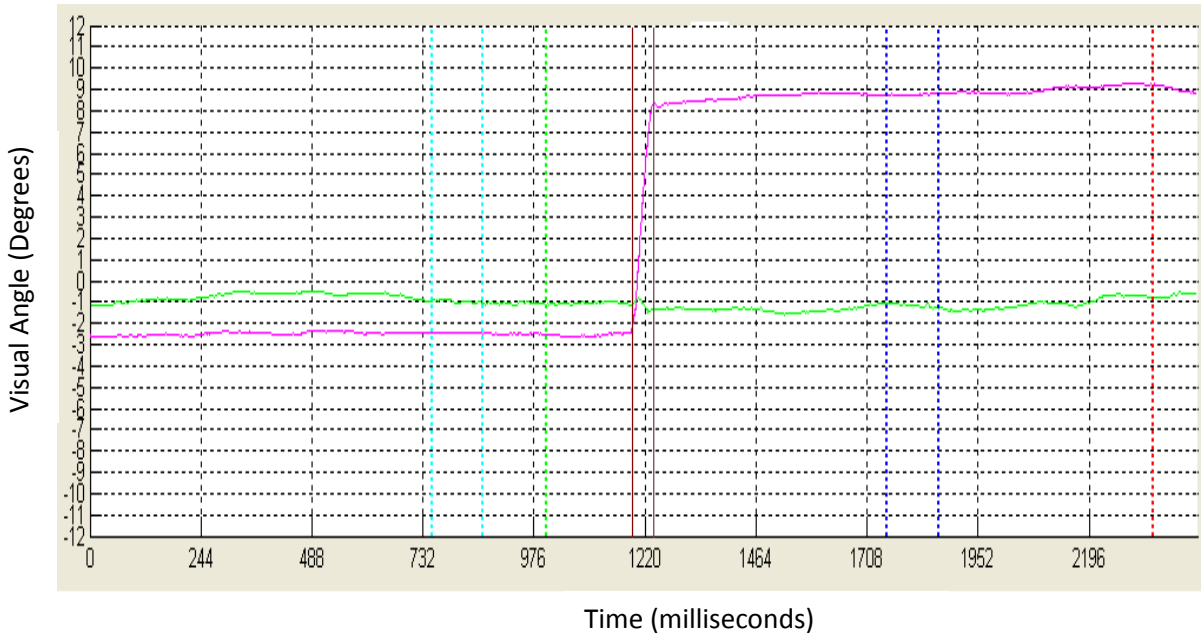


Figure 2.7: Eye movement signal during a saccade trial for one representative subject; recorded using the EyeLink 2.0 experimental setup-mounted eye tracker. Magenta line represents the eye position signal in the horizontal component and the green line represents the eye position in the vertical component.

CHAPTER 3

ROLE OF EARLY VISUAL CORTEX IN TRANS-SACCADIC MEMORY OF OBJECT FEATURES

(an un-submitted manuscript in *Journal of Neuroscience* format)

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Abstract

Visual information is retained and integrated across saccades to maintain a continuous spatiotemporal representation of the world. Here, we tested the role of early visual cortex (EVC) in trans-saccadic memory/integration with the use of functional magnetic resonance imaging (fMRI) guided repetitive transcranial magnetic stimulation (rTMS) protocol. fMRI localizers were used to identify EVC activity corresponding to the bottom-right and bottom-left visual quadrants. Subsequently, these quadrants were visually stimulated by placing gaze fixation to the left or right (and above) a briefly presented Gabor patch. After a short memory interval, participants were required to detect the relative change in orientation of a re-presented test patch. In our *fixation task*, participants maintained gaze for the entire trial. In the *saccade task*, during the memory interval, participants made an eye movement that either maintained or reversed (left vs. right) the visual quadrant of the test stimulus. Three rTMS pulses (coinciding with the pre-, peri- and post-saccade intervals) were applied to the left or right EVC. rTMS had no effect when 1) fixation was maintained, 2) saccades kept the stimulus in the same visual quadrant, or 3) when quadrant corresponding to the first Gabor patch was stimulated. However, rTMS affected performance (relative to opposite EVC rTMS) when saccades brought the remembered visual stimulus into the magnetically stimulated quadrant. This effect increased with saccade amplitude. These results show that EVC and/or its close network connections are involved in the memory and 'remapping' of visual features across saccades.

Keywords: Trans-saccadic memory, spatial constancy, visual remapping, spatial updating, early visual cortex, transcranial magnetic stimulation, functional magnetic resonance imaging, saccade, fixation, visual quadrants

Introduction

Humans typically make 3-5 rapid eye movements, per second in order to maximize foveal vision (Rayner 1978; Rayner 1998; Prime et al. 2008; Prime et al. 2010; Ibbotson and Krekelberg 2011; Prime et al. 2011; Ahissar and Arieli 2012). Visual processing is mostly suppressed during these saccades so useful visual information is limited to discrete fixations (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011). And yet we are able to perceive the world in a continuous and coherent manner, without the gaps and delays that would be expected if we waited for new visual input after each saccade (Matin 1974; Melcher and Colby 2008; Prime et al. 2011). This requires the active retention of information in a continuous, constantly updated internal representation of the external world. Psychophysical experiments suggest that humans are able to retain three-four attended objects across saccades (Irwin 1996; Prime et al. 2008). This process, known as trans-saccadic perception consists of three steps: 1) trans-saccadic visual memory, 2) updating/remapping this retained information in gaze-centered coordinates, and 3) trans-saccadic integration (TSI) of the retained and updated information with new visual information (Irwin 1996; Melcher and Colby 2008; Prime et al. 2011).

Recent functional magnetic resonance imaging (fMRI) studies have implicated early visual cortex (EVC) in both visual memory (Harrison and Tong 2009) and trans-saccadic updating of object locations (Merriam et al. 2007). Several recent transcranial magnetic stimulation (TMS) studies have also investigated the role of EVC in visual perception and memory during gaze fixation (De Weerd et al. 2012; van de Ven et al. 2012; van de Ven and Sack 2013). One such study implicated EVC in the retention of

object shape information, at least with higher memory loads (van de Ven et al. 2012). However, to our knowledge, the role of EVC in the trans-saccadic memory and updating of object features such as orientation has not been tested.

Here, we investigated the functional role of the human EVC in spatial remapping using TMS. We hypothesized that if EVC plays an important role in integrating visual feature information to help maintain spatial constancy, TMS over this region would alter participant's abilities to perform a trans-saccadic visual feature discrimination task. In this study, participants saw a visual stimulus in either the bottom-right or bottom-left quadrant of the visual field (VF), relative to gaze and had to report whether a subsequent probe had rotated in the clockwise or counterclockwise direction, in comparison to the previously presented target stimulus. We administered triple-pulse repetitive TMS (rTMS) to the right and left EVC, during the pre-, peri- and post-saccade intervals which allowed us to directly test the functional role of EVC in spatial remapping. Based on previous TMS studies (van de Ven et al. 2012), we predicted that TMS would not influence performance corresponding to the stimulated VF but might influence performance if and when EVC is involved in the trans-saccadic remapping of remembered feature information into the opposite cortical hemisphere.

Methods and Materials

Subjects

Sixteen healthy subjects (7 females; 9 males; age range: 20-40; mean age 28.8 years) participated in our preliminary psychophysical experiments (see below), after providing written informed consent. Thirteen healthy subjects (4 females; 9 males; age range: 19-40; mean age 28.8 years) qualified to participate during fMRI scans. Nine healthy subjects (2 females; 7 males; age range: 20-40; mean age 30.7 years) participated in the TMS sessions. One subject's data was excluded from the analysis due to poor eye movement recordings, leaving 8 participants in our final analysis. All subjects had normal or corrected-to-normal vision and no history of neuropsychiatric disorders, according to self-report. All procedures were approved by the York University Human Participants Review Committee.

Laboratory Set-up

During psychophysics and TMS sessions, participants were seated in a dimly lit room at a distance of 51 cm from the display screen. A personalized dental impression bar was used to stabilize their head. A customized computer network of three personal computers was used to display the stimulus, record eye-movement data and record subject response data. Stimulus was presented on a Dell Trinitron P1130 CRT monitor with a circular aperture placed over the display area to remove all external orientation cues such as the ones from the edges of the screen. This circular aperture had a diameter of 32.8° in visual angle. The monitors' refresh frequency was 75 Hz and the resolution was set at 1024 X 786 pixels. The luminance level for the probes was 30.9 cd/m^2 (Figure

3.1; Page 54). Eye position was monitored during each TMS session using an EyeLink 2.0 eye tracker (SR Research Ltd. 2002), which was mounted to the bite bar.

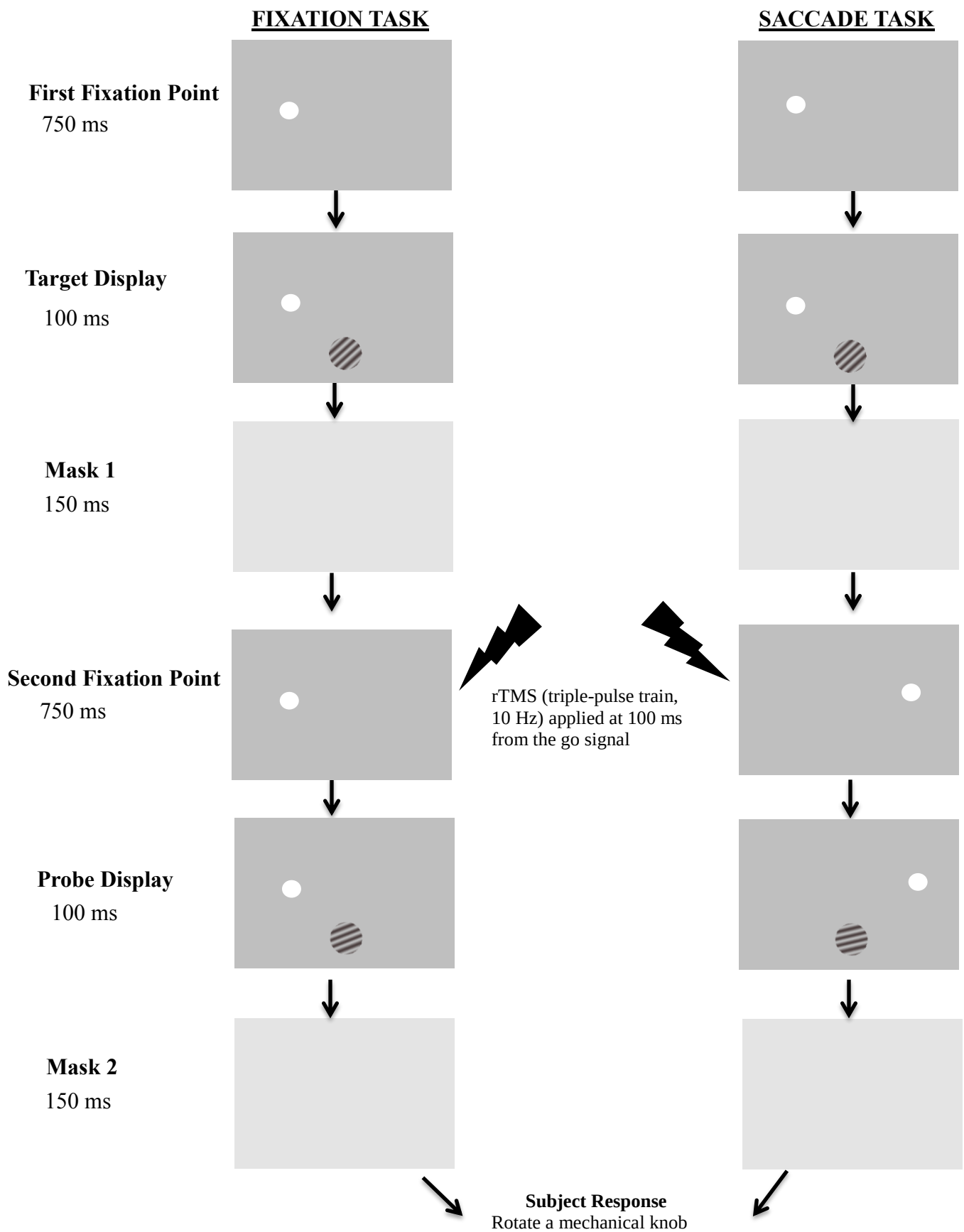

FIXATION TASK
SACCADE TASK
First Fixation Point
750 ms
Target Display
100 ms
Mask 1
150 ms
Second Fixation Point
750 ms
rTMS (triple-pulse train, 10 Hz) applied at 100 ms from the go signal
Probe Display
100 ms
Mask 2
150 ms
Subject Response
Rotate a mechanical knob

Figure 3.1: Illustration of the experimental design for the fixation task and saccade task. Subjects were required to make a two-alternate forced choice response, making a comparison of the orientation of the probe to a previously presented target. Subjects were required to fixate at a fixation point (diameter = 0.16°), presented randomly at 3° or 9° to the right or left of the subjects' head-centered location which was designated as 0°. This was followed by a target (Gabor patch = 2.9°), presented either in the bottom-right or bottom-left quadrant of the visual field, relative to fixation. During the fixation task, subjects were required to maintain fixation at the same location such that the following probe appears in the same retinal location. Subjects were then required to make a response by rotating a mechanical knob to indicate a comparison of the orientation of the probe with the previously presented target. During the saccade task, the second fixation point was presented at a different location. A 10 Hz rTMS train of 3 pulses was applied 100 milliseconds after the appearance of the second fixation point.

Eye Movement Recordings and Analysis

A nine-point grid of fixation points was used to calibrate the eye tracker before the start of each session for all subjects. Stability of the eye position during *fixation* and *saccade* trials was evaluated using a custom program written using Matlab 7.0.0 (The Math Works Inc. 2004). During the *fixation task*, eye data was evaluated on the basis of maintaining relatively stable eye position throughout the trial with eye movement of 1° or less. Furthermore, during the *saccade task*, eye data was evaluated based on 1) saccades were made within 400 ms of the onset of the second fixation point, and 2) saccades made of appropriate size in comparison to the saccade size required for a given trial (discrepancy of 1.5° or less was considered acceptable). If these criteria were not met during any given trial, the data from that trial was discarded and was excluded from the analysis.

Psychophysical Paradigm

In a preliminary (behavioural) version of our experiment participants were required to discriminate orientation change in the stimulus (Gabor patch; diameter = 2.9°) during *fixation* and across *saccades* (Figure 3.1; Page 54). A two-alternate forced choice procedure was used which required the subject to rotate a mechanical knob in the direction of the perceived orientation change.

Each trial began with a circular fixation point (diameter = 0.2°), presented at either 3° (Target eccentricity = 3.6°) or 9° (Target eccentricity = 9.2°) to the right or left from the subjects' head-centre which was designated as 0° (see Figure 3.2; Page 59 for the detailed combinations). Following a period of 750 ms to allow for fixation, the first oriented Gabor patch was presented for 100 ms either in the bottom-right or bottom-left

quadrant of the VF, relative to gaze. This was immediately followed by a grey mask for 100 ms in order to reduce external effects of after images.

During the *fixation* trials, the second circular fixation point was presented at the same position; whereas during the *saccade* trials, the second fixation point was presented at one of the other three possible fixation locations (see Figure 3.2 for the detailed combinations). As such, during the *saccade* trials, subjects were required to make a saccade either within the same quadrant of the VF or from one quadrant to another (right to left or left to right quadrant). Subjects re-fixated on the second fixation point for 750 ms, which was immediately followed by a probe (Gabor patch; diameter = 2.9°) presented in the same location but in an altered orientation for 100 ms. A second grey mask was presented for 150 ms to reduce after images. This was followed by an interstimulus interval of 1000 ms during which a white screen was presented. Subjects were required to rotate a mechanical knob with their right hand, either in the clockwise or counterclockwise direction to indicate the perceived change in orientation of the probe in comparison to the previously presented target. Subjects were asked to make their response as soon as the trial ended and to make their best guess if they were unsure. Accuracy was given a greater emphasis than the speed of response.

Sixteen subjects were tested on this preliminary no-TMS task. The amount of stimulus rotation was adjusted in 5° steps to obtain a psychometric function (averaged across clockwise and counterclockwise rotation trials and across *fixation* and *saccade* trials). During this session, data was collected using a block design (8 blocks, 4 fixation task blocks and 4 saccade task blocks) presented in a randomized order (AB-AB-BA-BA; A: *fixation task*, B: *saccade task*). Each block contained 72 trials, corresponding to a total of 288 *fixation* trials and 288 *saccade* trials. Of these subjects, three were unable to meet

our fixation criteria (see above) or perform the orientation discrimination with sufficient proficiency. For the subjects who went on to perform all experiments, we used the individual psychometric functions obtained from this task to set an orientation shift that would obtain a performance level between 75-85% in the similar TMS experiment.

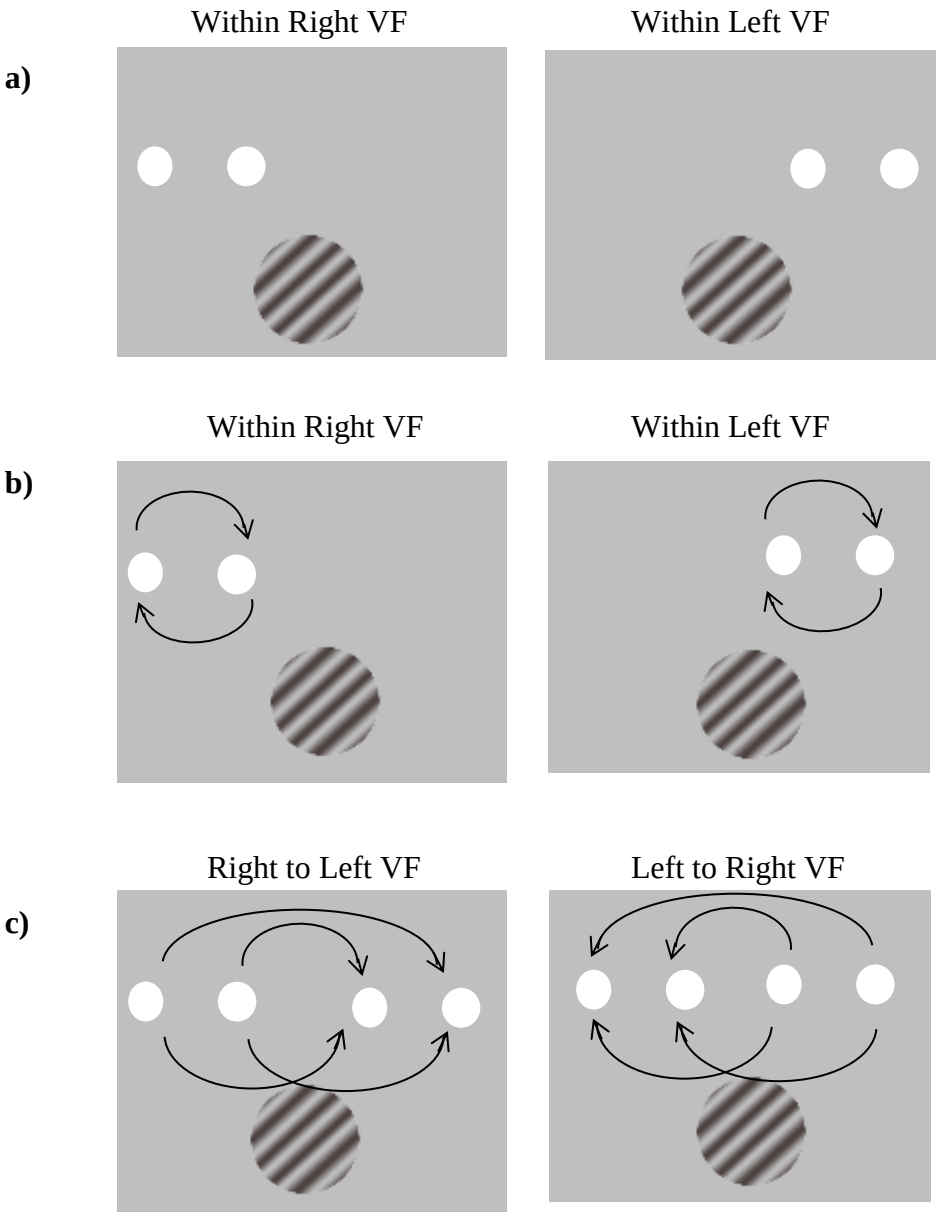


Figure 3.2: a) Location of fixation points (-9, -3, +3, +9°) during the fixation task; **b)** during the within hemisphere conditions for the saccade task; and **c)** during the across hemisphere conditions for the saccade task.

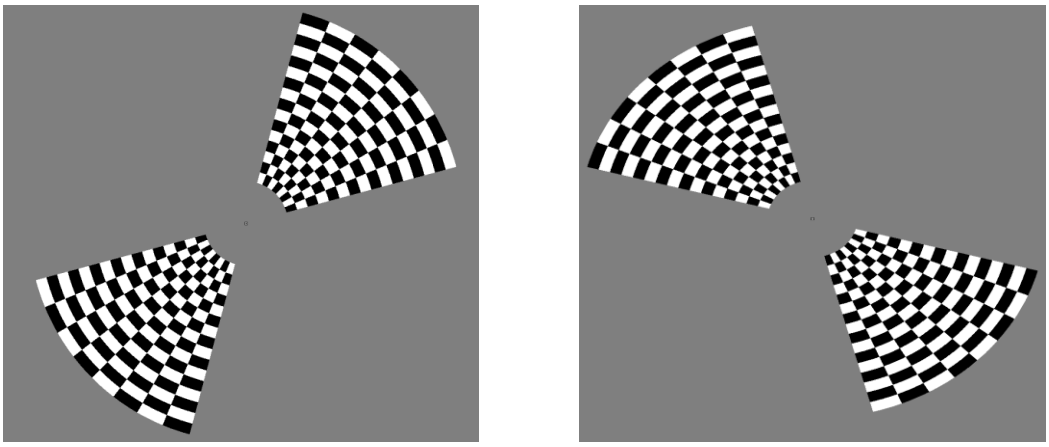
fMRI Localizer Task and Positioning the TMS Coil

Our main experiment (see next section) required the placement of TMS coil over the portions of EVC corresponding to the bottom-left and bottom-right visual hemifields. Therefore, a fMRI localizer task was used to first identify peak visual quadrant EVC activity in the participants who passed the first stage of exclusion in our psychophysical task. A bifield alternating checkerboard wedge stimulus was used because it is well-suited for identification of EVC, particularly V1 (Kraft et al. 2005). Subjects were required to fixate on the centre fixation point while checkerboard wedges appeared in the bottom-right, bottom-left, upper-right and upper-left VF. Subjects were scanned using a 3.0 Tesla Siemens 32 channel head coil whole body scanner at the Neuroimaging Centre at Sherman Health Sciences Research Centre, York University. First, anatomical scans using the MPRAGE sequence, 1 mm^3 (isotropic) voxels were obtained for each subject. Second, four identical scanning runs (256 seconds) were performed using the EPI sequence (TR = 2 seconds; TE = 30 seconds; 29 horizontal or oblique interleaved slices; 3 mm slice thickness with 0.75 mm gap between slices; A --> P phase encoding; 64 X 64 in-plane matrix, field of view = 192 mm, 3 X 3 X 3 mm^3 voxel size; flip angle of 90°; parallel imaging acceleration factor = 2; bandwidth = 762 Hz/pixel).

Localizer data was analyzed using BrainVoyager QX 2.10 (Goebel et al. 2011). Motion correction was performed to account for any possible movement of the subject's head in the scanner, thereby preventing misalignment of voxels to the respective brain areas. Functional data (from the 4 runs) was averaged and overlaid onto the anatomical scan. Activation threshold was increased in order to determine the voxel with peak activation corresponding to a given quadrant of the VF (Figure 3.3b; Page 62; Table 3.1; Page 63). This information was later used to navigate the TMS coil using the Brainsight 2

Neuronavigation system (Rogue Research Inc. 2011) during the TMS sessions. A calibration was performed with each subject in order to establish the spatial relationship between the anatomical image data uploaded into the software and the subject during the experiment. Registration was conducted by selecting common points on the image data and the subject such as nasion (the bridge of the nose), tip of nose, right ear and left ear (upper part of the tragus). These points are homologous point pairs that are used by the BrainSight 2 Neuronavigation system to calculate the spatial transformation from the subject's head to his or her image data (Rogue Research Inc. 2011).

a) **Orientation 1:** **Orientation 2:**



b)

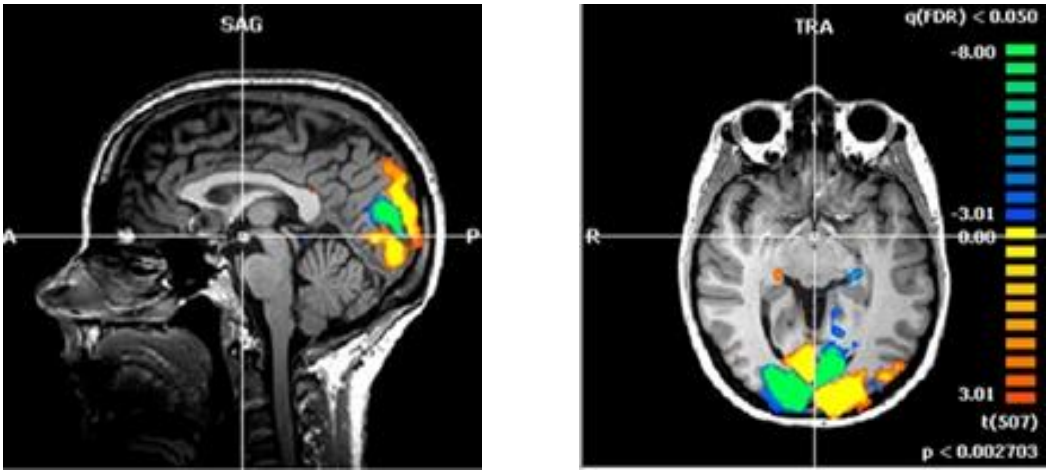


Figure 3.3: a) Localizer stimulus presented to subjects during the functional magnetic resonance imaging (fMRI) scans. Alternating checkerboard wedges were presented as 8 trials of 32 seconds for each run. A total of 4 runs (256 seconds each) were conducted for each subject and the data was averaged for analysis purposes, and **b)** functional localizer analysis for a representative subject, conducted using BrainVoyager QX 2.10, illustrating clusters of activation seen in the various quadrants of the visual field, in the sagittal and transverse planes.

Table 3.1: Talairach coordinates of the peak activation voxel in the early visual cortex of the right and left hemispheres, determined via functional localizers and analysis using BrainVoyager.

	Left EVC			Right EVC		
SUBJECT ID	**X**	**Y**	**Z**	**X**	**Y**	**Z**
1	-19.44	-82.82	15.91	3.24	-85.33	16.71
2	-15.49	-86.26	-1.38	6.45	-87.15	-1.17
3	-8.93	-87.14	-7.59	7.03	-87.25	-7.41
4	-11.89	-84.73	-1.66	6.14	-84.46	-1.47
5	-7.21	-93.39	3.87	13.10	-86.01	3.15
6	-11.75	-92.58	-7.34	7.43	-100.53	-7.19
7	-13.38	-90.81	-16.36	7.88	-94.98	-16.58
8	-20.37	-96.99	-2.13	7.99	-96.58	-6.32

rTMS Experiment

Nine subjects passed the psychophysical assessment stage, showed clear fMRI localizer results and were willing to continue with the rTMS experiment. This experiment utilized the same psychological paradigm as that shown in Figure 3.1 (Page 54), with the additional application of rTMS as follows. During TMS experiments, rTMS (triple pulse train) was applied unilaterally with the aim of stimulating EVC to modify transmission of visual input in a field specific fashion. The TMS coil was positioned based on retinotopically-defined EVC quadrants (bottom-right and bottom-left VF) defined in the previous section. We did not use a separate TMS site as control, as we have done in other studies, because this study was designed to compare the effects of TMS over left vs. right EVC across specific symmetric behavioural conditions (see next section) and these two sites would clearly provide better controls for each other than another arbitrarily chosen site. The TMS coil was held at an angle of 45 degrees over the subject's scalp and the position was mirrored for left EVC and right EVC. This allows for an alteration of cortical excitability of the primary visual cortex by using a 10 Hz rTMS train. The timing of the TMS pulses, starting at 100 ms from the onset of the second fixation point (Figure 3.1; Page 54) with a 100 ms interval in between was selected to ensure that we can capture the pre-, peri- and post-saccade timings with each one of the pulses (Figure 3.4; Page 65).

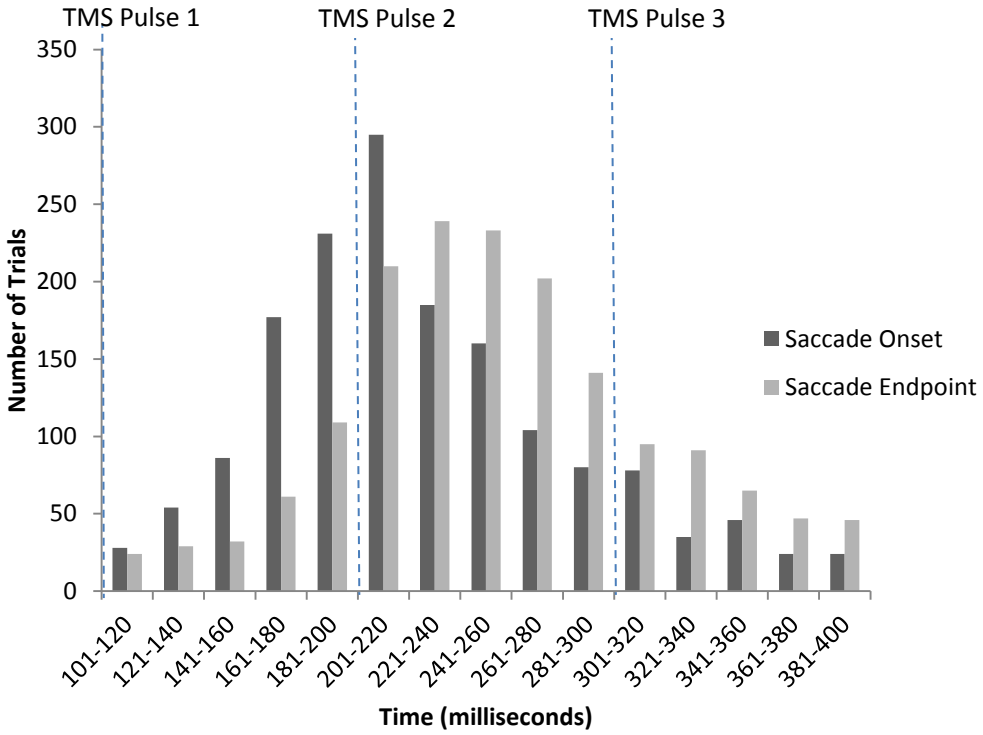


Figure 3.4: Comparison of the frequency distribution of saccade onset (dark grey) and saccade endpoint (light grey) with TMS pulse timings. Number of trials for each discrete range of 20 ms, starting at 100 ms to 400 ms are illustrated. Majority of saccades were found to be initiated between the 201-220 ms and completed between 221-260 ms time windows.

During the TMS sessions, rTMS was applied to retinotopically-defined regions of the right and left EVC. The no-TMS condition was used as a baseline control to determine how accurate subjects were in detecting orientation change in the absence of interfering effects of TMS. TMS (right and left EVC) and no-TMS baseline control trials for the *fixation* and *saccade tasks* were presented in a block design in a A-B-C-C-B-A, C-A-B-B-C-A and A-C-B-B-C-A design for the Left EVC (A), Right EVC (B) and no-TMS (C) conditions. Furthermore, a sub-block design of AB-AB-AB-BA-BA-BA and BA-BA-BA-AB-AB-AB was used for the *fixation* (A) and *saccade* (B) conditions. These orders were counter-balanced across subjects. Each block consisted of 80 trials for a total of 960 trials (480 *fixation* trials and 480 *saccade* trials) for the entire experiment for each subject. The TMS and no-TMS trials were presented in separate blocks to prevent any external anticipatory effects where subjects might expect rTMS pulses on certain trials.

Resting motor threshold (RMT) values were recorded via single pulse stimulation to area M1 in the left hemisphere for all subjects. For the purpose of this experiment, RMT values were thought to be the minimum intensity at which a noticeable movement was detected in the target muscles of the right hand at rest. All subjects received stimulation of 60% stimulator output intensity. At the end of each TMS experiment session, subjects were asked to report if they saw phosphenes during stimulation, however, none of the subjects reported seeing phosphenes. Subjects were also screened for health and safety at the start and end of each TMS experiment session.

Specific Hypotheses and Analysis

Figure 3.2 (Page 59) shows the different spatial combinations of trials in our study and how we grouped our data for analysis in terms of *fixation* trials (Figure 3.2a; Page 59), trials where *saccades* stayed on the same side of mid-line (Figure 3.2b; Page 59), and trials where *saccades* crossed mid-line (Figure 3.2c; Page 59). According to previous fMRI and neurophysiological studies, the trials in Figure 3.2b (Page 59) should be associated with remapping within one cortical hemisphere, whereas the trials in Figure 3.2c (Page 59) should involve remapping across hemispheres (Merriam et al. 2003; Colby et al. 2005; Heiser and Colby 2005; Medendorp et al. 2005; Merriam and Colby 2005; Berman et al. 2007, Merriam et al. 2007). Further, a previous study found that TMS over EVC does not influence memory of a single visual object during fixation (van de Ven et al. 2012), but our previous results (with other brain areas) suggest that TMS can have stronger suppressive effects on visual memory during *saccades* than *fixation*, presumably because saccade-dependent remapping is a more labile internally driven process than stimulus-driven perception (Prime et al. 2011).

Based on this logic and previous findings, we developed the following hypotheses: 1) with one visual stimulus, TMS would have little or no effect in the *fixation task*, whether TMS is applied to the visual quadrant of perception or the opposite visual quadrant, 2) TMS would affect performance in situations where visual information is expected to be remapped *into* the stimulated visual quadrant (i.e. during TMS to contralateral VF in Figure 3.2c; Page 59), and 3) TMS might produce intermediate or no effects when applied to the 'perceiving' visual quadrant and then visual information is either retained within that quadrant (Figure 3.2b; Page 59) or remapped out of that quadrant (i.e. when TMS is applied to the contralateral hemisphere in Figure 3.2c; Page

59). Our analysis was thus designed to test these hypotheses, using topographically identified regions of left EVC and right EVC as a control for each other.

Off-line analysis showed that one of our nine participants did not meet our fixation criteria and was excluded from further analysis. A paired sample t-test was conducted to compare baseline performance during the no-TMS control trials for the *fixation task* versus *saccade task*. For the *fixation task* (Figure 3.2a; Page 59), trials were divided based on the stimulus maintained within right VF or within left VF and percent accuracy was assessed based on the stimulation conditions (No-TMS, Left EVC and Right EVC). Repeated measures ANOVA was conducted to compare the effects of stimulation conditions on mean percent correct responses, for stimulus presented within right VF and within left VF separately. Since, this experiment was designed so that the opposite sides of EVC served as controls for each other. Paired sample t-tests were conducted to compare the effects of stimulation to the left EVC versus right EVC when the stimulus presentation was maintained within right VF and within left VF.

During the *saccade task*, for saccades that maintained the stimulus within the same visual hemifield (Figure 3.2b; Page 59), paired sample t-tests were conducted to compare the effects of stimulation to the left EVC versus right EVC when the stimulus presentation was maintained within right VF and within left VF, irrespective of the saccade. Percent accuracy in the *saccade task* where saccades crossed mid-line (Figure 3.2c; Page 59) causing a change in the location of the stimulus (from left VF to right VF and from right VF to left VF), resulting in remapping in the opposite hemisphere was compared using paired sample t-test. In addition, effects of stimulation conditions based on saccade size on mean percent correct responses across all subjects were analyzed using repeated measures ANOVA, along with pairwise comparisons using Bonferroni

corrections. In this situation, paired sample t-tests were also conducted to analyze the effect of saccade endpoints (near versus far from presented stimulus) on percent correct response. Results were also summarized based on relative percent accuracy (Post-saccadic VF – Pre-saccadic VF) for saccade direction and saccade size to visualize the effects of stimulation over the perceived VF versus remapped opposite VF.

Results

fMRI Localizers

Example localizer data are illustrated in Figure 3.3b (Page 62), and data from all 8 subjects are included in a supplementary figure (Figure S1, to be posted on our web-site). The Talairach coordinates of the peak activation voxels corresponding to the bottom-right and bottom-left quadrants of the VF (are shown in Table 3.1; Page 63). These coordinates were used to navigate the TMS coil using the BrainSight 2 Neuronavigation system (Rogue Research Inc. 2011) during the TMS experiment sessions. A comparison of the targeted coordinates (Average Left EVC: x = -13.56, y = -89.34, z = -2.08; Average Right EVC: x = 7.41; y = -90.29; z = -2.54) with literature values (Average Left EVC: x = -13, y = -63, z = 3; Average Right EVC: x = 9; y = -67; z = 5; Dougherty et al. 2003) confirmed that area V1 was likely targeted, although the spread of TMS likely influenced the same visual quadrant in area V2 (Dougherty et al. 2003). Based on these data and the well-known topography of this area (Dougherty et al. 2003; Merriam et al. 2003; Merriam and Colby 2005; Merriam et al. 2007), we made the assumption that TMS over these areas would primarily influence vision in the opposite hemifield, and thus the left EVC and right EVC would serve as controls for each other in the following TMS experiments.

Baseline (No-TMS) Psychophysical Performance

The mean percent correct responses of the no-TMS trials (obtained during the rTMS experiment) across all subjects for the *fixation task* was 84.7 ± 3.4% and for the *saccade task* was 73.9 ± 3.8%. Subject's performance in the two task types was significantly different ($t(7) = 3.59$; $p = 0.009$), determined via a paired-sample t-test. However, there was no difference in performance between the stimulus presented in the left or right VF in the *fixation task* (Figure 3.5; Page 73, *blue bars*). Similarly, the saccade data showed no difference in performance when saccades kept the stimulus in the same hemifield (Figure 3.6; Page 75, *blue bars*) or when saccades crossed mid-line and changed the location of stimulus presentation from one VF to another (Figure 3.7; Page 77, *blue bars*). Based on these control findings, we did not make an attempt to conduct comparisons between tasks in our TMS data, but instead focused on the within-task comparisons required to test our hypotheses (see *Methods and Materials*), in particular comparisons between left EVC and right EVC TMS effects.

TMS During Fixation Task

Figure 3.5 (Page 73) compares the mean percent correct responses of the No-TMS baseline control (*blue bars)*, Left EVC (*green bars)* and Right EVC TMS (*yellow bars)* conditions across all subjects for the *fixation task*, with data sorted according to the hemifield of the stimulus appearance (within right VF or within left VF; Figure 3.2a; Page 59). There was no significant difference in performance between the control (No-TMS), left EVC and Right EVC stimulation conditions ($F(2,14) = 0.38$; $p = 0.963$; $\eta_p = 0.005$) in the *fixation task* (where of course stimulus direction was maintained within the

same visual hemifield), determined via a repeated measures ANOVA. As such, there was no difference in performance for the **1)** TMS over left EVC vs. right EVC for stimulus presented within left VF ($t(7) = 0.69$, $p = 0.514$; Figure 3.5; Page 73), , determined via a paired-sample t-test and **2)** TMS over left EVC vs. right EVC for stimulus presented within right VF ($t(7) = -0.77$, $p = 0.464$; Figure 3.5; Page 73), determined via a paired-sample t-test. In summary, TMS over EVC had no effect in our *fixation task*, in agreement with previous findings that combined TMS over EVC and memory of a single visual stimulus (van de Ven et al. 2012).

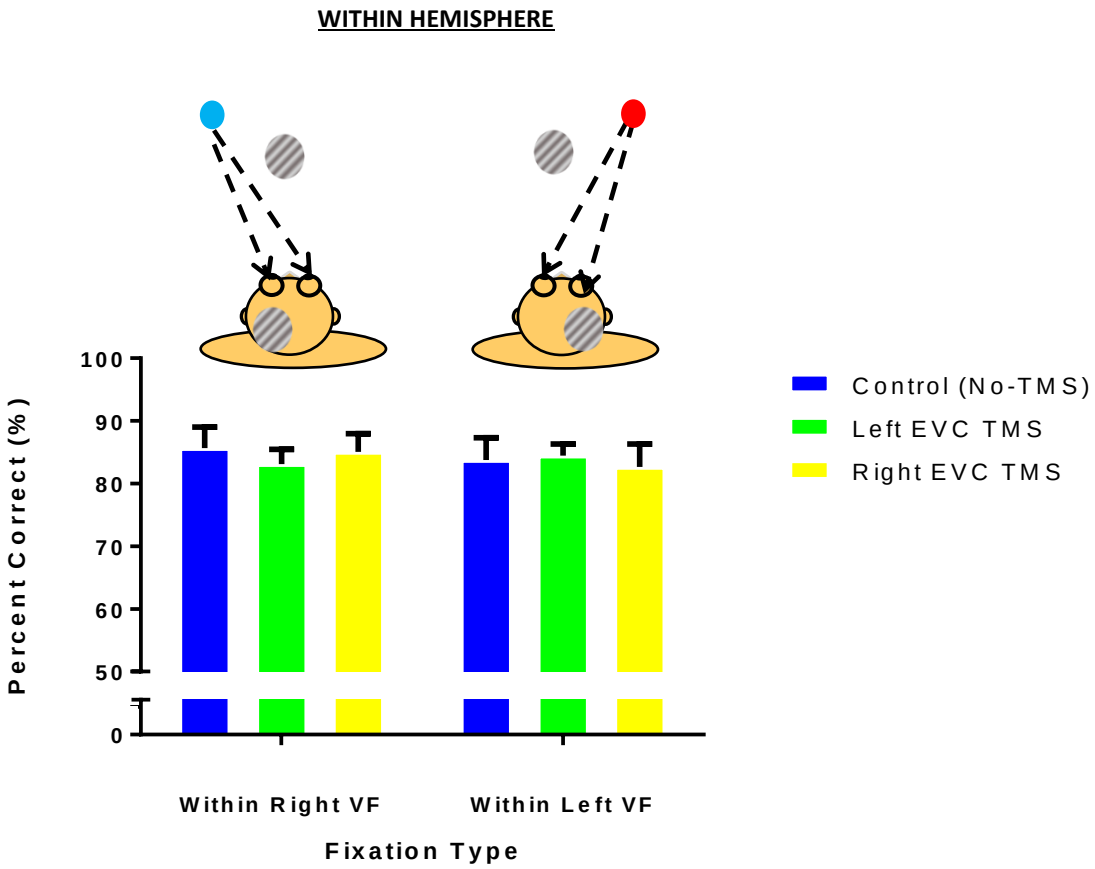


Figure 3.5: Results of the no-TMS baseline control (blue), left EVC TMS (green), and right EVC TMS (yellow) stimulation conditions during the *fixation task*. In these trials, the location of the stimulus is maintained within the right or left VF.

TMS During Saccades That Did Not Cross Mid-line

Figure 3.6 (Page 75) compares the mean percent correct responses of the No-TMS baseline control, Left EVC and Right EVC TMS conditions across all subjects for the *saccade task* in which eye position did not cross mid-line (Figure 3.2b; Page 59). Again, data were sorted according to the hemifield of the stimulus appearance (within right VF and within left VF; Figure 3.2b; Page 59). There was no significant difference in performance between the Left EVC and Right EVC TMS conditions in the *saccade task* where the stimulus was maintained within the right VF ($t(7) = 1.50$; $p = 0.178$; Figure 3.6; Page 75) and within the left VF ($t(7) = -0.59$, $p = 0.573$; Figure 3.6; Page 75), determined via paired-sample t-tests. There was also no difference for either left EVC or right EVC TMS from the no-TMS baseline for either side of visual stimulation (within right VF: $F(2,14) = 0.57$, $p = 0.580$, $\eta_p = 0.075$; Figure 3.6; Page 75, within left VF: $F(2,14) = 0.24$, $p = 0.787$, $\eta_p = 0.034$; Figure 3.6; Page 75), determined via repeated measures ANOVA. In summary, even in the *saccade task*, TMS had no effect when the stimulus was both perceived and retained in the same visual quadrant.

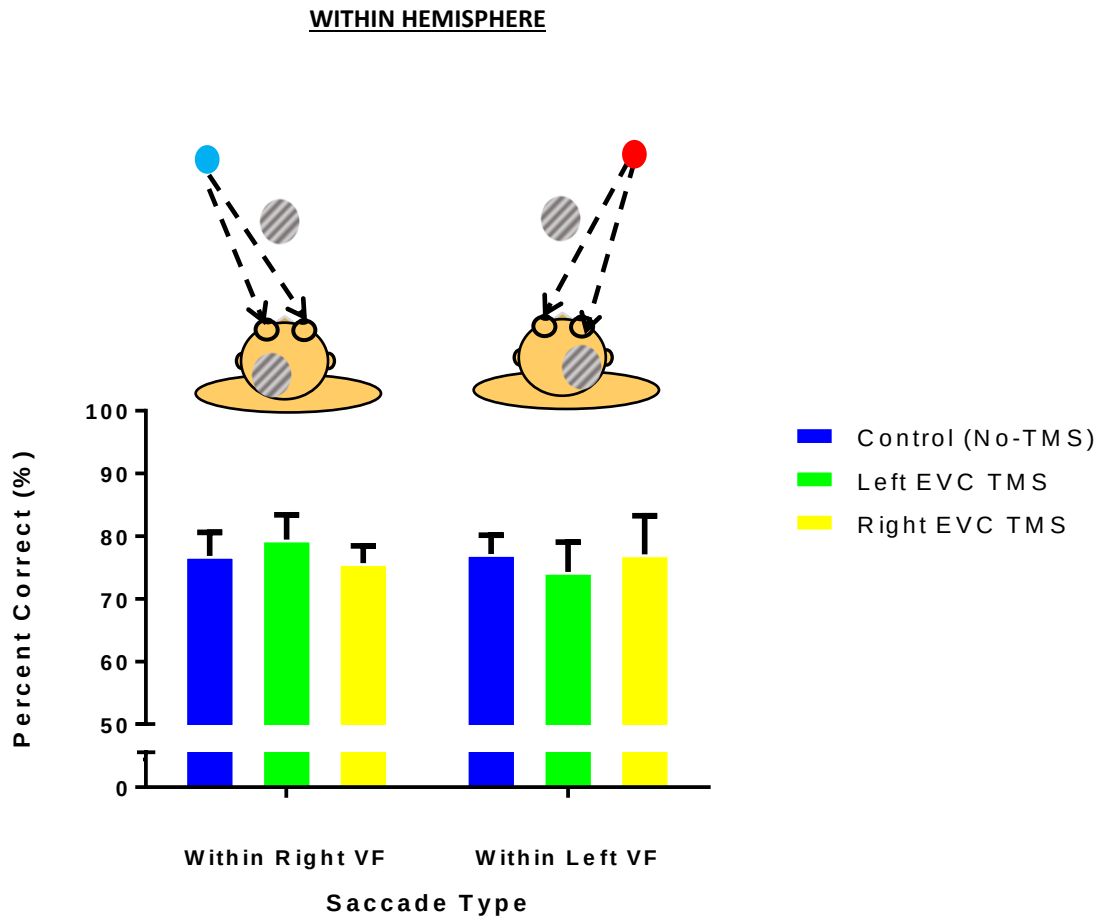


Figure 3.6: Results of the no-TMS baseline control (blue), left EVC TMS (green), and right EVC TMS (yellow) stimulation conditions during the *saccade task*. In these trials, the location of the stimulus is maintained within the right or left VF despite of an eye movement.

TMS During Saccades That Crossed Mid-line

In contrast to trials where saccades stayed on the same side of mid-line, when saccades crossed mid-line (as seen in Figure 3.2c; Page 59), causing the location of the stimulus to be remapped in the opposite hemisphere (Figure 3.2c; Page 59), we observed a suppression of performance during TMS over the quadrant corresponding to final (remembered and remapped) visual stimulus, compared to TMS over the opposite (perceiving) hemisphere (Figure 3.7; Page 77). A significant suppressive effect of TMS was found for the left EVC (in comparison to the contralateral right EVC TMS) when saccades were made from the left VF to the right VF ($t(7) = -2.46$; $p = 0.044$; Figure 3.7; Page 77), determined via a paired-sample t-test. Right EVC TMS (compared to left EVC TMS) when saccades were made from the right VF to the left VF showed no significant effects ($t(7) = 0.70$; $p = 0.506$; Figure 3.7; Page 77), determined via a paired-sample t-test. Thus, as predicted by our hypothesis, TMS suppressed performance when applied to the side of EVC that did not 'perceive' the visual stimulus, but would be expected to be activated by remapping.

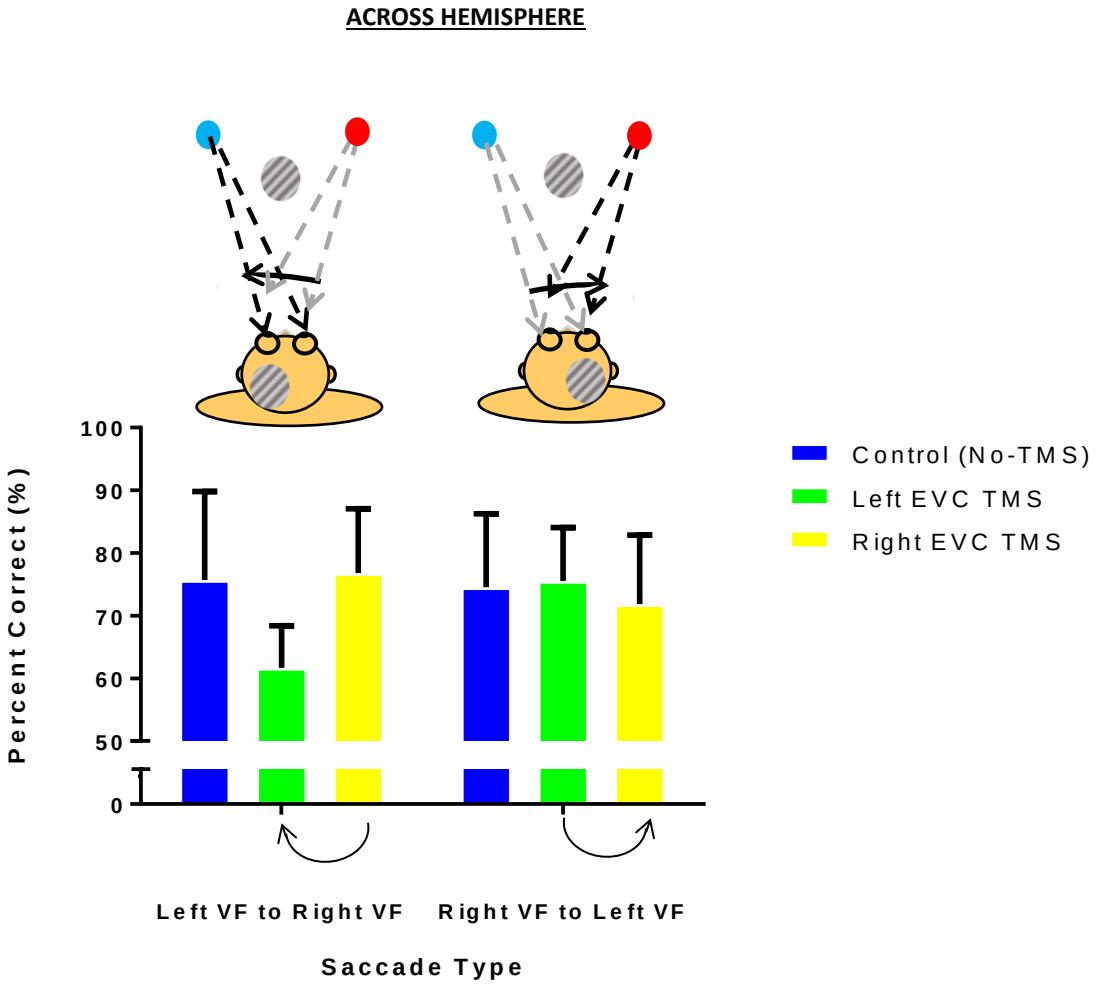


Figure 3.7: Results of the no-TMS baseline control (blue), left EVC TMS (green), and right EVC TMS (yellow) stimulation conditions during the *saccade task* that resulted in the stimulus to reverse the hemifield (bottom-right to bottom-left or vice versa).

TMS During Saccades of Different Sizes That Crossed Mid-line

A previous study found that performance in a somewhat similar task decremented as a function of saccade size (Prime et al. 2007) so we checked to see if the same occurred in our no-TMS and/or TMS data. Saccades that crossed mid-line were grouped into small (6°), medium (12°) and large (18°) for no-TMS, left EVC TMS, and right EVC TMS data (Figure 3.8; Page 80). This revealed no progressive drop in performance for no-TMS, but a clear drop in performance, as a function of saccade size, for the TMS conditions (especially over Left EVC).

A repeated measures 3x3 ANOVA with stimulation conditions (No-TMS, Left EVC and Right EVC) and saccade sizes (Small, Medium and Large) showed a significant main effect of saccade size ($F(2,14) = 4.70$; $p = 0.027$; $\eta_p = 0.402$) and a significant interaction between saccade size and stimulation site ($F(4,28) = 3.41$; $p = 0.022$; $\eta_p = 0.327$). Pairwise comparisons of the interaction effects revealed a significant difference between small versus medium ($p = 0.006$) and medium versus large saccades ($p = 0.031$) for the left EVC TMS and a significant difference between right versus left EVC TMS ($p = 0.015$), for the large saccade sizes.

Separate repeated measures ANOVA for just the no-TMS data revealed no significant effect of saccade size ($F(2,14) = 0.47$; $p = 0.635$; $\eta_p = 0.063$). There was no significant effect of saccade size for right EVC TMS ($F(2,14) = 0.95$; $p = 0.409$; $\eta_p = 0.120$), whereas a significant effect of saccade size was found for left EVC TMS ($F(2,14) = 10.54$; $p = 0.002$; $\eta_p = 0.601$). Bonferroni corrected pairwise comparisons were then made in the left EVC TMS data and revealed a significant difference in the subject's

performance for the small versus large saccade sizes (p = 0.006), and medium versus large saccades (p = 0.031) but not for small versus medium saccade sizes (p = 1.000).

Since these different saccade sizes tend to correlate with different saccade end points, a further analysis was conducted to test the effects of saccade endpoint (near or far in relation to the stimulus). No significant difference was found for the medium saccade sizes resulting in the final eye position near the stimulus versus far away from the stimulus ($t(7) = 1.00$, $p = 0.352$), determined via a paired-sample t-test. No significant difference was found for the medium saccade size resulting in the final eye position near the stimulus versus small saccade size ($t(7) = -1.74$, $p = 0.126$), determined via a paired-sample t-test. Similarly, no significant difference was found in performance during trials of medium saccade size resulting in the final eye position far away from the stimulus versus large saccade size ($t(7) = 1.61$, $p = 0.152$), determined via a paired-sample t-test. To summarize, performance was reduced as a function of saccade size for saccades that crossed mid-line, during TMS trials (especially for the Left EVC TMS condition).

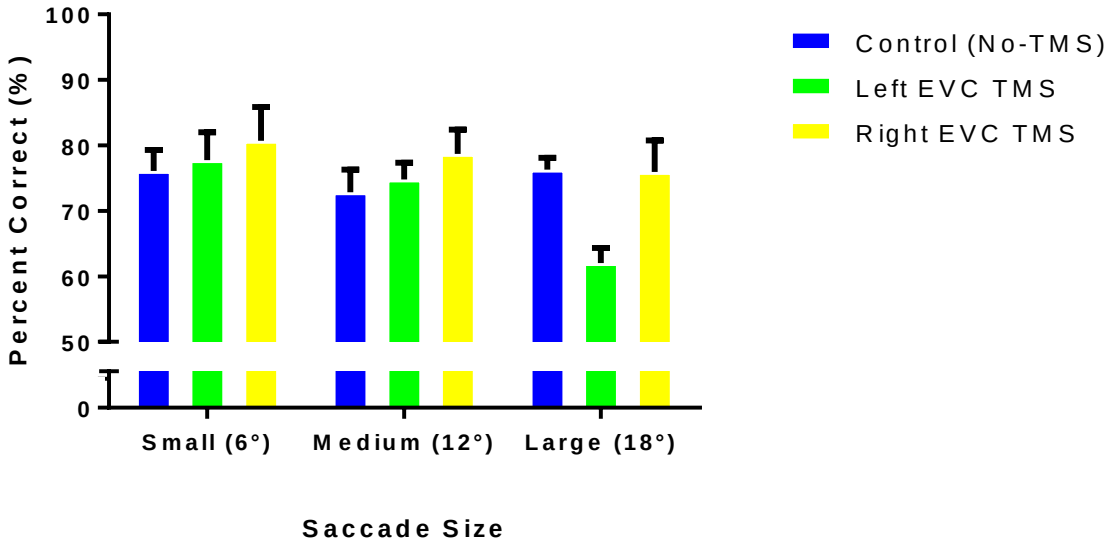


Figure 3.8: Results of the no-TMS baseline control (blue), left EVC TMS (green), and right EVC TMS (yellow) stimulation conditions during the *saccade task* when saccades crossed mid-line, analyzed on the basis of saccade size (Small = 6°, Medium = 12°, Large = 18°).

Discussion

Our findings are the first to show a causal role of human EVC (and/or its network connections) in the gaze-centered remapping trans-saccadic perception of visual feature information across saccades. Previous studies have shown that the striate cortex has access to memory representations in the visual short-term memory storage (Harrison and Tong 2009) and remapping of visual targets during saccades (Merriam et al. 2007). However, little research has been conducted to examine the functional role of EVC in the integration of visual feature information across saccades. Our results (summarized in Figure 3.9A; Page 87) suggest that orientation discrimination was inhibited when saccades across midline brought the gaze-centered location of the remembered stimulus in line with the stimulated VF, and that this effect increases with saccade size. This implicates EVC in remapping the stimulus attributes and suggesting that the neural representation for trans-saccadic memory is (at least at the early stages) retinotopically-defined.

We presented an orientation discrimination task and administered rTMS over regions of EVC corresponding to the bottom-right and bottom-left quadrants of VF, relative to gaze in order to investigate the functional role of EVC in spatial remapping and TSP in healthy human participants. Since the rTMS pulses were used to affect the contralateral VF (as confirmed by our fMRI localizers), the other VF served as a within-subject control. In our *fixation task,* the perceived and remembered visual stimulus was always on the same visual hemifield (ipsilateral or contralateral) to TMS, whereas in our *saccade task,* the visual stimulus could be maintained in the same hemifield, or the

hemifields of the perceived and remembered stimulus could be reversed, presumably requiring an internal remapping of visual information between the two sides of visual cortex (Dougherty et al. 2003; Merriam et al. 2003; Merriam and Colby 2005; Merriam et al. 2007). Our results showed that TMS over EVC could disrupt performance in our experiment, but only when saccades crossed the mid-line (causing a gaze-centered reversal of the perceived versus remembered stimulus) and only when TMS was applied to the side of EVC that corresponded to the target hemisphere of the hypothetically remapped stimulus. Further, this effect increased with saccade size, during the TMS conditions (Figure 3.9; Page 87). Previous studies have implicated EVC in short term visual memory (van de Ven et al. 2012) and remapping of object locations (Merriam et al. 2003; Merriam and Colby 2005; Merriam et al. 2007), but to our knowledge this is the first evidence for a role of EVC in remapping a visual feature (stimulus orientation). Note that our task requires not only trans-saccadic memory of a visual feature, but also trans-saccadic integration, in the sense that subjects had to compare orientation of a remembered stimulus with a test stimulus (which always appeared at the spatial location of the remembered stimulus). This raises the possibility that our TMS effects were actually caused by interfering with perception of the test stimulus rather than memory of the initial stimulus. This is unlikely, because TMS only had an effect when the remembered stimulus appeared on the opposite VF to the TMS site and the stimulus was then (presumably) remapped into the VF of the TMS site. The effect was otherwise unrelated to the side of the test stimulus (i.e. it had no effect when the perceived and remembered saccades were on the same side, whether contralateral or ipsilateral), during

fixation or *saccades*. Further, it is likely that TMS has a more disruptive effect on memory (perhaps because it must be maintained by internal activity) than it does on perception, where extrinsic information likely overrides the effects of TMS (Melcher and Colby 2008; Melcher 2009).

Our results show a suppressive effect of TMS on visual memory (specifically trans-saccadic memory) for a single visual object using a *saccade task* paradigm (Figure 3.9; Page 87). In a previous study (van de Ven et al. 2012), subjects performed a shape discrimination task with low (1 target) and high (3 targets) memory loads, presented in the bottom-left VF in a *fixation task* paradigm, while TMS (phosphene localized) was administered at 100, 200 and 400 ms into the retention interval. The authors found no significant effects of TMS at the low memory load condition (1 target). However, significant suppressive effects of TMS were determined when stimulation was administered at 200 ms during the higher memory load condition (3 targets), further implicating a role of EVC in short-term memory consolidation of sensory visual information. Thus, our *fixation task* results are consistent with the results of van de Ven et al. (2012) for a single visual target, but our *saccade task* results show an additional effect that depended on stimulation site, the gaze-centered location of the remembered stimulus, and saccade metrics.

Our laboratory previously used a similar TMS task to investigate the role of the parietal eye fields (PEF) and frontal eye fields (FEF) in trans-saccadic integration (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011). However, those experiments utilized multiple saccade directions and a range of different stimulus set sizes. As in the current

study, these studies showed greater effects during *saccades* compared to *fixation*, and as in van de Ven et al. (2012) these effects increased with set size. However, TMS over FEF produced no significant effect during saccades with a single memory target. The more important difference with the current study was that in those studies the TMS effect was independent of saccade and visual stimulus direction, whereas in the current study the effect was highly dependent on both. Thus, Prime et al. (2011) interpreted their results as a disruption of the saccade efference copy used to drive the remapping of the stimulus features (Prime et al. 2006; Prime et al. 2007; Sommer et al. 2008). The current results are consistent with a model in which EVC is involved in the early aspects of the visual memory storage mechanism (Lamme and Roelfsema 2000; Bullier 2001; Hochstein and Ahissar 2002; Ro et al. 2003; Prime et al. 2008; Prime et al. 2010; Prime et al. 2011; de Graaf et al. 2012). This is also consistent with fMRI results of Merriam et al. (2007) that showed that cortical visual areas ipsilateral to the stimulus respond during a single-step *saccade task.* Activation was thought to be in response to remapping from contralateral to ipsilateral hemisphere with the saccade. Such results demonstrated the presence of updated visual representations in cortical regions, thereby directly linking them to trans-saccadic perception.

Suppressive TMS effects seen over EVC may result due to interference with signal processing by decreasing the strength of such signals or overwriting the neural representation of memory trace in the visual cortex (Harris et al. 2008; van de Ven et al. 2012). These findings of lateralized TMS effects on a memory-based perception task further suggest that neural memory representation is retinotopically-defined, consistent

with suggestions made by van de Ven et al. (2012). This notion formed the basis of the hypotheses that we tested, and in general our results were consistent with this idea. An alternative is that TMS injects 'noise' into local cortical signals. This could account for our finding that TMS had greater effects as a function of saccade size. Larger saccades take longer to produce (Abrams et al. 1989), so this would allow more time for TMS to influence the signals (saccade efference copies and other computations) associated with remapping (Keith et al. 2010). Larger saccades have also been shown to reduce performance during egocentric updating and trans-saccadic integration tasks in the absence of TMS, presumably due to noisy internal signals (Prime et al. 2007; Byrne et al. 2010). This was not observed here, but it is possible that such internal noise interacted with the noise injected by TMS to produce the largest suppressive effects for larger saccades. Given that this noise might influence the structures that EVC connects to, we cannot be certain that our effects were caused primarily at the site of stimulation. Areas V2 and V3 (Nakamura and Colby 2002), V4 (Merriam et al. 2007), LIP (Duhamel et al. 1992; Goldberg et al. 1990; Gottlieb et al. 1998; Heiser et al. 2005; Kusunoki et al. 2000; Li and Anderson 2001), FEF, and SC (Nakamura and Colby 2002; Umeno and Goldberg 1997; Walker et al. 1995) have been observed to be involved in spatial remapping. Even if this were the case, it would still implicate a physiological role for EVC, since physiological noise within EVC would be expected to have similar effects.

In conclusion, our results confirm that a significant component of trans-saccadic memory and trans-saccadic integration must occur in gaze-centered coordinates, and involve the remapping of signals within these coordinates during saccades (Figure 3.9;

Page 87). Second, it supports the notion that trans-saccadic memory involves additional computations to visual working memory, at the least the saccade-dependent signals required for remapping (Merriam et al. 2003; Merriam and Colby 2005; Merriam et al. 2007). Finally, it supports the notion that EVC (or closely associated occipital structures) are involved, presumably with the aid of recurrent connections related to attention and saccades (Merriam et al. 2007). However, it remains likely that this is only part of the visual memory storage system during saccades; it is likely that other structures, including parietal, temporal, and frontal cortex (as well as subcortical structures) are involved more or less, perhaps depending on the detailed nature of the task and the subjects cognitive set (Prime et al. 2007; Prime et al. 2010; Thielscher et al. 2010; Prime et al. 2011; de Graaf et al. 2012).

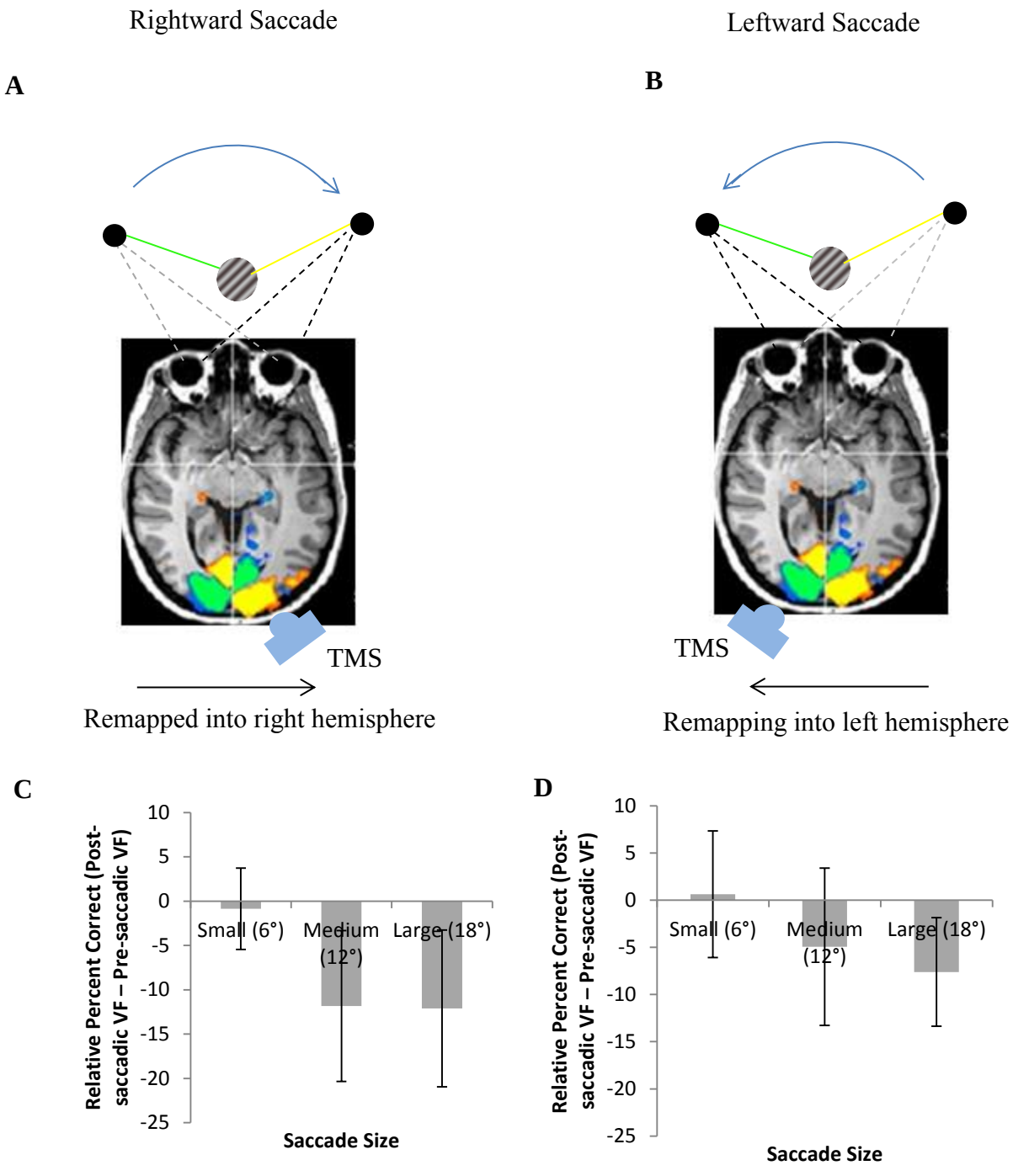


Figure 3.9: Hypothesis and summary of main results for the key EVC TMS / saccade across mid-line tasks. *Top Row*: hypothesis: TMS over EVC interrupts remapping of signals into the corresponding visual field. **A**: rightward saccade reverses gaze-centered internal representation of central oriented stimulus from right (outgoing; post-saccadic) to left (incoming; pre-saccadic) visual field, so TMS over right EVC should interfere with

remapped memory. **B**: leftward saccade reverses internal representation of stimulus from left to right visual field, so left EVC TMS should interfere with remapped memory. *Lower Row*: Confirmation of hypothesis and summary of results using plots of performance (% correct) during EVC TMS corresponding to the 'post-saccadic' visual field, minus the control site (TMS over opposite EVC, i.e., the 'outgoing' visual field), done separately for each saccade amplitude. The data correspond to the situations shown in the upper row, so in **C** the 'post-saccadic' site is right EVC, and in **D** the 'post-saccadic' site is left EVC. In each case, as predicted by the hypothesis, there is a reduction in performance (negative going bars) relative to the opposite control site, and also this effect increases with saccade size. (See RESULTS section for statistical analysis of the results summarized here).

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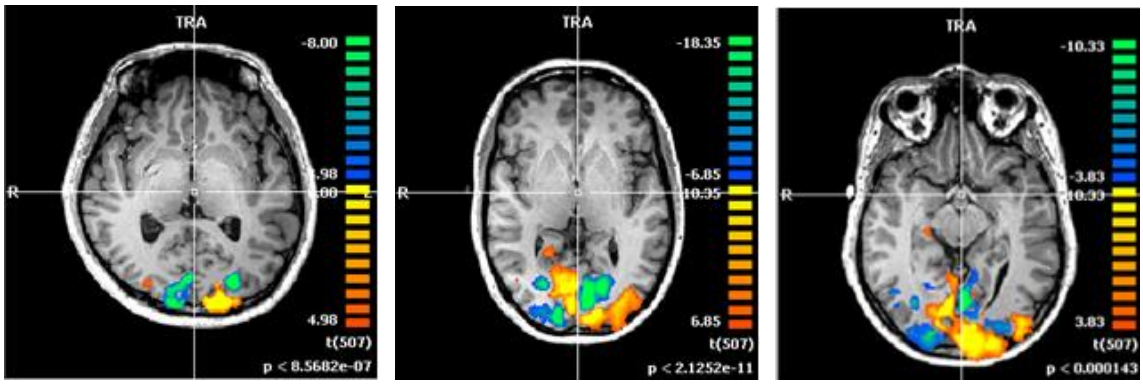
SUPPLEMENTARY FIGURES AND TABLES

Subject 1 Subject 2 Subject 3



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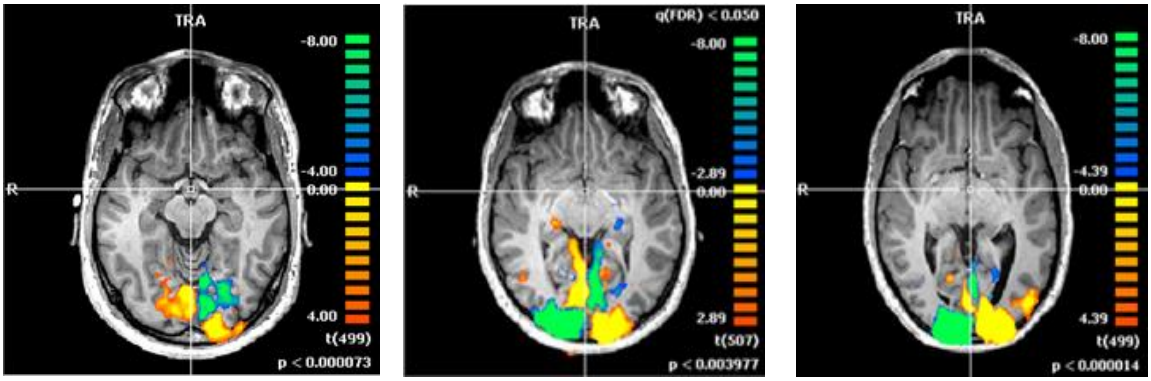

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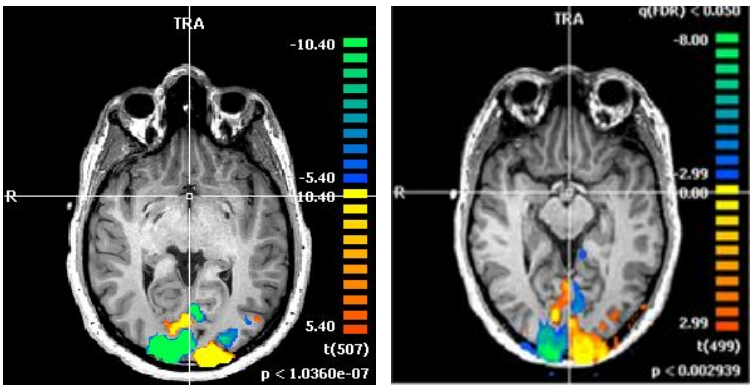

Figure S1: Functional localizer analysis for all subjects (n = 8) that participated in the TMS experiment and their data was used for the analysis, conducted using BrainVoyager QX 2.10. This figure illustrates the clusters of activation seen in the various quadrants of the visual field, in the transverse plane.

Table S1: Resting motor threshold recorded for each subject during the TMS sessions.

SUBJECT ID	RESTING MOTOR THRESHOLD (PERCENT)
1	58
2	54
3	60
4	59
5	70
6	62
7	61
8	65

Contributions

Designed the experiment (PM, JCD, JDC), conducted the experiments (PM), wrote code for data analyses (JCD), data analyses (PM). The text was written by PM and edited with input from JDC and JDC.

CHAPTER 4

GENERAL DISCUSSION

4.1 SUMMARY

In this thesis, I investigated the role of the striate EVC during the process of TSP of low level visual features (i.e. orientation). The results of this experiment (presented in Chapter 3) showed how low level visual feature information is retained and integrated via spatial remapping during TSP to provide a unified visual perception of the natural world. These findings provide evidence that the human EVC plays a crucial role in spatial remapping and integration of low level visual features and stimulus locations, presented in discrete fixations or separated across saccade.

In this chapter, I will discuss the relevance and implications of the results and how they can be used in addition to previous studies (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011; van de Ven et al. 2012; Tanaka et al. Unpublished) to further enhance our understanding of spatial remapping and TSP from the perspective of the visual cortex. I will also further expand on how this is a novel experiment and is different from previous studies. At last, I will suggest future research directions and discuss a follow-up experiment that I conducted during the time of my masters training to further enhance our understanding on the role of striate cortical visual regions in spatial remapping and TSP.

4.2 DISCUSSION

4.21 Trans-saccadic Perception

Trans-saccadic perception involves two steps: **1)** *Trans-saccadic memory* which is a short term memory store for discrete bits of visual information and **2)** *Trans-saccadic integration* which is a process through which the discrete bits of visual information from trans-saccadic memory are integrated together to give us a perception of a stable and unified visual world (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011). Two previous studies in our lab investigated the role of PPC (more specifically parietal eye fields (PEF)) and FEF in trans-saccadic integration using a spatial working memory task (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011). Both, FEF and PPC were found to have a crucial role in this process due to suppressive TMS effects over these regions. However, such TMS effects differed in temporal specificity. Prime et al. (2008) provided evidence for disruptive TMS effects at 200 ms over right PPC. In addition, another study by Prime et al. (2010) showed disruptive TMS effects over right FEF and left FEF at 100 and 200 ms during the *saccade task*. Therefore, these findings further suggested that right PPC, right FEF and left FEF serve an important role during spatial processing involved in trans-saccadic memory (Prime et al. 2008; Prime el al. 2010).

Another recent study in our lab investigated the role of dorsolateral prefrontal cortex (DLPFC) and provided evidence for a crucial role of this region in a spatial working memory task (Tanaka et al. Unpublished). More specifically, DLPFC was reported to play a key role in spatial working memory when stable *fixation* was

maintained. During such trials, suppressive TMS effects were reported at 100 ms over right DLPFC and at 200 ms over Left DLPFC. However, during the *saccade task*, TMS was stated to have facilitative effects at 300 ms over right DLPFC and 200 ms over Left DLPFC. These effects suggested that the role of DLPFC depends on the requirements of a given task type and TMS may have resulted in a dis-inhibition of trans-saccadic processing. As such, during the *saccade task*, memory signals may be transferred to areas associated with the remapping network (Tanaka et al. Unpublished).

Furthermore, a recent study by van de Ven et al. (2012) provided evidence for a key role of EVC in memory representations, especially with higher memory loads, using a *fixation task* paradigm. A shape discrimination task was used where stimuli were presented at varying angles in the bottom right visual field, relative to gaze. No significant TMS effects were reported with a low memory load condition (1 target), whereas significant suppressive TMS effects were reported at 200 ms into the retention interval with a higher memory load condition (3 targets). Overall, the study by van de Ven et al. (2012) suggested that sensory areas such as EVC are involved in short term memory and TSP of object feature information. However, the role of EVC in the process of spatial remapping required for the integration of visual information acquired before, during and after eye movements had not been previously investigated.

4.22 Current Study

The experiment presented in Chapter 3 tested whether the human EVC plays an important role in the process of trans-saccadic perception (trans-saccadic memory and trans-saccadic integration of low level visual features). The questions posed for the study included: **1)** Does TMS over EVC disrupt trans-saccadic visual memory?; **2)** Specifically, does TMS at the time of a saccade affect remapping of the stimulus into the post-saccadic visual field (compared to the pre-saccadic visual field where the object was viewed)?; and **3)** Do such effects depend on saccade metrics (saccade size and/or target eccentricity)?

To date, only two studies have looked at the role of human EVC in the process of trans-saccadic perception using visual feature memory task in a *fixation paradigm* (De Weerd et al. 2012; van de Ven et al. 2012). However, neither of them used a *saccade task* paradigm to study the role of EVC in spatial remapping. Furthermore, neurophysiology studies have revealed neuronal activity in the monkey parietal cortex and intralateral parietal cortex in remapping object locations across saccades (Duhamel et al. 1992; Bays and Hussain 2007). More recently, with the advancement of fMRI, neuroimaging studies have provided evidence of the role of the striate cortex (Merriam et al. 2007), lateral intraparietal cortex (Goldberg et al. 1990; Duhamel et al. 1992; Gottlieb et al. 1998; Kusunoki et al. 2000; Li and Anderson 2001; Heiser et al. 2005; Merriam et al. 2007), FEF and SC (Merriam et al. 2007) in the process of visual remapping and updating

spatial information. However, no such study has yet looked at spatial updating of visual features across saccades.

As such, this experiment was novel in the experimental paradigm as well as the use of fMRI-guided TMS neuronavigation. The main findings of this experiment include: **1)** No significant TMS effects when stimulus was maintained within the same visual field for the *fixation* and *saccade tasks*; **2)** Significant suppressive TMS effects when pulses were administered over the EVC region corresponding to post-saccade VF, in comparison to the pre-saccade VF (especially for left EVC TMS); and **3)** Suppressive TMS effects (as stated in finding 2, above) were higher as the saccade size increased, however the effects did not depend on the saccade endpoint.

The trans-saccadic perception task used in this study requires the location and visual feature information (i.e. orientation) of the stimulus to be remapped as a result of a saccade. For example, a target appearing in the left visual field, relative to gaze must be remapped into the opposite hemisphere as its location changes to being in the right visual field following a leftward saccade, and vice versa. Previous studies in our lab have established the role of PPC, FEF (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011) and DLPFC (Tanaka et al. Unpublished) in the updating of memory signals and spatial remapping using a *fixation* and *saccade task* paradigm (Figure 4.1; Page 102). Prime et al. (2008; 2010; 2011) provided evidence for a suppressive effect of TMS over human PPC and FEF. Additionally, Tanaka et al. (Unpublished) provided evidence of the role of DLPFC during the *fixation task* due to suppressive TMS effects, and facilitative TMS effects during the *saccade task* due to dis-inhibition of trans-saccadic perception. Other

TMS studies by van de Ven et al. 2012 have provided evidence of the role of human EVC in VSTM and storage of visual feature information using a *fixation task* paradigm in a shape discrimination task. The study presented in this thesis is the first to provide evidence for the role of EVC in spatial remapping using a *saccade task* paradigm for an orientation discrimination task. As such, the work presented in this thesis builds upon the work previously conducted by Prime et al. (2008; 2010; 2011), Tanaka et al. (Unpublished) and van de Ven et al. (2012), and further contributes to the understating of the processes of trans-saccadic perception and spatial remapping along with the role of human EVC. It has been proposed that there may be several distinct yet interconnected networks for trans-saccadic perception and spatial remapping. The current data provides support for the role of an additional area, namely EVC within the trans-saccadic perception and spatial remapping network. It is also possible that other regions may also be involved in the network and further research is necessary.

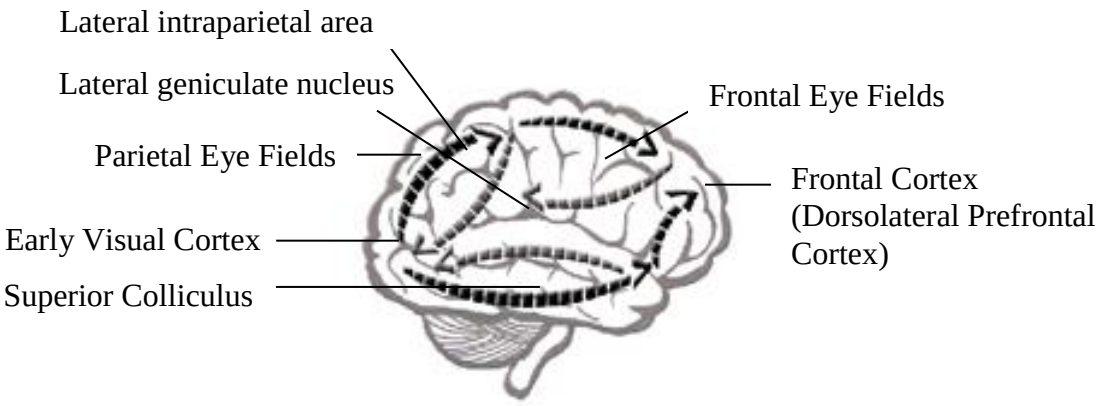

Figure 4.1: Illustration of the detailed brain anatomy, showing projections from saccade centres to EVC and other higher order visual areas (Beckers and Homberg, 1992; Cowey and Walsh, 2000; de Graaf et al., 2012; Duhamel et al., 1992; Gottlieb et al., 1998; Heiser et al., 2005; Kusunoki et al., 2000; Merriam et al., 2007; Nakamura and Colby, 2002; Pascaul-Leone and Walsh, 2001; Walker et al., 1995).

4.23 Suppression with rTMS

TMS has been known to produce either suppressive or facilitative effects when administered at different frequencies, over different cortical regions and at different stimulator outputs. For example, lower frequencies in the 1 Hz range over the motor cortex can have a suppressive effect whereas, higher frequencies in the 20 Hz range can result in a temporary increase in cortical excitability (Kobayashi and Pascual-Leone 2003). These effects may also vary among individuals (Kobayashi and Pascual-Leone 2003). However, the effects of low frequency rTMS are robust and long-lasting. TMS can also result in muscle twitches when administered over the motor cortex or phosphenes when administered over the visual cortex. Such effects indicate an increase in the excitability of the targeted neural population (Baker et al. 1985). rTMS to EVC during saccades may suppress the strength of signals being sent to/from this region or overwriting the neural representation of memory traces in the visual cortex (Harris et al. 2008; van de Ven et al. 2012). As such, rTMS at 10 Hz during a trans-saccadic perception task was found to have a suppressive effect when administered over the region of the EVC into which the stimulus is remapped as a result of a saccade. Our findings of suppressive TMS effects suggest that human EVC and/or its neural connections play a role in the process of trans-saccadic perception.

It is also possible that the noise added due to TMS might also influence the structures connected to V1 such as areas V2 and V3. In such situations, we cannot be certain that our effects were caused primarily at the site of stimulation. However,

previous studies have also observed remapping signals in areas V2 and V3 (Nakamura and Colby 2002). As such, even if this were the case, our results would still implicate a physiological role for EVC, since physiological noise within EVC would be expected to have similar effects.

4.24 Hemispheric Asymmetry

Human EVC is known to be asymmetric between hemispheres. The results of the current study indicate a left hemispheric dominance with greater suppressive TMS effects for the left EVC in comparison to the right EVC. A histological comparison of the neural population in the left and right primary visual cortices using 5 autopsy specimens from healthy (non-dyslexic) subjects revealed that the left primary visual cortex had larger neurons (Jenner et al. 1999). Further, a majority of subjects were right-handed, thus having a left hemispheric dominance and may have had an increased activation of the left hemisphere when required to perceive the stimulus and make a response. As such, these can be possible reasons for the asymmetric effects of rTMS seen during the experiment presented in Chapter 3. During the *saccade task*, performance was greatly suppressed when rTMS was administered over the 'post-saccadic' visual field into which the target is remapped due to a saccade (especially for the Left EVC TMS). Such findings were consistent for all saccade size (small 6°, medium 12° and large 18°) conditions and increased as the saccade size increased. A similar trend of suppressive TMS effects were seen over the right EVC, however, the drop in performance was not found to be significant. As such, it is clear that the left EVC plays a much more important role in

spatial remapping and trans-saccadic memory storage of low level visual features and its role becomes more complex and more susceptible to disturbances due to rTMS during the *saccade task.*

4.25 Possible Physiological Mechanisms

The "what" and "where" pathways are represented in EVC, including areas V1 and V2 (Figure 1.1; Page 9). The "what" pathway projects to area V4, lateral occipital cortex, and temporal cortex and the "where" pathway projects to the middle temporal area, medial superior temporal area, parietal cortex, frontal cortex, and superior colliculus (Daw 2012; Figure 1.1; Page 9). There are many interconnections and feedback projections between the two pathways.

Saccades involve rapid jumps between different points in the field of view. The main purpose of a saccade is to bring an object of interest into the fovea (Daw 2012). In spite of such saccades, our abilities to perceive a stable, coherent visual world is due to the process of *spatial remapping*. Neurophysiology studies have found a role of various brain regions in the process of spatial remapping. Single-unit recordings from the macaque LIP in a task where a stimulus is presented outside the receptive field of the neuron and the monkey makes a voluntary eye movement, changing the location of the stimulus, relative to gaze (i.e. bringing the receptive field onto the recently stimulated screen location) have provided evidence for a role of LIP in remapping, implicating that memory traces of brief visual stimulus are stored in this region (Duhamel et al. 1992; Goldberg et al. 1990; Gottlieb et al. 1998; Heiser et al. 2005; Kusunoki et al. 2000). Moreover, inactivation of LIP also impaired performance on tasks involving updated

spatial information (Li and Anderson 2001). Neurons in FEF, SC, and EVC have also been found to be involved in remapping due to their spatially selective visual and peri-saccadic responses (Nakamura and Colby 2002; Umeno and Goldberg 1997; Walker et al. 1995). Single-unit and multi-unit recordings from macaque V1 neurons during a *fixation task* showed activation dependent on luminance and changes in lightness (Kinoshita and Komatsu 2001), and bars of a particular orientation (Van Hooser et al. 2005). V4 neurons have been reported to be tuned to the length and width of bars (Desimone and Schein 1987).

More recently, a fMRI study has shown activation in EVC in response to spatial updating (Merriam et al. 2007). The current study aimed to test the role of human EVC in spatial updating using TMS. Our findings revealed a suppressive effect of TMS, especially over the left hemisphere during the *saccade task* which required spatially updated visual information. Such effects were found to increase as the saccade size increased. This shows that TMS interferes with signal processing by decreasing its strength, overwriting memory traces or by injecting noise into local cortical signals. As such, remapping takes place in gaze-centered coordinates and recurrent connections in EVC related to attention and saccades are affected by TMS. However, it is also possible that other closely connected regions to EVC may also be affected by TMS. Areas V2 and V3 (Nakamura and Colby 2002), V4 (Merriam et al. 2007), LIP (Duhamel et al. 1992; Goldberg et al. 1990; Gottlieb et al. 1998; Heiser et al. 2005; Kusunoki et al. 2000; Li and Anderson 2001), FEF (Nakamura and Colby 2002; Prime et al. 2008; Prime et al. 2010; Prime et a. 2011; Umeno and Goldberg 1997; Walker et al. 1995), PEF (Prime et

al. 2008; Prime et al. 2010; Prime et a. 2011), SC (Nakamura and Colby 2002; Umeno and Goldberg 1997; Walker et al. 1995), and DLPFC (Tanaka et al. Unpublished) have been observed to be involved in spatial remapping.

4.3 CONCLUSIONS

Previous studies by Prime et al. (2008; 2010) have demonstrated that single pulse TMS to the PPC and FEF has a suppressive effect on performance during a trans-saccadic memory task. However, Tanaka et al. (Unpublished) provided evidence of facilitative effects of TMS over DLPFC. Since trans-saccadic memory is one of the stages of the process of TSP where visual feature information is stored temporarily, such findings implicate overall suppressive effects (for PPC and FEF) and facilitative effects (for DLPFC) of TMS. These studies also implicate that TMS may disrupt spatial updating required for the remapping of memory representations and may possibly compromise efferent copy signals related to saccades.

Since there is a high abundance of photoreceptors including rods and cones in the fovea, there is a greater visual acuity in this region. As such, when humans make eye movements, visual information from a relatively small area of the retina is used for the purpose of TSP. Previous studies have demonstrated that natural vision is a snapshot of a given scene that is spatially and temporally separated due to saccadic eye movements. Despite of this separation, we are able to perceive the world as a continuous perceptual whole. TSP is a complex process and several previous studies have provided evidence for the involvement of different brain regions (shown in figure 4.1; Page 102) including PPC

(PEF) and FEF (Prime et al. 2008; 2010; 2011), DLPFC (Tanaka et al. Unpublished), LIP (Melcher and Colby 2008) and SC (Walker et al. 1995). Therefore, it is clear that low level visual feature information and spatial location relative to gaze is stored and transferred across a distributed network. Further research needs to be conducted to investigate the role of these potential regions using a similar *saccade task* paradigm in healthy human participants.

4.4 FUTURE RESEARCH DIRECTIONS

The results of this experiment provide evidence of the role of human EVC in the process of spatial remapping for TSP of low level visual features. As such, these results causally implicate human EVC (and/or its network connections) in the gaze centered remapping TSI *visual feature information* across saccades. However, the role of human EVC at a specific time in the feedforward pathway has not yet been established.

Several key questions raised by the results of this study include: **1)** Why the significantly different performance between the *fixation* and *saccade tasks* fundamentally differs from findings reported in previous studies that investigated the role of PPC and FEF (Prime et al. 2008; Prime et al. 2010; Prime et al. 2011); **2)** Why are their asymmetric effects of TMS over the human EVC?; and **3)** What are the temporally specific effects of TMS over the human EVC (i.e. Human EVC plays an important role at what point in the feedforward pathway?).

One of the key questions is the precise timing of the effect which I could not show with a rTMS paradigm. So, I attempted a follow-up experiment to the one presented in Chapter 3 to investigate the temporal specificity of the role of EVC in the processes of spatial remapping and TSP using a single pulse TMS paradigm. A brief summary of the results of this follow-up experiment are described in Appendix A. In this follow-up experiment, single pulse TMS was administered over functionally localized (via fMRI) regions of the EVC corresponding to the bottom-left and bottom-right visual fields while two targets were presented simultaneously, one in the upper-left or bottom-left visual

field and the second in the upper-right or bottom-right visual field. As such a higher memory load was used and single pulse TMS was administered at 100, 200 or 400 ms after the appearance of the second fixation point, cuing the subject to make a saccade. Based on the results of the main experiment (Chapter 3), saccade onset was found to be between 201-220 ms and saccade offset was determined to be between 221-260 ms on a majority of trials (Figure 3.4; Page 65). As such, the administration of single pulse TMS at 100, 200 or 400 ms from the onset of the second fixation point confirms that TMS was applied pre-saccade, peri-saccade and post-saccade on an equal frequency of trials. Unlike the rTMS paradigm presented in the main experiment, the single pulse paradigm was designed to separate the effects of TMS at the different timing conditions.

Performance was compared for trials where the stimulus was presented in the upper versus lower VF (3 timing conditions: 100, 200 and 400 ms). Additional comparisons were also made to look at the effects of TMS timings during the *fixation task* (stable fixation maintained); *saccade task* (stimulus maintained within the same VF; or stimulus location was changed from one VF to another, contralateral hemisphere stimulation served as a within-subject control). Overall, there was a significant difference in performance between the *fixation* and *saccade tasks* (Figure A1), similar to the findings of the main experiment (Chapter 3). Performance in trials during which the probe was presented in the upper visual field had a facilitation effect on performance and trials where the probe was presented in the lower visual field had a suppressive effect. Furthermore, no significant difference was found between the different TMS timing conditions when stable fixation was maintained (*fixation task*); stimulus location was

maintained within the same visual field (*saccade task*) and stimulus location was moved to the opposite visual field due to an eye movement (*saccade task*; comparison of relative performance (Post-saccadic 'remapped' VF – Pre-saccadic 'perceived' VF). Thus, this experiment failed in its current form.

A lack of temporally specific TMS effects seen during the follow-up experiment may be due to the low efficiency of single pulse TMS (in comparison to rTMS). Due to the differences in TMS effects to the upper versus lower visual field (Figure A7; Page 136), this experiment can be further improved by first using a rTMS paradigm with a higher memory load (two targets: one in the upper VF and the other in the lower VF). Based on the rTMS results, a follow-up experiment can be done using single-pulse TMS at varying timing conditions (100, 200 and 400 ms). It would also be useful to examine the findings demonstrated in this experiment using a fMRI or concurrent fMRI-TMS paradigm with a similar task. fMRI or concurrent fMRI-TMS could be used to examine whether the behavioural effects of TMS to EVC is also correlated with an increase in BOLD activity. Activation results of such fMRI or concurrent fMRI-TMS paradigm can also help to identify other potential areas in the trans-saccadic perception and spatial remapping network. These potential regions can be further examined using TMS.

Overall, the results discussed in this thesis provide evidence for the relevance and implications of the human EVC in the processes of spatial remapping and TSP of object feature information across eye movements. More specifically, our results confirm that a significant component of trans-saccadic memory and trans-saccadic integration must occur in gaze-centered coordinates, and involve the remapping of signals within these

coordinates during saccades. These results support the notion that trans-saccadic memory involves additional computations to visual working memory, at the least the saccade-dependent signals required for remapping (Merriam et al. 2003; Merriam and Colby 2005; Merriam et al. 2007). Results also support that EVC (or closely associated structures) are involved, presumably with the aid of recurrent connections related to attention and saccades (Merriam et al. 2007). Finally, these results help to further enhance our understanding of the importance of low-level visual areas in integrating spatial location and visual feature information to give us a perception of a stable continuous world.

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APPENDIX A

FOLLOW-UP EXPERIMENT

TRANSCRANIAL MAGNETIC STIMULATION OF THE HUMAN STRIATE EARLY VISUAL CORTEX DURING VISUAL SHORT TERM MEMORY AND TRANS-SACCADIC INTEGRATION

A.1 BRIEF INTRODUCTION

In chapter 3, I provided evidence to show that EVC (and/or its network connections) play a crucial role in spatial remapping and TSP. These findings suggested that subject's ability to perceive orientation change is suppressed due to rTMS (triple-pulse; 10 Hz) when saccades crossed mid-line and reversed visual fields of stimulus presentation. But, the exact temporal window of such suppressive TMS effects over EVC is still not known. In this follow-up experiment, a higher memory load (2 stimuli), with one stimuli presented in the top-right or top-left and the other stimuli presented in the bottom-right or bottom-left quadrants of the visual field, relative to gaze, was used during the *fixation* and *saccade tasks*. Single pulse TMS at various timing conditions (100, 200, and 400 ms from the appearance of the second fixation point) was administered.

Additionally, van de Ven et al. (2012) proposed that TMS has greater disruptive effects on short term memory consolidation when administered over EVC at a higher memory load (3 stimuli) in comparison to a low memory load (1 stimulus). Such suppressive effects were seen at 200 ms with the higher memory load condition (van de Ven et al. 2012). As such, their findings suggested that sensory areas such as EVC may also play a role in short term visual memory. Several other studies have also shown EVC to be involved in short term visual memory (Harrison and Tong 2009) and remapping of visual targets during saccades (Merriam et al. 2007). So, we have proposed that EVC is also involved in TSP of low level visual features such as orientation (Prime et al. 2006; Prime et al. 2008), and we predict to see TMS effects in the 'remapped' hemisphere (Chapter 3).

Given the findings of the first experiment, it is reasonable to further ask **1)** whether such suppressive TMS effects are temporally specific, and **2)** whether the effects depend on the memory load. So, in order to investigate the effects of TMS with various memory load conditions (high versus low), two stimuli were presented simultaneously where one stimulus served as an experimental test target and the other served as a distracter.

In this appendix, I discuss a similar experimental task (as the one discussed in Chapter 3) for studying the role of EVC in TSP with a higher memory load condition and temporally distinct TMS pulses (100, 200 and 400 ms from the appearance of the second fixation point; Figure A1; Page 129). Subjects were presented with two Gabor patches, one in the upper-right or upper-left and the other in the lower-right or lower-left quadrants of the visual field, relative to gaze. One target served as the experimental test target while the other served as a distracter. Subjects were required to judge the change in orientation of the probe in comparison to the previously presented target. Thus, to perform this task, subjects must be able to remember the orientation and spatial location of the pre-saccadic and post-saccadic targets across saccades made in the *saccade task.*

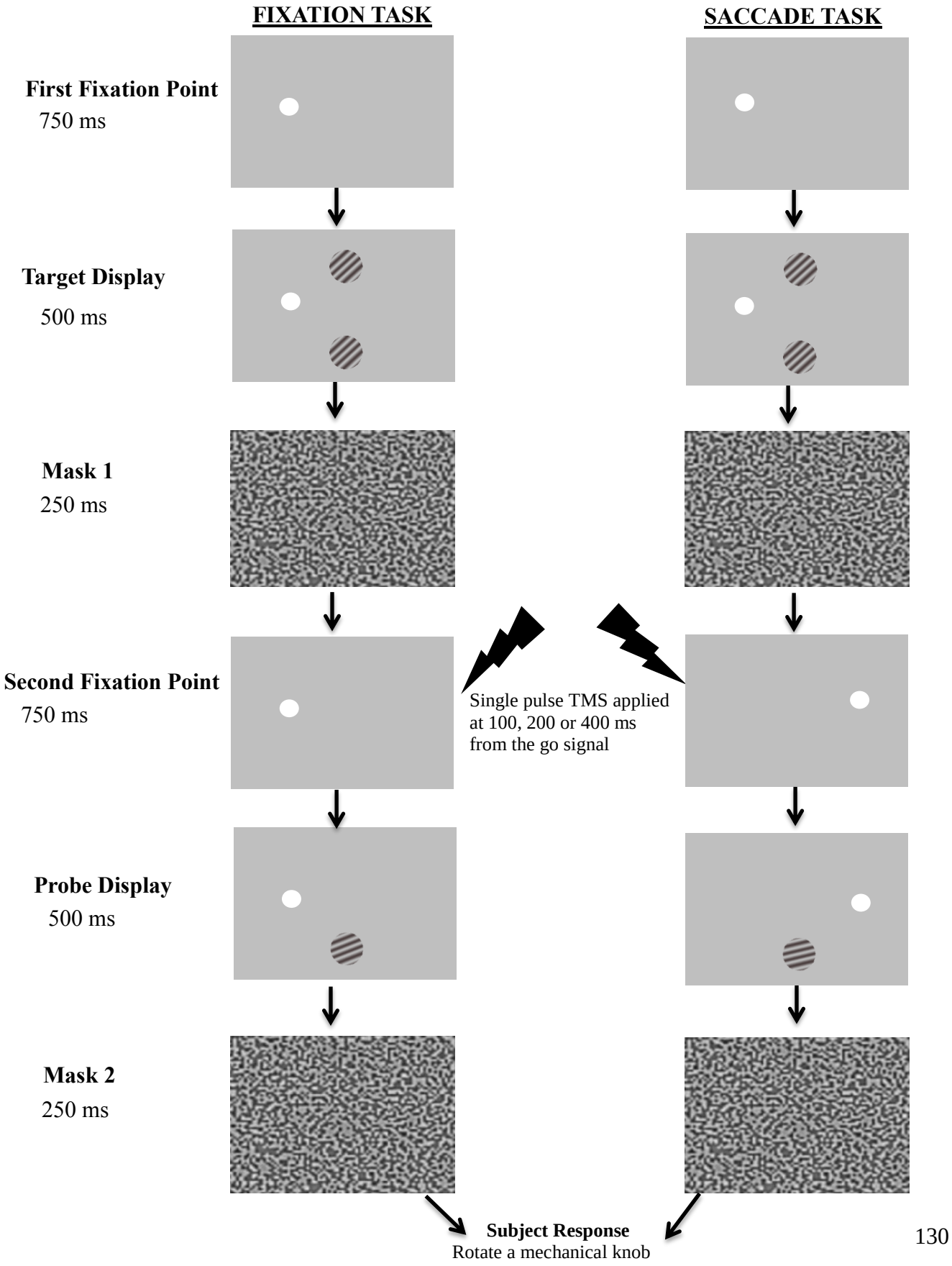
FIXATION TASK
SACCADE TASK
First Fixation Point
750 ms
Target Display
500 ms
Mask 1
250 ms
Second Fixation Point
750 ms
Single pulse TMS applied
at 100, 200 or 400 ms
from the go signal
Probe Display
500 ms
Mask 2
250 ms
Subject Response
Rotate a mechanical knob

Figure A1: Illustration of the experimental design for the *fixation task* and *saccade task*. Subjects were required to make a two-alternate forced choice response, making a comparison of the orientation of the probe to a previously presented target. Subjects were required to fixate at a fixation point (diameter = 0.16°), presented randomly at 6° or -6° to the right or left of the subjects' head-centered location which was designated as 0°. This was followed by two targets (Gabor patch = 2.9°), one in the lower-right or lower-left and the other in the upper-right or upper-left quadrant of the visual field, relative to fixation. During the *fixation task*, subjects were required to maintain fixation at the same location such that the following probe appears in the same retinal location. Subjects were then required to make a response by rotating a mechanical knob to indicate a comparison of the orientation of the probe with the previously presented target. During the *saccade task*, the second fixation point was presented at a different location such that the saccade cross mid-line and the visual field of stimulus presentation is reversed.

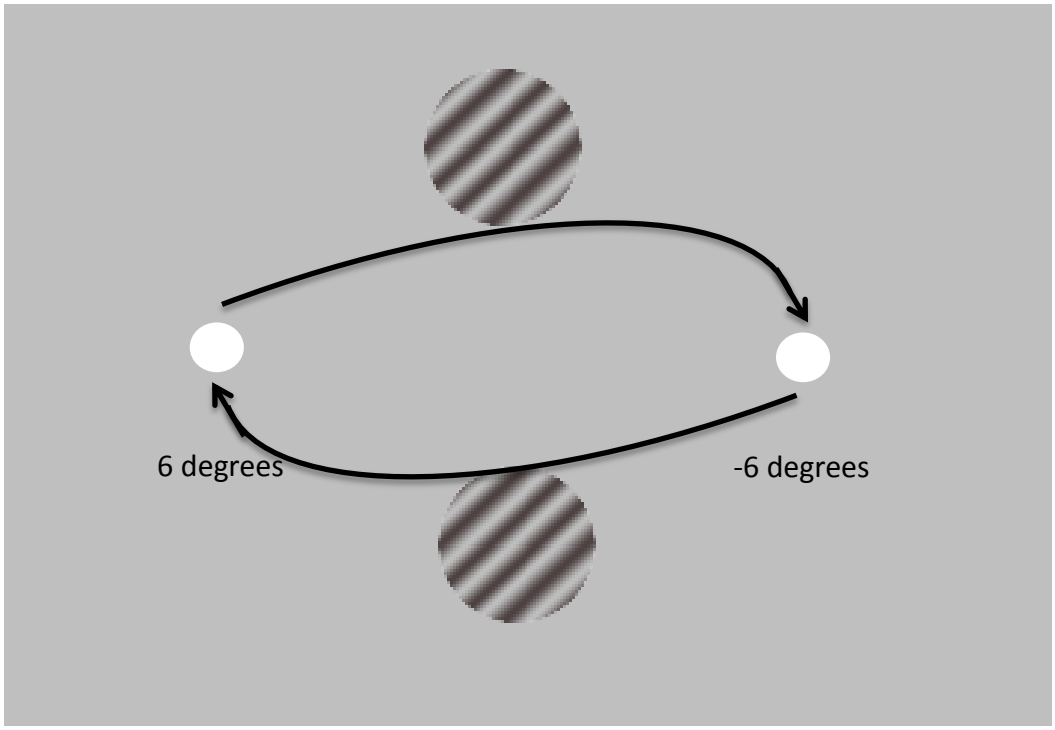

Figure A2: Possible locations of the fixation points and eye movement conditions for the *saccade task.*

RESULTS

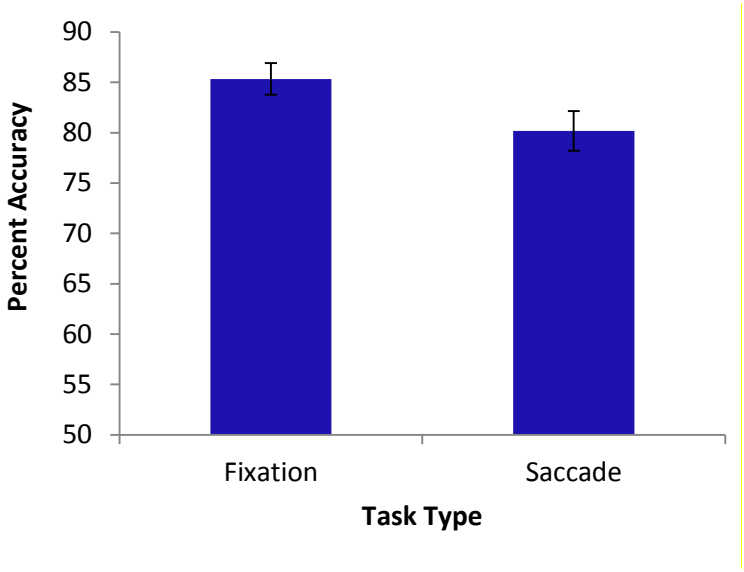

Figure A3: Comparison of subject's performance during the no-TMS baseline control trials for the *fixation* versus *saccade tasks*. Subject's performance was found to be 85.34±1.56% for the *fixation task* and 80.18±1.98% for the *saccade task*. A significant difference was found in the subject's performance during the two task types ($t(8) = 2.560$; $p = 0.034$), as determined via a pared-sample t-test.

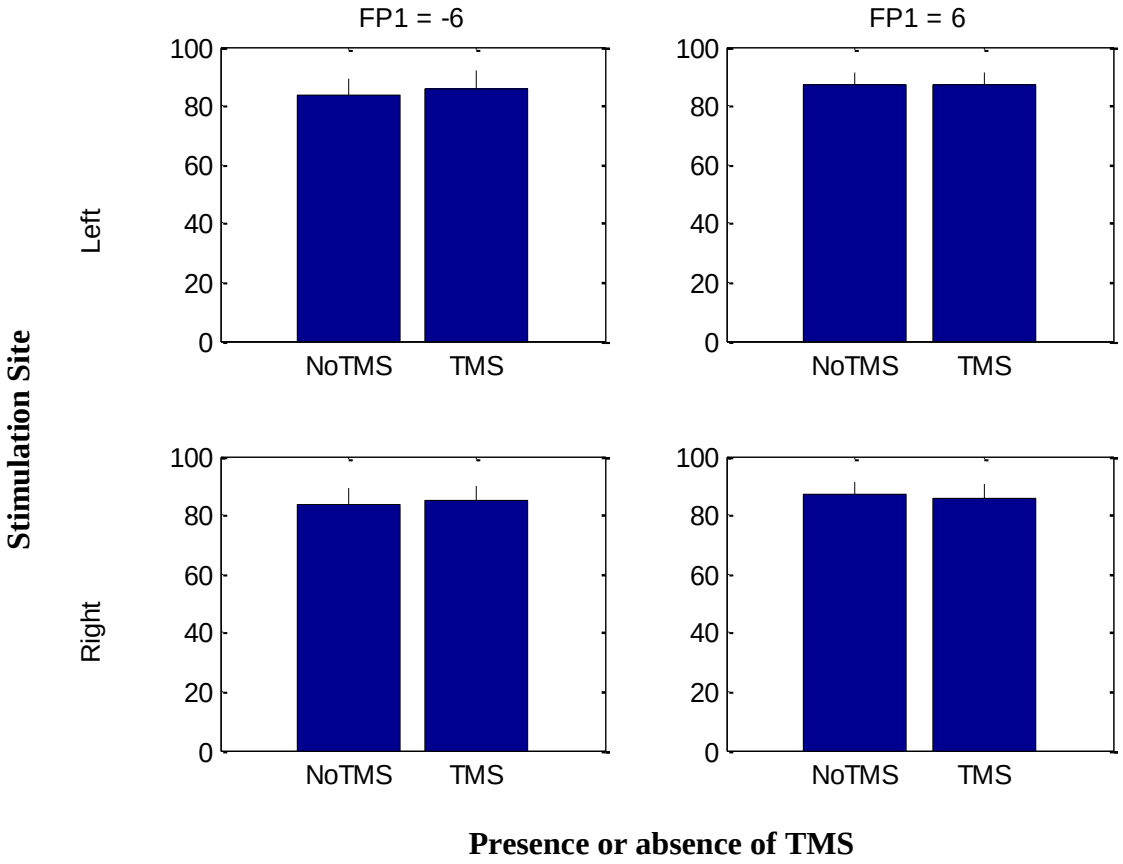

Figure A4: During the *fixation task*, comparison of subject's performance on the basis of right and left visual field for the right and left EVC stimulation revealed an average performance of 85.34±1.17% for left fixation point (+6°) and right EVC TMS and 84.79±1.48% for right fixation point (-6°) and right EVC TMS. A paired sample t-test revealed no significant difference between these conditions ($t(53) = 0.483$; $p = 0.631$). Similarly, an average performance of 85.76±1.60% for right fixation point (-6°) and left EVC TMS and 85.06±1.40% for left fixation point (+6°) and left EVC TMS. A paired sample t-test revealed no significant difference between these conditions ($t(53) = -0.841$; $p = 0.404$).

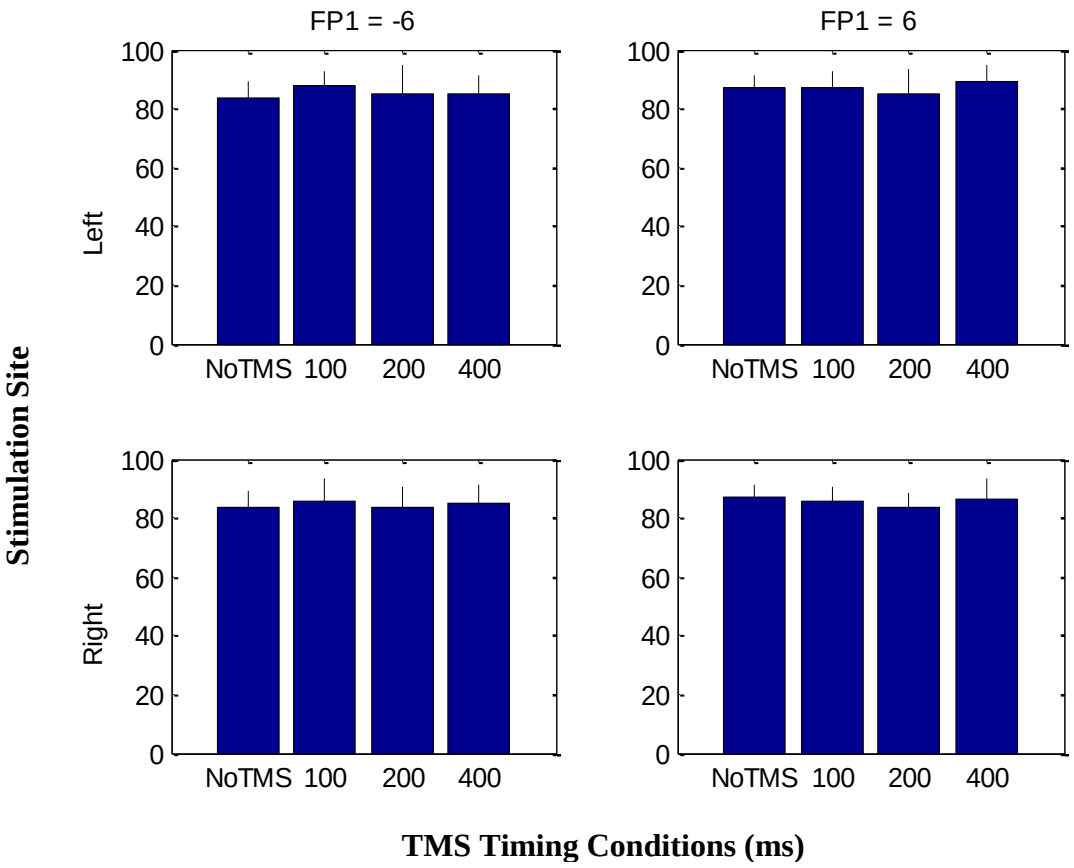

Figure A5: Average data for the *fixation task*, based on TMS timing conditions, site of stimulation and fixation point locations. No significant difference was found in the subject's performance ($F(2,16) = 0.714$, $p = 0.505$), as determined via a repeated measures ANOVA.

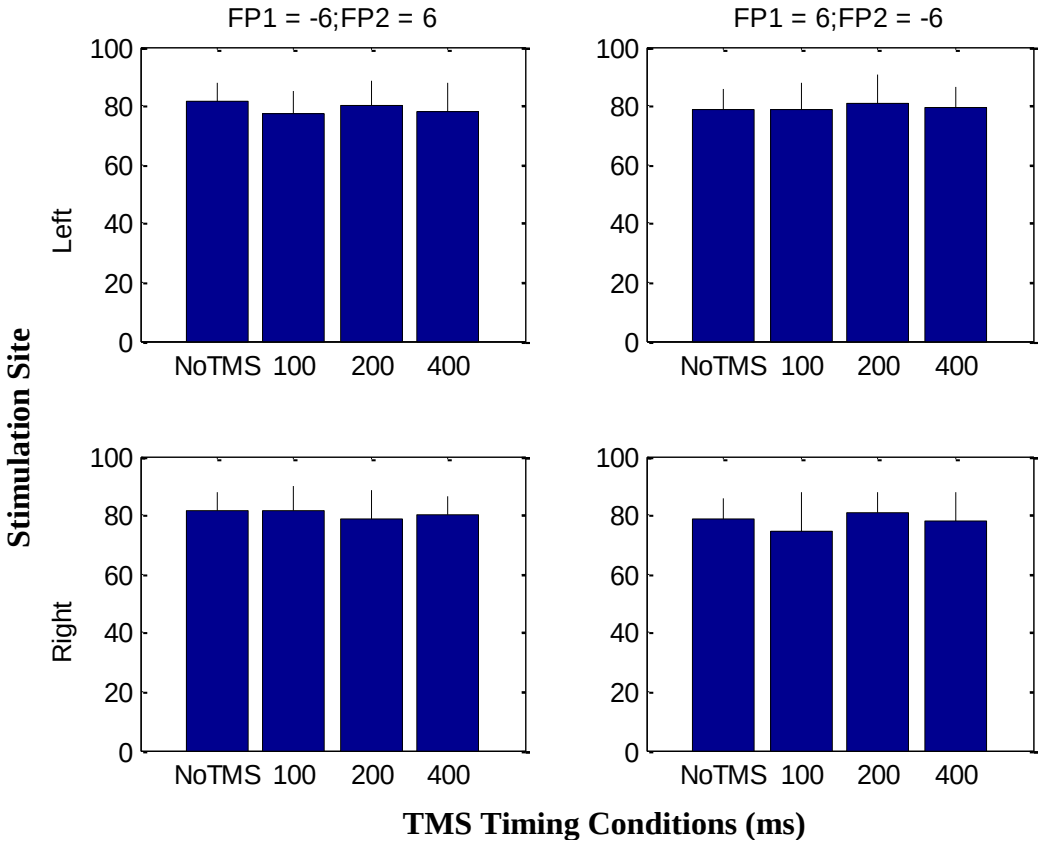

Figure A6: Average data for the *saccade task*, based on TMS timing conditions, site of stimulation and fixation point locations. A slight drop in performance was seen when TMS was applied to the remapped visual field at 100 ms from the appearance of the second fixation point, for both right and left EVC. However, no significant difference was found in the subject's performance ($F(2,16) = 0.255$, $p = 0.778$), as determined via a repeated measures ANOVA.

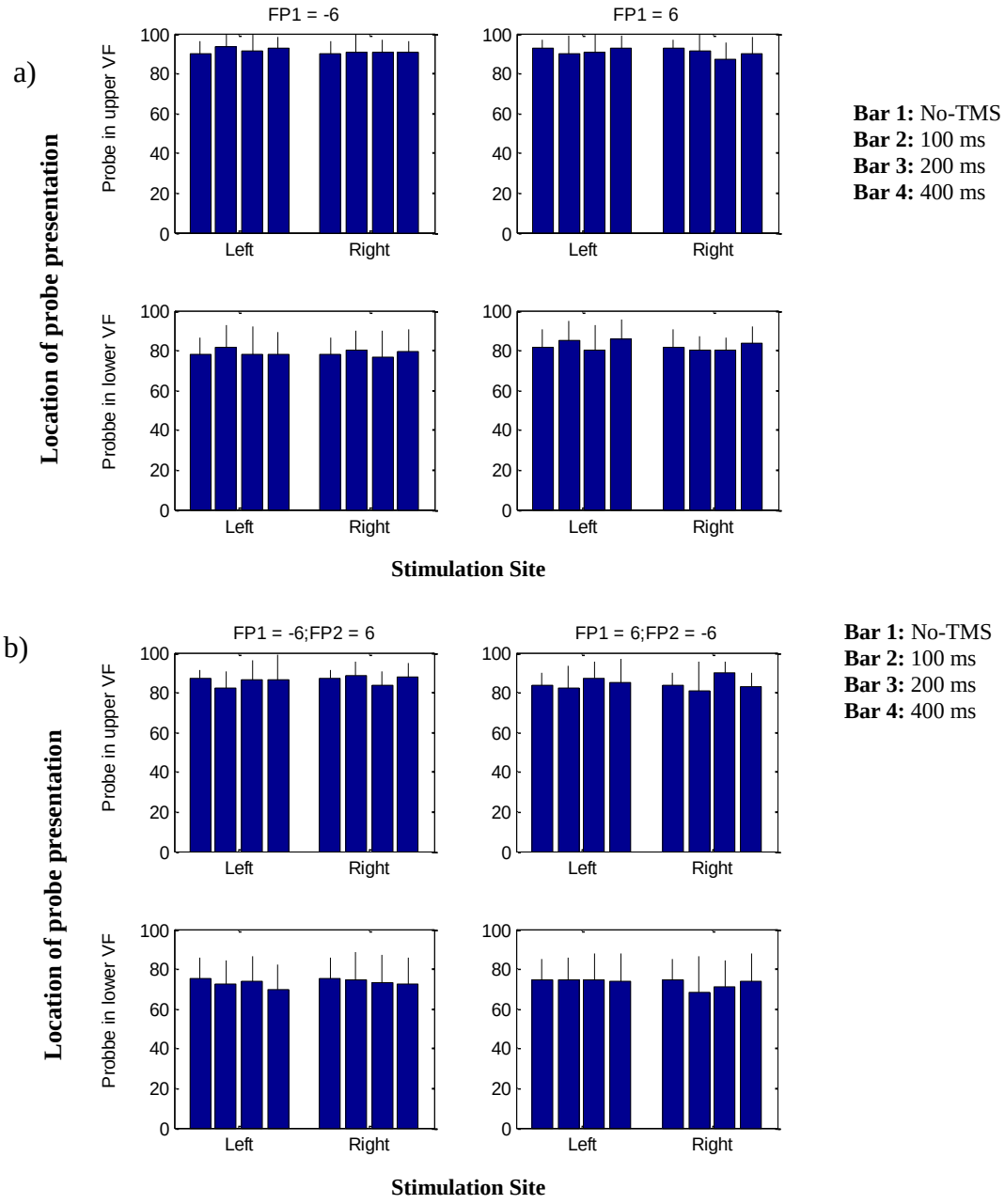

Figure A7: Mean performance for the **a)** *fixation task*, and **b)** *saccade task*, based on the probe presented in the upper versus lower visual field. In general, a lower performance was seen for the *fixation* and *saccade task*, when the probe was presented in the lower visual field (lower panel), and a higher performance was seen was presented in the probe was presented in the upper visual field (top panel). Stimulation was administered only to the lower visual field.

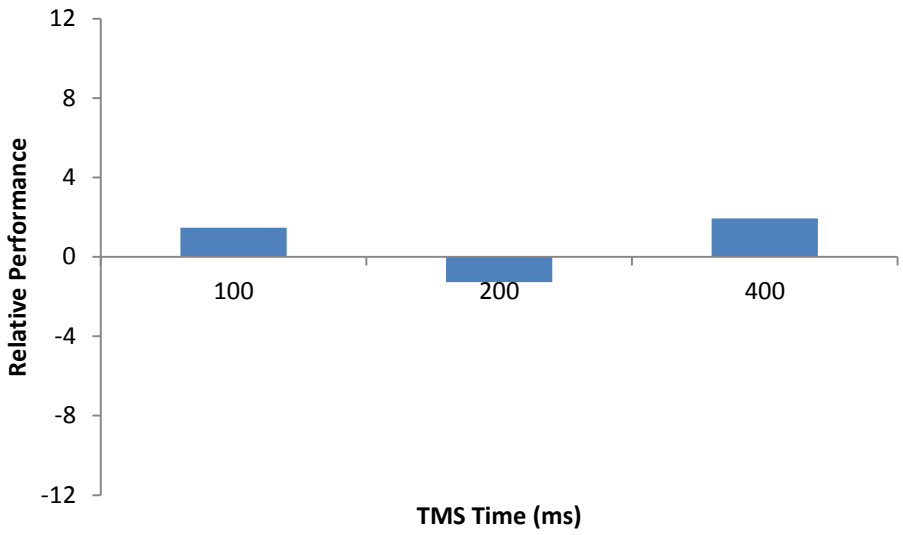

Figure A8: Relative accuracy measured in percent correct responses (Post-saccadic 'remapped' VF – Pre-saccadic 'perceived' VF) during the *fixation task*, for the probe displayed in the lower visual field, based on the timing of TMS pulse administration. A repeated measures ANOVA revealed no significant difference in the relative performance when stimulated at different timings ($F(2,16) = 0.362$, $p = 0.702$). A further comparison of the relative percent accuracy to zero also showed no significant difference during the different TMS timing conditions (100 ms: $t(8) = 0.976$, $p = 0.358$; 200 ms: $t(8) = -0.420$, $p = 0.685$; 400 ms: $t(8) = 0.620$, $p = 0.552$).

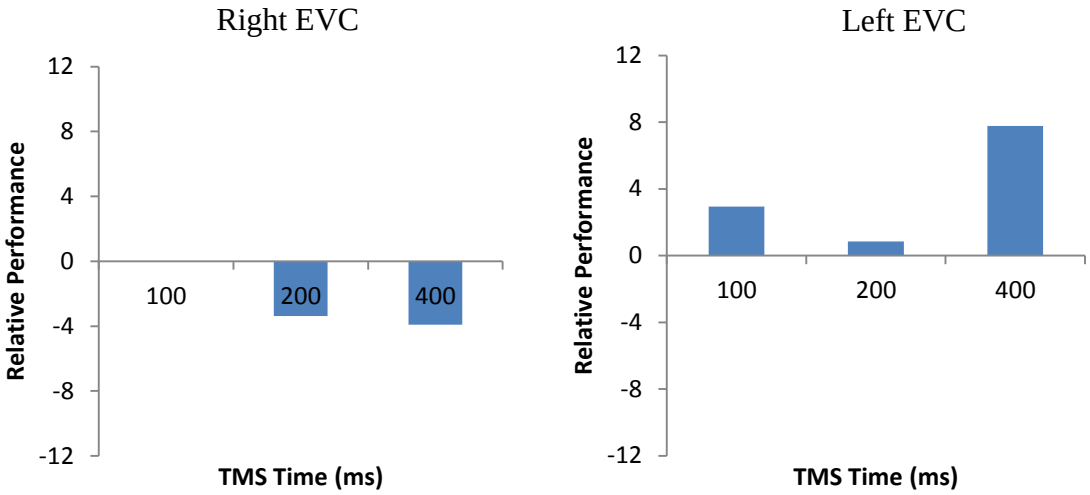

Figure A9: Relative accuracy measured in percent correct responses (stimulated VF – non-stimulated VF) during the *fixation task*, for the probe displayed in the lower visual field, based on the timing of TMS pulse administration. For Right EVC TMS, a repeated measures ANOVA revealed no significant difference in the relative performance when stimulated at different timings ($F(2,16) = 0.367$, $p = 0.698$). A further comparison of the relative percent accuracy to zero also showed no significant difference during the different TMS timing conditions (100 ms: $t(8) = 0.004$, $p = 0.997$; 200 ms: $t(8) = -0.964$, $p = 0.363$; 400 ms: $t(8) = -1.243$, $p = 0.249$). Similarly, for Left EVC TMS, a repeated measures ANOVA revealed no significant difference in the relative performance when stimulated at different timings ($F(2,16) = 0.629$, $p = 0.546$). A further comparison of the relative percent accuracy to zero also showed no significant difference during the different TMS timing conditions (100 ms: $t(8) = -0.862$, $p = 0.414$; 200 ms: $t(8) = 0.170$, $p = 0.870$; 400 ms: $t(8) = 1.338$, $p = 0.218$).

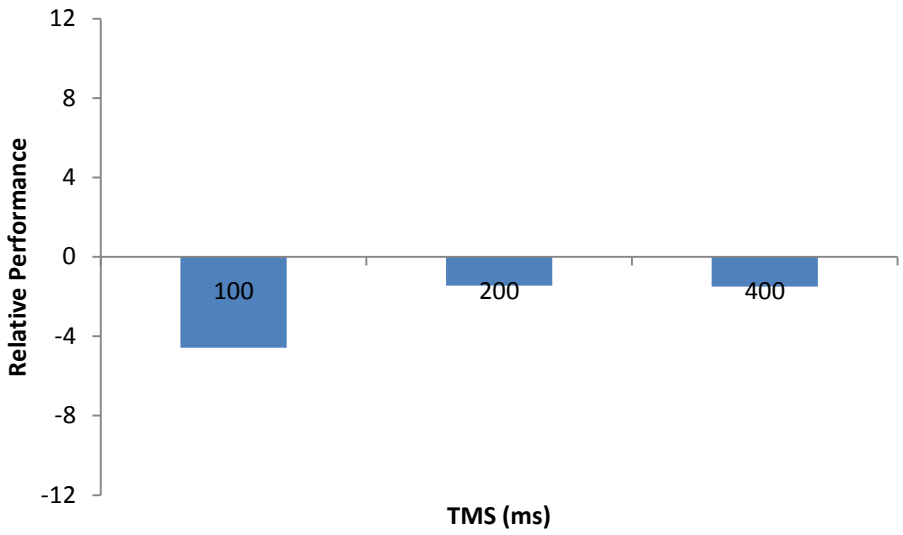

Figure A10: Relative accuracy measured in percent correct responses (Post-saccadic 'remapped' VF – Pre-saccadic 'perceived' VF) during the *saccade task*, for the probe displayed in the lower visual field, based on the timing of TMS pulse administration. A repeated measures ANOVA revealed no significant difference in the relative performance when stimulated at different timings ($F(2,16) = 0.189$, $p = 0.829$). A further comparison of the relative percent accuracy to zero also showed no significant difference during the different TMS timing conditions (100 ms: $t(8) = -1.094$, $p = 0.306$; 200 ms: $t(8) = -0.403$, $p = 0.697$; 400 ms: $t(8) = -0.392$, $p = 0.705$).

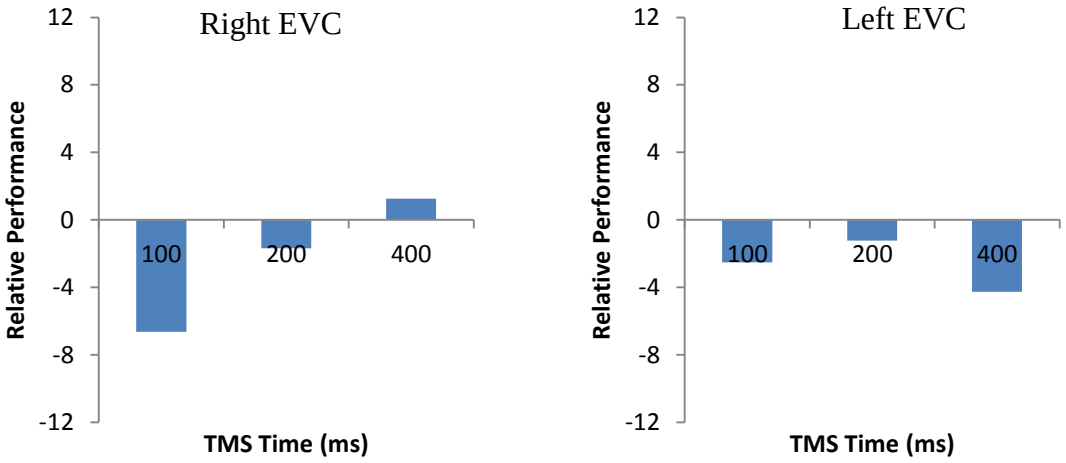

Figure A11: Relative accuracy measured in percent correct responses (stimulated VF – non-stimulated VF) during the *saccade task*, for the probe displayed in the lower visual field, based on the timing of TMS pulse administration. For Right EVC TMS, a repeated measures ANOVA revealed no significant difference in the relative performance when stimulated at different timings ($F(2,16) = 0.680$, $p = 0.521$). A further comparison of the relative percent accuracy to zero also showed no significant difference during the different TMS timing conditions (100 ms: $t(8) = -1.223$, $p = 0.256$; 200 ms: $t(8) = -0.284$, $p = 0.784$; 400 ms: $t(8) = 0.655$, $p = 0.531$). Similarly, for Left EVC TMS, a repeated measures ANOVA revealed no significant difference in the relative performance when stimulated at different timings ($F(2,16) = 0.096$, $p = 0.909$). A further comparison of the relative percent accuracy to zero also showed no significant difference during the different TMS timing conditions (100 ms: $t(8) = -0.559$, $p = 0.591$; 200 ms: $t(8) = -0.252$, $p = 0.808$; 400 ms: $t(8) = -0.673$, $p = 0.520$).

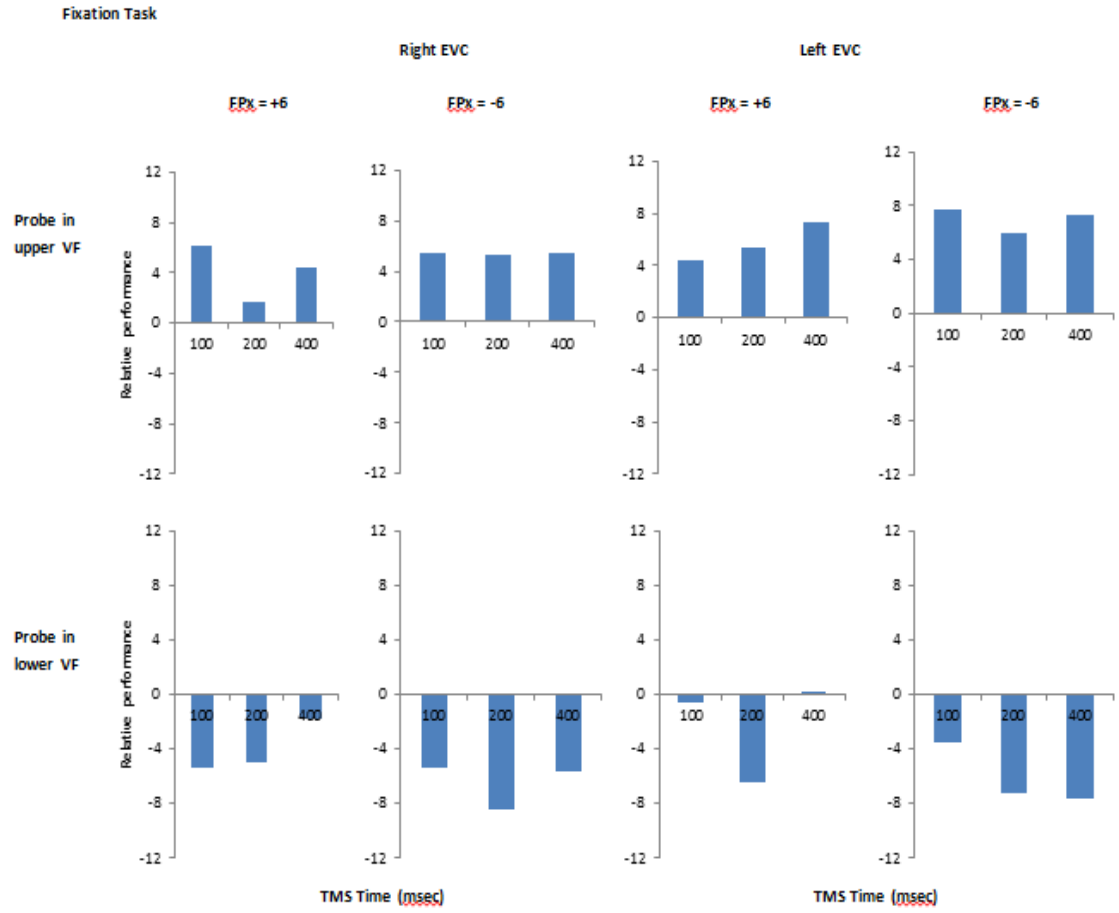

Figure A12: Relative accuracy measured in percent correct responses (Post-saccadic 'remapped' VF – Pre-saccadic 'perceived' VF) during the *fixation task*, for the probe displayed in the lower VF versus upper VF, based on the timing of TMS pulse administration. A repeated measures ANOVA revealed a significant difference in performance when the probe was presented in the upper VF versus lower VF ($F(1,8) = 19.42$; $p = 0.002$). There were no significant interactive effects of stimulation at different timing conditions and probe presentation locations ($F(2,16) = 0.255$, $p = 0.778$).

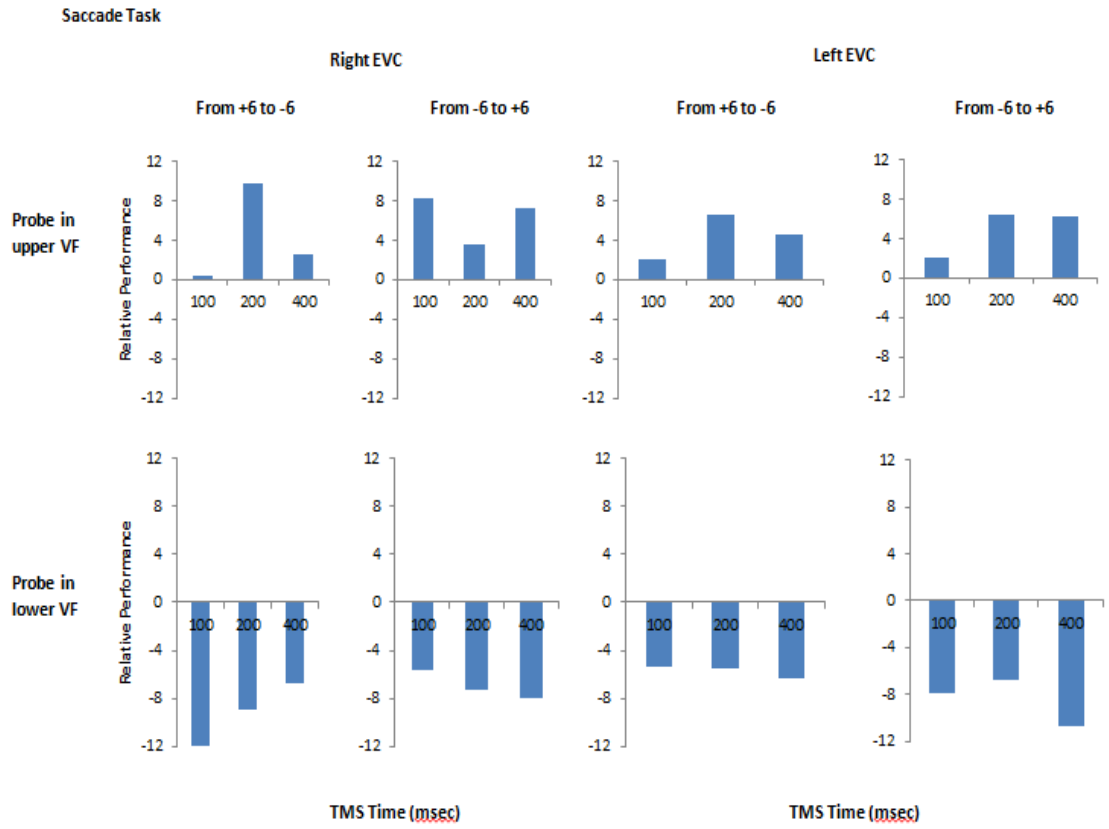

Figure A13: Relative accuracy measured in percent correct responses (Post-saccadic 'remapped' VF – Pre-saccadic 'perceived' VF) during the *saccade task*, for the probe displayed in the lower VF versus upper VF, based on the timing of TMS pulse administration. A repeated measures ANOVA revealed a significant difference in performance when the probe was presented in the upper VF versus lower VF ($F(1,8) = 13.36$; $p = 0.006$). There were no significant interactive effects of stimulation at different timing conditions and probe presentation locations ($F(2,16) = 0.714$, $p = 0.505$).