THE EFFECTS OF TMS OVER DORSOLATERAL PREFRONTAL CORTEX ON MULTIPLE VISUAL OBJECT MEMORY ACROSS FIXATION AND SACCADES

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Abstract

Trans-saccadic memory, the process by which the visual system maintains the spatial position and features of objects across eye movements, is thought to be a form of visual working memory (Irwin, 1991). It has been shown that TMS over the frontal and parietal eye fields degrades trans-saccadic memory of multiple object features (Prime et al., 2008, 2010). We used a similar TMS protocol to investigate whether dorsolateral prefrontal cortex (DLPFC) is also involved in trans-saccadic memory. We predicted that performance would be disrupted similarly during either fixation or saccades. Instead, we found both task and hemisphere-dependent effects. During fixation, TMS over left DLPFC produced inconsistent effects, whereas TMS over right DLPFC reduced performance, consistent with its known role in working memory (Goldman-Rakic, 1987). In contrast, TMS over both sides of DLPFC enhanced trans-saccadic memory, suggesting a dis-inhibition of trans-saccadic processing. These results suggest that visual working memory during fixation and trans-saccadic memory may be supported by different, but interacting, neural circuits.

Introduction

Constructing a unified visual percept from temporally and spatially discontinuous sensory input requires the integration of information across successive fixations that interact with a number of dynamic cognitive processes. As humans typically make around three ballistic eye movements, or saccades per second (Rayner, 1998), perception of the visual environment is compiled from discrete fixations when the eyes are stationary (Matin, 1974). Yet, despite the disjointed manner in which visual information is obtained, the clarity of our perceptual experience suggests a mechanism to maintain visual stability. Information about objects and their spatial position must be retained and integrated across saccades in order to uphold visual stability, a process referred to here as trans-saccadic memory (Irwin, 1996). Visual information is obtained as the eye is directed to different points in space and an internal representation of objects and scenes is created.

The aim of this thesis is to contribute to a larger body of work concerning the neural mechanisms of trans-saccadic memory, by specifically investigating the role of the dorsolateral prefrontal cortex (DLPFC) using transcranial magnetic stimulation (TMS).

1.1 Vision and spatial perception

The retina is often referred to as the window to the brain in both a figurative and literal sense, due to its suitability for scientific inquiry and as the point of entry for visual stimuli. A significant portion of the brain is attributed to processing visual information, from encoding, to maintaining and manipulating information for goal-directed action, and a number of cortical structures are used to mediate these processes. **Figure 1** (page 3) illustrates the regions of the brain associated with visual processing.

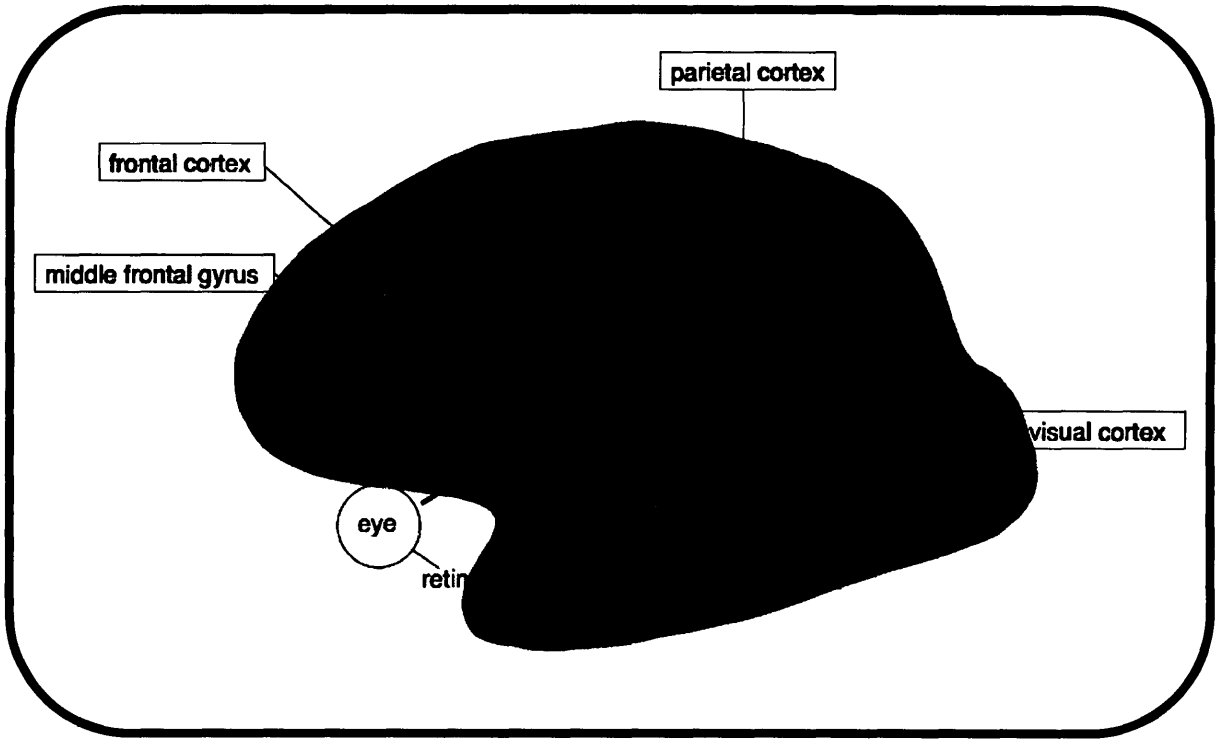

Figure 1. Illustration of the human brain. Visual Information from the retina travels along two pathways, through the LGN or the SC to the visual cortex. Processing after V1 through V5 continues along the ventral stream which projects to the temporal cortex and dorsal stream, which projects to the posterior parietal cortex. The dorsolateral prefrontal cortex (DLPFC) is shown here as part of the middle frontal gyrus, of the frontal cortex.

The retina is a thin (150-300μm) layer of tissue that lies on the interior surface of the eye (Leibovic, 1990). Light from the surrounding environment is projected onto photoreceptors of the retina through the combined refractive potential of the cornea and lens (Leibovic, 1990). Photoreceptors, consisting of rods and cones, are organized such that those responsible for detailed acuity and colour vision are most densely distributed in the fovea (Osterberg, 1935). Photoreceptors connect to retinal ganglion cells, whose axons leave the eye via the optic nerve and project to several different brain areas. Neural pathways for the perception of colour and form arise from two types of retinal ganglion cells, parasol and midget cells (Leventhal et al., 1981). Midget cells have small dentridic fields, high spatial density and are most sensitive to detail and colour, while parasol cells are much larger in size, have a small spatial density, and are most sensitive to motion. These cells travel primarily along two pathways, the geniculostriate pathway that extends from the eye, to the LGN, to the visual cortex (Perry, Oehler, & Cowey, 1984); and the tectopulvinar pathway, extending from the eye to the superior colliculus, and the pulvinar and lateral nucleus of the thalamus, before reaching the visual cortex (Hubel, LeVay, & Wiesel, 1975).

The visual cortex consists of the primary visual cortex (V1 – or striate cortex), and extra-striate areas V2, V3, V4, and V5 (Felleman & Van Essen, 1991; Belliveau et al., 1991), organized hierarchically. At early stages within the occipital cortex, perception of visual imagery is decomposed into simple visual

features such as edges, orientation, colour and form (Hubel & Wiesel, 1959). At later stages, the temporal cortex combines these features along with those related to binocular disparity (V2; Livingstone & Hubel, 1988), and motion (V3 and V5; Braddick & O'Brian, 2001; Kreiter & Singer, 1996) to construct complex scenes.

Visual information is transferred to higher cortical areas, along two complimentary streams of processing: the ventral "what" stream which projects to the temporal cortex for object identification, and the dorsal "where" stream which projects to the posterior parietal cortex for spatial analysis and motor planning (Ungerleider & Mishkin, 1982). It is incorrect however, to view these divergent streams as independent of one another. The ventral and dorsal streams have reciprocal connections with one another, as well as feedback or re-entrant connections to early visual areas (Ungerleider & Haxby, 1994).

The roles of the ventral and dorsal streams were revised by Milner & Goodale (1995), who instead of emphasizing the input characteristics of visual information (ie. object features, or spatial location), emphasized the output requirements of the two systems. In this case, information processing by the ventral stream is primarily utilized to facilitate perception. Neurons in the inferiortemporal cortex (IT) of the ventral stream are remarkably tolerant to variations (size, shape, position) of an object's appearance on the retina (Logothetis & Sheinberg, 1996). It has been suggested this is due to coupling

with the natural experiences of the subject, that the ventral stream is able to leverage prior knowledge to maintain feature stability (Li & DiCarlo, 2012). Functional magnetic resonance imaging adaptation (fMRIa) paradigms have been used to elucidate ventral stream representations in humans, by showing a decrease in neuronal responses with repeated exposure to a given stimulus (Grill-Spector, Kushnir, Edelman, Avidan, Itzchak, & Malach, 1999). Lateral occipital (area LO) an area primarily concerned with object recognition, displays adaptation to repeated presentations of the same shape, even when the viewpoint is varied or size is altered (James, Humphrey, Gati, Servos, Menon, & Goodale, 2002; Grill-Spektor et al., 1999). Consistent with this notion, TMS studies using face, body, and object discrimination tasks, found site selective impairments when their corresponding cortical regions were targeted (Pritcher, Charles, Delvin, Walsh, & Duchaine, 2009). Here, TMS to areas responsible for processing faces (occipital face area, OFA), bodies (extrastriate body area, ESB), and objects (area LO), had no negative impact on performance for discrimination tasks outside their preferred category. Importantly, these adjacent areas show strong category preferences, lending support to the notion that the ventral stream has functionally segregate areas to perceive characteristics of the visual environment.

The dorsal stream is involved in specialized processing of the spatial location of objects in the visual environment relative to the observer, to calculate

a motor plan and facilitate action (Goodale & Milner, 1992). Neuronal activity in the dorsal stream has been shown to represent both sensory related, and movement related activity (Mountcastle et al., 1975). In the primate brain, the intraparietal sulcus which delineates the superior and posterior regions of the parietal lobe supports spatial processing for a number of different modes of action, including: reaching (Scherberger & Andersen, 2007), grasping (Murata et al., 2000), and saccadic eye movements (Pierrot-Deseilligny & Muri, 1997). In humans, homologous regions for reaching movements have been identified using fMRI , as mIPS (Culham & Kanwisher, 2001; Prado, Clavagnier, Otzenberger, Scheiber, Perenin, 2005), and the medial region of the PPC (Connolly et al., 2003; Vesia, Prime, Yan, Sergio & Crawford, 2010). Similarily, positron emission tomography imaging (PET) and fMRI has shown activation of dorsal stream regions anterior intraparietal sulcus (AIP) and inferior postcentral sulcus (IPS), when subjects imagined themselves grasping an object or were presented with images of graspable objects (Grafton et al., 1996; Culham, 2003). Therefore it is useful in the present context to view visual spatial processing conducted by the dorsal stream as a collection of sub-processes involved in generating action (Grill-Spektor & Malach, 2004).

1.2 Visual working memory

Visual working memory can be described as a set of processes that maintain a representation of visual information in short-term storage, to be utilized for recall or additional processing (Baddeley, 1986). To view working memory as a system that represents this ability to maintain relevant information on-line for subsequent behaviour is a necessary but problematic generalization. There has yet to be a composite definition of the processes involved in working memory and how they relate to and interact with visual perception (Luck & Hollingworth, 2008). Lending to this perplexing notion are discrepancies in the limits of working memory, and inconsistent accounts of the processing domains involved (Brady, Konkle, & Alvarez, 2011).

At least two general classes of models exist in an attempt to classify several converging areas of research of visual working memory. One approach, introduced by Miller, Galanter and Pribram (1960), and later adopted by Baddeley and Hitch (1974), views working memory as a storage system with a set of specialized buffers, controlled by a central executive. A schematic representation of this model is shown in **Figure 2** (page 11). This model exercises two central views, one theoretical and one based on evidence from neurophysiology. The theoretical tenet emphasizes the functional contributions of a multi-component system: the phonological loop for maintaining speech-based information and visuospatial sketchpad for visual information (Baddeley & Hitch,

1974). Here, the central executive is responsible for allocating processing capabilities to the control and regulation of information within modality specific buffers (Kiss, Pisio, Francois & Schopflocher, 1998). The central executive resembles attention, but is also a limited capacity storage site in and of itself. The empirical tenet is rooted in the attention-based contribution of the prefrontal cortex, revealed by activity during memory delay periods (Goldman-Rakic, 1987). Baddeley and Wilson (1998) identified a dysexecutive syndrome that accompanied frontal cortex impairment, which presumably represents the locus of the central executive. Critics of Baddeley's model (including Baddeley himself) however, have attempted to rectify the notion that the central executive exists as a unitary structure of the frontal cortex (Parkin, 1998; Baddeley & Wilson, 1988; Baddeley, 1986). Instead, the central executive may be considered a set of processes, which engage different cortical regions, whose function has yet to be explicitly defined.

Alternatively, working memory may be viewed not as a separate component system, but as an emergent property or the coordinated recruitment, of existing neural systems involved with sensory representation and action related functions (Postle, 2006). Here, the maintenance of visual information is achieved by areas of the occipital and parietal cortex, which support visual perception. The prefrontal cortex is not the actual substrate for storing visual information, but supports the sensory representation areas using attentional

processes (Curtis & D'Esposito, 2003; Postle, 2006). It has proven difficult to discern between these two approaches, as studies designed to investigate working memory often rely on a memory delay to isolate memory activity. It is conceivable that delay period activity could be representative of either of the aforementioned models of visual working memory.

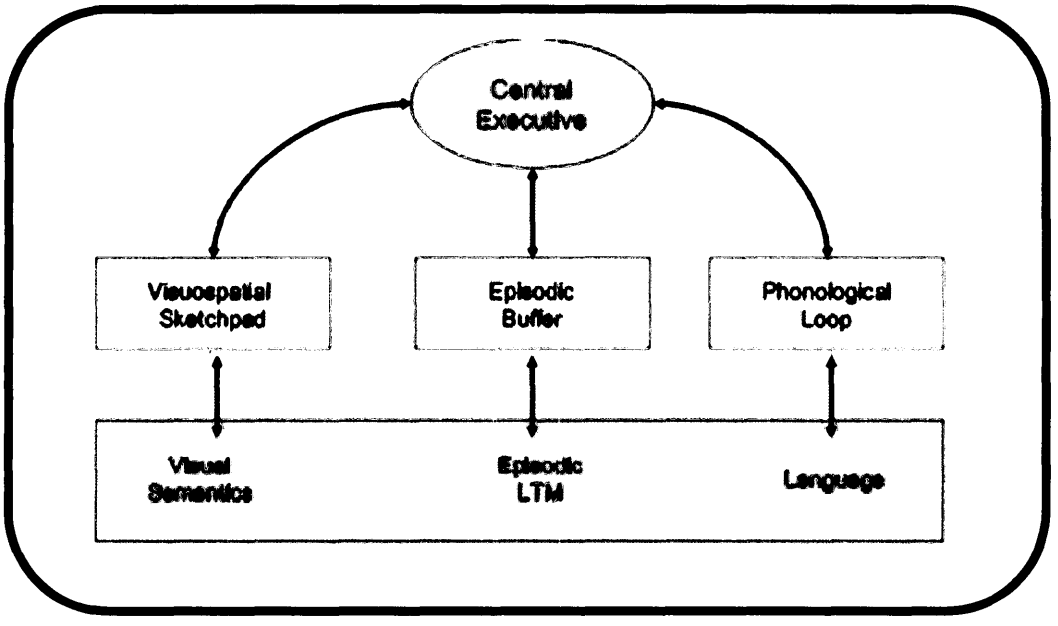

Figure 2. Working memory system, as described by Baddeley & Hitch (1974). The central executive is the attentional controller, part of the frontal cortex. It is aided by two "fluid" subsiderary systems, the visuospatial sketchpad which holds visual information, and the phonological loop which holds speech-based information. The model was revised to include areas capable of including long-term knowledge, or "crystallized" memory representations (last row, visual semantics, episodic LTM and language). (Image by Zimmer, 2008).

1.2a Psychophysics

Visual working memory appears to have a capacity limit of 3-4 items (Irwin, 1991; Luck & Vogel, 1997), but may vary with across different experimental paradigms, and stimuli parameters (Brady, Konkle & Alvarez, 2011; Prime, Tsotsos, Keith & Crawford, 2007). Much of the research aimed at defining the capacity of this system examines the fidelity of the memory trace and the rate at which it becomes inaccessible, either decaying over time, or being interfered with by distracting stimuli.

The study conducted by Luck and Vogel (1997) used a change detection task of features and conjunctions of features, and was the first to quantitatively apply the capacity restriction of visual working memory to 3-4 items. On a given trial, participants were presented with an array of coloured squares and were asked to remember them. After a delay of one second, the squares reappeared, either being the same as before, or with one switching to a different colour. Participants were required to indicate whether the array was the same, or different than before. Subjects' performance declined steadily as the array increased above four objects. However, this does not indicate how well each item was retained; performance relied on the global representation of the items as a whole. To examine how individual object features are retained in visual working memory, Alvarez and Cavanagh (2004) manipulated the amount of feature information ascribed to a given stimulus. They found that there was a

trade-off in performance: when more information was attributed to a given object, the total number of objects successfully remembered was less.

A commonly used method to study working memory capabilities is a visual search task, where the participant is required to search for a predefined target, amongst the presence of distracters (Hollingworth & Luck, 2009; Oh & Kim, 2004). When coupled with manipulations of content in working memory, these tasks can provide insight into the processes involved in working memory and visual perception, and how closely they are related. In 2001, Woodman, Vogel and Luck found no detrimental effect on search ability, using a dual-task paradigm where participants were required to maintain zero, two, or four visual objects in working memory. The presence of these distracter items added a constant delay to visual search times irrespective of the set-size of the search array, indicating that working memory load did not slow the search process. When participants were required to remember a location in space however, reaction time increased as the number of items in the search array increased, indicating a reduction in search efficacy (Woodman & Luck, 2004).

Another frequently used method is the delayed match-to-sample task, where an attribute of a given stimulus must be discriminated after a varying time interval. In these instances, the characteristic of a stimulus (such as size, contrast or orientation) may be used to test the subject's ability to remember specific stimulus dimensions, and provides a quantitative measure of working

memory capabilities by indicating the necessary threshold values for reliable preservation (Pasternak & Greenlee, 2005). In a series of experiments, Magnussen and colleagues examined the properties of visual short-term memory for spatial frequency (size) of simple visual patterns, by varying the interstimulus interval in a two-interval forced-choice paradigm (Magnussen et al., 1991). The results of the initial experiment revealed that subjects could successfully discriminate spatial frequencies for all interstimulus intervals tested (up to 30 seconds). A second experiment attempted to replicate these findings after introducing a "memory masker" placed in the interstimulus interval, found that the perfect discrimination capabilities described above, could be disrupted.

1.2b Neural mechanisms

Further evidence for ventral and dorsal stream independence has been acquired through the use of visual working memory paradigms. Human neuroimaging studies have supported the perception for action view of the ventral and dorsal streams by illustrating their role in object identification, and object location (Thompson-Schill, Aguirre, D'Esposito, & Farah, 1999; Martin, Haxby, Lalonde, Wiggs, & Ungerleider, 1995; Thompson-Schill, 2003). Studies aimed to discern perception-related processing have found activity along the ventral stream (fusiform, right posterior inferior temporal cortex; PIT) associated with object size and colour (Chao & Martin, 2000; Kellenbach et al., 2005). Similarly,

areas of the dorsal stream including the posterior parietal cortex, superior parietal lobe and intraparietal sulcus, have been associated with spatial computations in working memory tasks (Corbetta & Shulman, 2002; Curtis, 2006; Rizzolatti & Matelli, 2003).

The domain specific view of ventral and dorsal stream activity in working memory extends to the prefrontal cortex, an area thought to consolidate and integrate information from the ventral and dorsal processing streams (Miller & Cohen, 2001). Understanding the role of this region in visual working memory is important in understanding the implications of the aforementioned studies, and will be discussed further in section 1.6*a*.

1.3 Saccades

The visual system is supported by saccadic eye movements, which orient the visual axis to different locations in space. Saccades are rapid rotations of the eye, which align objects in view to the high acuity fovea, for detailed visual analysis. Occurring at a rate of approximately three per second, saccadic eye movements are alternated with periods of fixation where the eyes are relatively stable. It is during these periods of retinal stability that visual processing occurs, making saccades the essential vehicle through which we experience our visual world. Research involving eye movements have spanned across scientific disciplines and incorporate a number of different experimental paradigms. First

introduced in the classical work by Buswell (1935), eye movement research is prevalent to this day, suggesting there are still pertinent questions to be answered.

1.3a Behavioural aspects

The metrics of a saccade are highly predictable. The term main sequence has been adopted to describe the relationship and regularities between duration, velocity, and magnitude of human saccadic eye movements (Bahill, Clark, & Stark, 1975). Trajectories are stereotyped, with duration and velocity increasing monotonically as the amplitude of a saccade increases (Dodge & Cline, 1901; Yarbus, 1956). Similarily, peak velocity increases with the size of the saccade, in a linear fashion for small saccades, and approaches a soft saturation limit for larger saccades (Westheimer, 1954). These regularities are upheld in all circumstances where saccades are made, including voluntary, reflexive, and memory-guided saccades (Bahill, Clark, & Stark, 1975).

The total duration of a saccade following the presentation of a visual stimulus is on the order of 120-250 ms (Young, Zuber, & Stark, 1966). Duration increases with the size of the movement, and is estimated to be 100 ms for a 10 degree saccade (Young, Zuber, & Stark, 1966). If the initial eye movement is off-target, a second corrective saccade may be executed. A refractory period has been proposed to limit the number of saccades that can be generated within a

certain time. This is a contentious point however, as it has been shown that two saccades may occur without an intersaccadic interval using double-step stimuli (Aslin & Shea, 1987; Becker & Jurgens, 1979). Here, subjects exhibited a single curved saccade instead of two successive saccades, suggesting the saccade trajectory has been modified on-line.

There are three general classes of experimental saccade paradigms that will be examined for our purposes here, namely, visually-guided, delayed or memory-guided, and anti-saccades. A visually-guided or reflexive saccade, perhaps replicates the most natural of experimental saccade types. Here, a visual stimulus is presented to the observer, and the subject is cued to make an eye movement to that location. The metrics of a visually guided saccade are well defined, and can be used to gauge the effects of saccade manipulation in other tasks. During memory-guided saccade tasks, a peripherally presented stimulus is cued prior to a delay period, which may last milliseconds, or several seconds long. This requires the participant to saccade to the remembered location of the target, after a temporal separation when the target is no longer visible. Evidence from non-human primates have shown that introducing a memory delay in saccade paradigms is accompanied by increases in saccade error and decreases in duration (Gnadt, Bracewell, & Andersen, 1991; Stanford & Sparks, 1994). When visual feedback is provided, accuracy may be restored to baseline levels after a few days (Opris, Barborica, & Ferrera, 2005).

In the anti-saccade task, the saccade occurs in the direction opposite to the cued location, which requires the more reflexive response to be suppressed (Hallett, 1978). Anti-saccade tasks allow for the decoupling of stimulus encoding and response preparation since the participant is made aware of the trial type after the target has been presented (Munoz & Everling, 2004). Here, saccades display longer reaction times, durations and larger errors, indicative of the additional demands required with inhibiting the automatic saccade response (Amador, Schlag-Rey, & Schlag, 1998). As the complexity of a saccade increases, and additional cognitive demands are incorporated in the task, the saccade metrics may become more variable. Anti-saccade paradigms have been used in clinical studies to examine saccade patterns in patients with unilateral frontal lobe removal (Guitton, Buchtel, & Douglas, 1985). The majority of this population displayed difficulty in suppressing a saccade when the cue appeard in the visual field, as well as correcting this erratic saccade and generating the desired anti-saccade. A decrease in saccade latency in these initial erroneous saccades was observed, suggesting that the frontal regions that were ablated (dorsolateral and mesial cortex) generate saccades after a number of computations have already been calculated. This also provides evidence that the prefrontal cortex, particularly DLPFC is important in suppressing reflexive behaviour, which will be discussed in more detail below.

1.3b Neural mechanisms

The critical neural regions involved in generating saccadic eye movements have been well established, and include the frontal and parietal cortices, basal ganglia, thalamus, superior colliculus, cerebellum and brainstem reticular formation (Wurtz & Goldberg, 1989; Bruce & Goldberg, 1985; Leigh & Zee, 1991; Munoz, 2002; Sparks 2002). The neural circuitry describing these regions is shown in **Figure 3** (page 20). Visual input to the system is processed through several extrastriate areas, before reaching the lateral intraparietal area (LIP) in the posterior parietal cortex. Area LIP has considerable projections to the intermediate layers of the SC, and areas of the frontal cortex associated with eye movement generation, including the frontal eye fields (FEF), supplementary eye fields (SEF), and the dorsolateral prefrontal cortex.

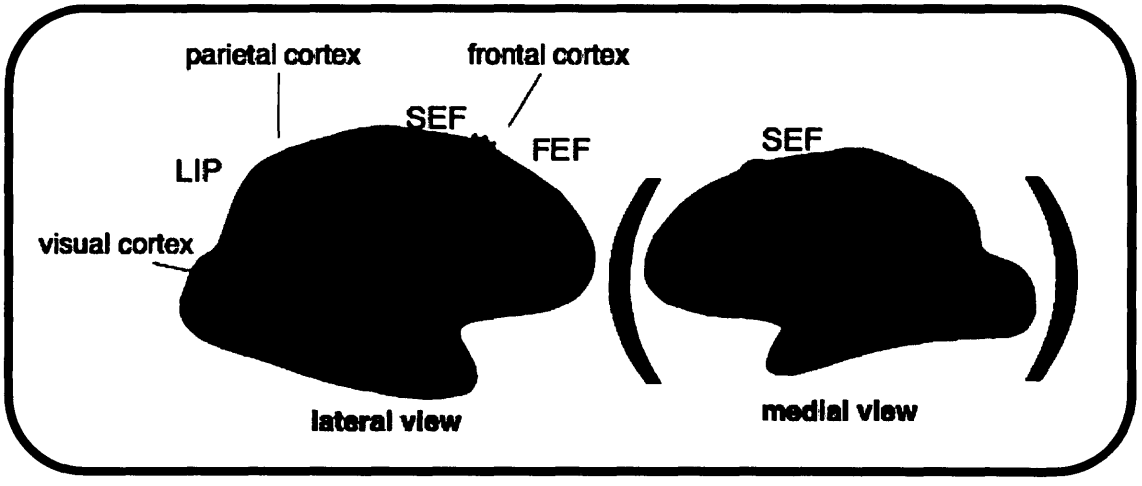

Figure 3. Illustration of an inflated human brain (right hemisphere), showing the neural circuitry of saccadic eye movements. Visual information from the visual cortex travels to the lateral intraparietal area (LIP) of the parietal cortex. Area LIP projects to the SC, SEF and FEF. Medial structures on the lateral view of the brain are shown with dashed lines.

Both the SC and FEF are associated with a variety of signals relating to eye movement generation, perhaps most commonly, the execution of voluntary saccades (Mohler, Goldberg, & Wurtz, 1973; Bruce & Goldberg, 1985). The SC comprises the rostral portion of the midbrain, and is composed of seven layers that receive input and project to a number of visual and motor-related cortical areas (Gandhi & Katnani, 2011). To generate an accurate eye movement to a specific target, the precise location of the target position must be encoded – a task attributed to the SC (Glimcher & Sparks, 1992). SC has been shown to code visual targets in retinotopic, or eye-centered coordinates (Klier, Wang & Crawford, 2001; DeSouza, Keith, Yan, Blohm, Wang & Crawford, 2011). Although there are a number of projections to motor-related areas, it is generally thought that the SC does not specify the motor plan needed to get to the desired location (Sparks & Gandhi, 2003). To distinguish between activity related to target selection and movement initiation, electrophysiological studies implement a delay period where the animal is required to respond only when the cue appears (Basso & Wurtz, 1998). Two important findings have emerged from the delay activity recorded from SC, before a saccade is initiated. First, in a study conducted by Glimcher and Sparks (1992), "prelude burst neurons" were identified that exhibited a build-up activity during the selection of a target and required metrics of the impending saccade, but was not associated with saccade initiation itself. Second, this build-up activity could be changed between one of

two targets selected for a given trial, consistent with activity associated for saccade preparation (Munoz & Wurtz, 1995). Similarily, Basso & Wurtz (1998) demonstrated that adding multiple distracter targets (ie. adding uncertainty about the required saccade) reduced delay activity before the saccade was made. These studies suggest that SC contains neurons that discriminate the target from distracters during delay period (or before a cue to make a saccade appears), and are involved in target selection, independent from the eye movement made.

The frontal eye fields are another region delineated by its contribution to visual target selection and saccade generation. FEF was initially identified in the macaque monkey as a region of the prefrontal cortex where electrical stimulation incited saccadic eye movements (Robinson & Fuchs, 1969; Bruce & Goldberg, 1985). Lesion studies in the monkey have shown that FEF ablation impairs saccade accuracy and distorts saccade latencies during memory-guided saccade tasks (Schiller & Chou, 1998; Deng et al., 1986). Humans with FEF damage show similar deficits during memory-guided saccade tasks yet are able to perform visually guided tasks without concern (Pierrot-Deseilligny et al., 1991). Imaging studies have shown increased FEF activity while making memory saccades, although some activity for visually guided, and anti-saccades persist as well (Anderson et al., 1994; O'Driscoll et al., 1995).

The generality of FEF activity before making a saccade may indicate an allocation of attention to prospective visual targets. Studies that utilize a singleton

search task, have illustrated that initial neuronal activity does not discriminate between targets and distracters, but the later phase of activity does differentially distinguish the two stimuli categories (Schall & Haines, 1993). The same pattern of activity is demonstrated, even when an eye movement is withheld, that is the predictive activity in FEF is maintained even when there is no action (Sato et al., 2003).

Both SC and FEF show spatially selective, predictive activity in a number of experimental paradigms. Using a direction-discrimination task, SC neurons exhibited predictive prelude activity during target selection of two separate visual targets (Horowitz & Newsome, 2001). The target was selected by the degree of coherence of a random dot display, where increased coherence led to an increase of the predictive activity. Similarly, SC neurons have shown predictive activity caused by shifting the receptive field in response to a visual target (Walker, Fitzgibbon & Goldberg, 1995). Functional MRI evidence in humans have revealed FEF to be involved in a preparatory set of activation using an anti-saccade task (Connolly et al., 2003; DeSouza, Menon, & Everling, 2003). Instructions to make either a saccade to, or away from a given target are given before a temporal delay is implemented. Activation during this gap period associated with the "readiness" or "intent" to make a saccade can be teased apart from the motor command itself. FEF exhibits preparatory activity before

saccade initiation (Connolly et al. 2003), and even before the spatial location of the target is revealed (DeSouza, Menon, & Everling, 2003).

Dorsolateral prefrontal cortex has direct connections to the aforementioned saccade generating regions (FEF, SEF), as well as motor and decision-making areas, such as the parietal eye fields (PEF), and the anterior cingulated cortex (ACC; Pierrot-Deseilligny, Muri, Nyffeler, & Milea, 2005). Patients with DLPFC ablations have exhibited difficulty inhibiting unwanted reflexive saccades, and increased errors when the target position must be held over a delay period, suggesting a role in the decisional and spatial memory processes of saccade generation (Pierrot-Deseilligny et al., 2005). These patients are able to make visually guided and smooth pursuit eye movements normally, adding further support to a more cognitive, decision making role of the structure during ongoing oculo-motor behaviour.

The saccadic system exists to support exploration of the visual environment, and also acts as a window into cognitive control mechanisms. Not only do saccadic eye movements work to direct our line of vision to objects of interest, but they interact with our other facets of visual perception that allow for efficient comprehension and navigation of our surroundings.

1.4 Spatial updating of object locations for spatial vision and movement control

Objects in the environment as well as spatial perception and body position of the observer are often in motion, raising the question of how perceptual information is constructed from successive fixations (Irwin, 1991). Several theories of visual cognition have emerged to attempt to explain how visual information obtained from separate glances can create a continuous percept of the surrounding environment. A longstanding assumption of visual perception outlined a detailed visual account of our surroundings being stored from one view to the next. This phenomenology motivated a surplus of theoretical work of visual perception, beginning with Herman Von Helmholtz in the nineteenth century. Helmholtz observed that despite movement of the eye and shifts in objects' retinal positions, the visual environment maintains a constant spatial arrangement. In contrast, during passive eye movement when the eye is gently pushed with ones finger, the visual environment is displaced. These observations led Helmholtz to propose that the distance and direction of the eye movement is calculated to infer the position of items in the visual world from one fixation to the next (Helmholtz, 1886). An internal copy of the metrics of the eye movement is used to remap spatial information and fuse contents from successive fixation points together. Now termed corollary discharge, or efference copy, these extraretinal signals are used to define object location in environmental

coordinates, rather than retinal coordinates (von Holst & Mittelstaedt, 1950; Sperry, 1950).

As visual signals are encoded relative to the retina, representation of object location based on retinal disparity and eye position signals requires recurrent updating of the representation of spatial location in the brain (Hallett & Lightstone, 1976; Mays & Sparks, 1980). It has been proposed that this is mediated by saccade-specific mechanisms that remap visual information, where spatial representations of objects are maintained and updated based on predictive signals related to self-motion (Sommer & Wurtz, 2008; Crawford et al., 2004). Here, a number of neurons have receptive fields that cover the location of a given stimulus or object in the visual environment. Before a saccade is initiated, a copy of the anticipated eye movement command causes the stored representation of the object to be shifted to the new retinal location. Now neuronal activity from the original receptive field is transferred to neurons whose receptive fields will encompass the new spatial location, occurring even before the saccade is made (Duhamel, Colby, & Goldberg, 1992; Nakamura & Colby, 2002).

Evidence from non-human primates have shown predictive remapping in neurons in areas associated with eye movements, such as lateral intraparietal sulcus (LIP; Duhamel et al., 1992), extrastriate visual areas (Nakamura & Colby, 2002), frontal eye fields (Umeno & Goldberg, 1997) and superior colliculus

(Walker et al., 1995). Neuroimaging experiments have demonstrated remapping using remembered movement goals (Medendorp et al., 2003) and passively remembered stimuli (Merriam et al., 2003), in PPC neurons between the intraparietal sulci (IPS) on opposite hemispheres across saccades. TMS to the posterior region of IPS has been shown to disrupt spatial updating using a double-step saccade paradigm (Morris, 2007). It appears perceptual stability may be maintained, provided the brain compensates for motion of the eye by deriving a predictive representation of visual space.

1.5 Perception of object features

Perceiving the qualities of an object involves not only visual characteristics such as size, shape, texture or colour, but also the manner in which it fits into the surrounding schema. Early studies of disorder in the visual system, highlighted the complexity of perceiving object properties. Case studies conducted in single patient populations exhibited selective deficits in certain areas of visual processing, including: colour (Verrey, 1888), shape (Lissauer, 1890), and depth (Holmes 1918), support the view that different object features may be processed independently.

Luck and Vogel (1997) conducted a series of experiments to examine the elemental aspects of feature memory, using variants of the sequential comparison procedure designed by Phillips (1974). Here, subjects view a delay-

separated sample and test array, and are required to indicate whether the two arrays were identical, or whether they differed on a given feature, or conjunction of features. The authors' tested memory capacity for colour or orientation, or a combination of both. They found that accuracy was the same for colour or orientation with a set-size of up to four items. Interestingly, this level of accuracy held for the conjunction condition, where subjects were required to retain both colour and orientation. This finding suggests that individual features were integrated into a representation of the entire object.

The process of object binding has been proposed as the mechanisms by which object features are wound into a cohesive whole (see Robertson, 2003 for a review). Treisman and colleagues (1980) elaborates this concept with a two-stage process of feature integration with a focus on attention. Here, salient regions are selected for by integrating multiple object features, then objects are identified within those salient regions (Choi & Christensen, 2009). A bottom-up model of visual processing identifies salient regions based on object features, and saccadic eye movements are harnessed for higher-level processing (Choi & Christensen, 2009).

The ability to detect and maintain the features and spatial location of an object is an essential hallmark of human behaviour. A number of routine actions depend on the capacity for quick and flexible action, for instance, identifying a potentially harmful or beneficial object, and making the decision to avoid or obtain

it (McAfoose & Baune, 2009). For this reason, visual processing is extremely adaptable and may be viewed as the product of two functions: object recognition and spatial cognition, or ventral and dorsal stream processing. How these aspects are woven together amidst continuously changing visual input (the position, size luminance of an object as you move through space) is an important area of contention.

1.5a Trans-saccadic memory of object features

First defined experimentally as a form of spatiotopic memory, Hogben & di Lollo (1974) showed that the stable visual environment we experience is the result of a summation of images from successive fixations. This view of trans-saccadic integration postulates that a memory image is complied across fixations, essentially stacking on top of each other (Jonides et al., 1982). However it is now largely accepted that detailed visual information is not fused across saccades in a point-to-point manner (Bridgeman & Mayer, 1983; Irwin, 1991). If trans-saccadic integration relied on high-capacity, spatiotopic memory, stimulus displacements across saccades should be easily detected. In contrast, little or no detailed information may be retained across eye movements as under normal conditions, visual information is readily available (O'Regan & Levy-Schoen, 1983, O'Regan, 1992). The visual environment itself acts as an external memory store from which we have continuous access. Evidence for this comes

from studies of change detection, where even obvious changes in two alternating visual scenes go unnoticed if there is disruption of the visual signal at the time of the change (Simons, 1996; O'Regan, 1998; Rensink et al., 2002). This suggests strict capacity limits for objects in the visual environment, where objects that are not directly attended to may escape our conscious awareness.

Converging evidence indicates that trans-saccadic memory is supported by the visual working memory system originally identified by Phillips (1974). Visual working memory capacity for simple features without eye movements is typically estimated at three to four items (Irwin, 1991; Luck & Vogel, 1997). When a saccade is introduced visual features must be retained and updated relative to the new eye position, thus placing additional computational demands on simple short-term memory. In a series of experiments, Irwin (1991) elucidated two important properties of trans-saccadic memory, using delayed tasks where participants were required to identify a letter of a given sequence, after an eye movement was made. The first important finding identified a capacity limit of 3-4 items, or the same as visual working memory. The second finding outlined an increase in accuracy for letters that were near the spatial location of saccade target. It has since been framed in the context of attention, that stimuli closer to the final eye position is accompanied by a covert shift of attention (Mathot & Theeuwes 2011; Kowler et al., 1995). Prime (2007), found that correctly cueing a spatial target also increased accuracy, lending further support to the attentional

benefit that convoys eye movements. It may be helpful to consider trans-saccadic memory an extension of visual working memory that is capable of incorporating saccadic signals into its representation of visual information.

1.5b Trans-saccadic integration of features

Trans-saccadic integration involves not only remapping visual information across saccades, but also integrating that information to form a complete perceptual representation. Several studies examining trans-saccadic integration have demonstrated remapping of object features. Hayhoe et al. (1998) showed that the spatial position of simple stimuli (dots) could be constructed to form a unified whole (acute or obtuse triangle). More recently, Prime et al (2006) demonstrated that subjects were able to integrate object orientation and spatial location across eye movements as well as they could during stable fixation, during a line bisection task. Here, subjects were required to remember and integrate information from two slanting lines and approximate where they would hypothetically intersect.

Evidence from studies examining predictive remapping, suggest that unattended objects that remain stable in the periphery are not remapped (Gottlieb et al., 1998). Remapping has only been identified in cases using salient, attended objects. Perhaps it is not necessary to view each object within scene with such scrutiny. Visual perception of the global environment is subserved by

previous experience and knowledge of familiar and universal features of the world, to rapidly process and interpret a detailed scene. It would be inefficient to analyze each object within a scene, at every glance. Akin to Gestalt psychology, the objects within a scene are summated and work together to create what we perceive to be an integrated whole (the "gist" of a scene; Potter, 1976). Formulating the gist of a scene is an abstraction of visual features, and does not require point-to-point remapping in retinotopic coordinates (Melcher & Colby, 2008). If an object is to be retained across a saccadic eye movement, it must be within the limits of the short-term memory store, and it must either posses a germane quality or be relevant to the task at hand.

1.5c Neural mechanisms

If one is to consider the classification of trans-saccadic memory as an extension of the visual working memory system, the question arises of where in this system extra-retinal signals are being integrated. Remapping of object representations in retinotopic coordinates has been shown in area LIP, and FEF during saccades (Duhamel, Colby & Goldberg, 1992; Heiser & Colby, 2006; Umeno & Goldberg, 1997; Khayat, Spekreijse, & Roelfsema, 2004). Similarly, several areas have been implicated in remapping of object features in trans-saccadic memory, including PPC and FEF (Prime et al., 2008, 2010), which will be discussed in section 1.7.

1.6 Frontal cortex and executive function

The prefrontal cortex is (PFC) most elaborate in primates, indicative of a highly flexible repertoire of behaviour. It is comprised of a collection of interacting neocortical areas that send and receives projections from sensory and motor systems, and subcortical structures (Fuster, 1997). Executive function is considered to be central to PFC function, and is involved in regulating processes operating on the contents of working memory for goal-directed, purposeful action (Smith & Jonides, 1999). Executive function has been termed a multi-dimensional concept encompassing several cognitive control operations mediated by different underlying regions. The PFC may be viewed as the cognitive control mechanism by which neural network communication involved with executive function is orchestrated (Zanto et al., 2011).

Miller and Cohen (2001) have outlined a theory of PFC function that envelops several aspects of cognitive control, and spans a distributed neural network. Here, the PFC guides control via top-down excitatory neurons, of areas where processing occurs (Herd, Banich, O'Reilly, 2006). This is illustrated by the Stroop effect (Stroop, 1935), where internal goals must suppress automatic responses. The Stroop task involves reading colour names aloud, as either the word itself, or the colour it is presented in. It requires subjects to selectively attend to one feature of the stimulus (ie. word, or colour). This becomes difficult during 'colour' trials as there is a tendency read the word automatically, rather

than state the colour it is printed in. This sense of internal conflict must first be suppressed, before the correct response can be calculated. It is this aspect of PFC function that is central to understanding the influence on cognitive control. Referred to as top-down excitatory biasing (TREB) by Herd and colleagues, excitatory PFC neurons contribute to groups of neurons engaged in task-relevant processing (2006). This increases activity for a task-relevant processing neuronal set, compared to task-irrelevant, or competing stimuli. This increase in activity is enough to enable a participant to "override" the habitual response of an otherwise dominant or more prepotent response, to complete the task at hand.

Implementation of control involves modulating neural activity in accord with task demands, and biasing working memory processes such that the manipulation of task-relevant information is emphasized (Milham et al., 2002). It has been proposed that the dorsolateral portion of the prefrontal cortex (DLPFC) may work to allocate top-down attentional control mechanisms in accord with such task demands, by modulating neural activity within posterior regions (Milham et al., 2002).

1.6a Dorsolateral prefrontal cortex

The dorsolateral prefrontal cortex (DLPFC, Brodmann areas 9, 46) is located as part of the anterior portion of the middle frontal gyrus, shown in **Figure 1** (page 3). DLPFC shares reciprocal connections with motor regions (basal

ganglia, premotor area, supplementary motor area) and sensory regions (association areas, parietal cortex), making it well situated anatomically to harness cognitive control of sensory representations for action (MacDonald et al., 2000).

Although the DLPFC has been implicated in working memory systems, its specific role remains unclear. Evidence from non-human primates have shown sustained DLPFC activation during the delay period of delayed response tasks, which may be attributed to maintaining perceptual information (Funahashi, Bruce, & Goldman-Rakic, 1993; Sawaguchi & Yamane, 1999). Animals with prefrontal lesions experience deficits in delayed-response, memory guided saccade tasks that become progressively worse as the delay period is extended (Funahashi, et al.,1993). Additionally, a proportion of DLPFC neurons are tuned to the preparatory set, suggesting they are being utilized to link information maintained during the delay period to upcoming task related actions (Barone & Joseph, 1989; Funahashi et al., 1993). Similarly, evidence in humans has shown that patients with DLPFC focal lesions are able to maintain spatial information in working memory, but show impairments when this information must be utilized in upcoming tasks (Ferreira-Texeira et al., 1998). Neuroimaging studies have shown increased DLPFC activity during delay periods in spatial memory tasks, relative to making simple perceptual judgments about the stimuli (McCarthy et al., 1996; Smith et al., 1996).

The dorsolateral prefrontal cortex interacts with the saccade network in a number of ways. DLPFC is most commonly associated with reflexive saccade inhibition in anti-saccade tasks. DLPFC lesion or disruption result in longer reaction times during the anti-saccade task, as well as an increase in incorrect, initial saccades to the flashed target (Pierrot-Deseilligny et al., 1991; Nyffeler et al., 2007). In humans, DLPFC activation during the anti-saccade task is higher than that during prosaccades (Sweeny et al., 1996; DeSouza et al., 2003). DLPFC is also involved in the spatial component during memory-guided saccades, where an internal representation must he maintained while the target is no longer visible (Pierrot-Deseilligny et al., 2003; Muri et al., 1996; Muri et al., 2000). In the monkey with DLPFC ablated, errors in accuracy in memory-guided saccade tasks increase as the length of the delay period increases (Funahashi et al., 1993). Single-unit recordings have found spatially selective activity in DLPFC neurons, during stimulus presentation, and the delay period in memory-guided saccade tasks (Funahashi, Bruce, & Goldman-Rakic, 1983, 1990). The role of DLPFC in guiding oculomotor behaviour is highlighted by the fact that it has extensive connections to integral sensory and motor related areas (Fuster 1997, Petrides, 1994). DLPFC has reciprocal connections with PPC, acting to integrate sensory information for goal-oriented behaviour (Fuster, 1997; Quintana & Fuster, 1999). It is thought that DLPFC influences oculomotor behaviour through

top-down cognitive control mechanisms of the brain regions with which it is connected (Pierrot-Deseilligny et al., 2005).

It is believed that DLPFC function is largely concerned with maintaining and utilizing sensory information to guide action. Variability in DLPFC activation across different imaging studies has suggested different functional roles for the area, depending on task requirements (Cieslik et al., 2012). Specifically, evidence for a topographic organization of DLFPC suggests the posterior region controls simple mappings of stimuli to action, while the anterior region dictates the relationship between behaviour and task demands (Taren et al., 2011; Christoff & Gabrieli, 2000). Here, information flow occurs along a hierarchy, from anterior to posterior regions.

Damage to DLPFC can affect an array of both oculo-motor and cognitive behaviours. Patients with DLPFC lesions have reported increased errors in anti-saccade and memory-guided saccade tasks and decreased anticipatory behaviour in conducting sequences of predictive saccades (Pierrot-Deseilligny et al., 2003). These deficits implicate DLPFC at each level of the decisional processes related to saccade behaviour: preparation, maintenance of pertinent information, and predicting future saccades. These processes are dynamic in nature, and must be able to be adapted to comply with current task demands. DLPFC is thought to support this aspect of flexible, goal-driven oculo-motor behaviour. Similarly, a number of cognitive impairments have been observed with

DLPFC lesions. Subjects have difficulty in tasks that require on-line maintenance or updating of information (working memory tasks, Stroop task, card-sorting tasks) and exhibited lower scores on tests that examine both general intelligence and executive function (Kimberg et al., 1993; Barbey & Farah, 2013). The diversity of performance deficits with seemingly distinct tasks highlights the complexity of DLPFC function, and solidifies the notion that DLPFC is a region associated in global control aspects of purposeful behaviour.

Recall that visual processing occurs through two separate, but concurrent cortical streams, ventral and dorsal, that originate in primary visual cortex and take distinct paths through the parietal and occipital corticies. Previous work by Prime et al. (2007) has emphasized the importance of these complimentary processing streams in trans-saccadic memory, and has outlined four possible ways in which they may direct perception, outlined in **Figure 4** (page 40). The first possibility postulates that the dorsal and ventral streams operate in complete independence of one another, but is unlikely if we adopt the view that successful integration across eye movements requires information from both streams. Alternatively, information from both streams may be integrated through feed-forward pathways in areas of the prefrontal cortex, or through parallel connections en route. A fourth possibility proposes information about object's features from the ventral stream, and saccade-related remapping signals from

the dorsal stream, are merged in early visual areas through re-entrant feedback connections that send information back through the visual cortex.

It is possible that the interaction between the dorsal and ventral streams in trans-saccadic integration is modulated by a common top-down control mechanism that works to allocate attention to pertinent visual information in the environment. DLPFC is known to play a role in harnessing cognitive control properties, and may be a useful candidate for examining trans-saccadic memory capacity.

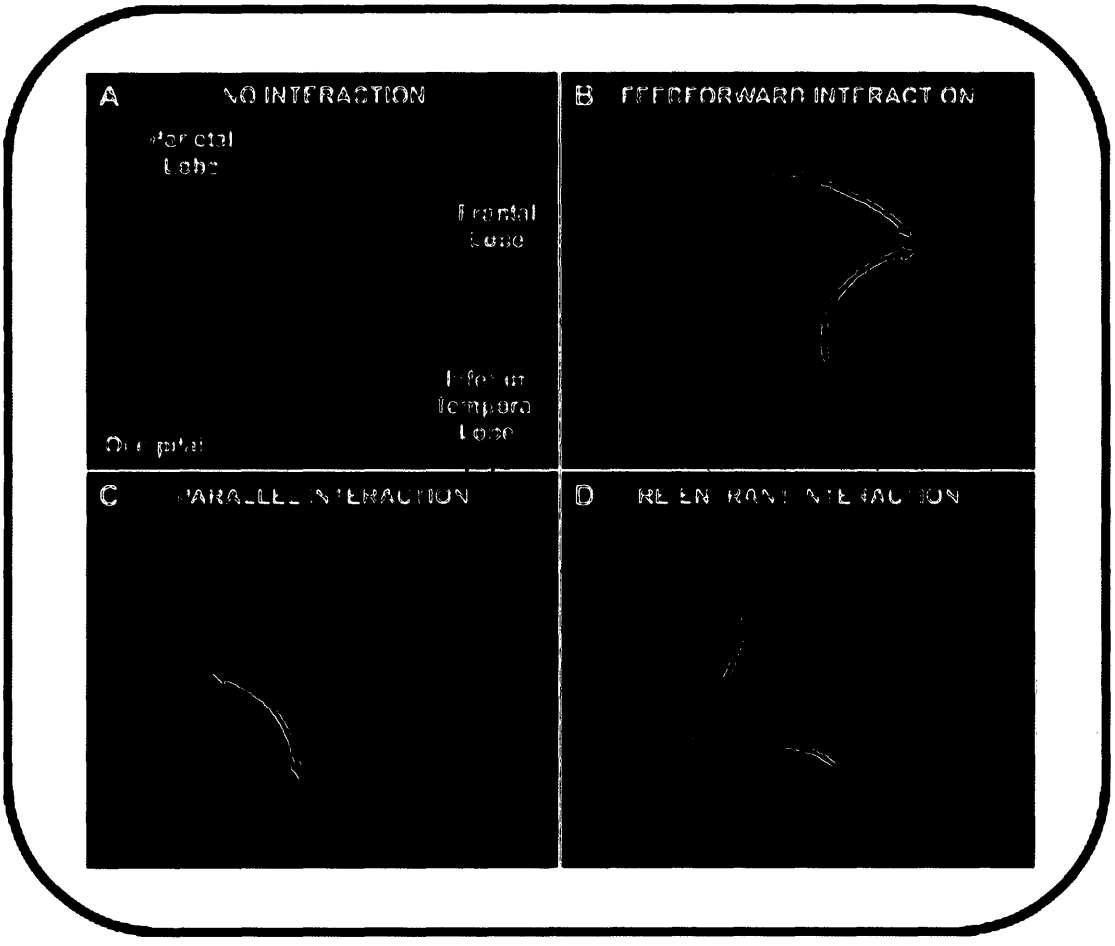

Figure 4. Four possible explanations of how the ventral and dorsal visual streams may be involved in trans-saccadic memory. **A.** Illustrates the no-interaction hypothesis. Visual information from the ventral and dorsal streams do not rely on binding. **B.** Visual information from the ventral and dorsal streams is integrated via feedforward connections to the frontal cortex. **C.** The ventral and dorsal streams exhibit parallel connections. **D.** Visual information may be integrated through re-entrant pathways to earlier visual areas. (Image by Prime et al., 2008).

1.7 Previous studies conducted in this lab

In 2007, Prime and colleagues conducted a series of experiments aimed to estimate the capacity of visual memory for two basic features: luminance and orientation. In both instances, participants were required to remember a single feature of a probe item, and compare it to a target item following a delay period of stable fixation, or an intervening eye movement. Results from both the fixation and saccade tasks indicate subjects were able to successfully retain up to 3-4 items, after which performance gradually declined. To investigate the cortical mechanisms involved in trans-saccadic memory, Prime et al. applied TMS to PPC and FEF while subjects engaged in a multiple visual object memory task (shown in **Figure 9** (page 57). Here, information about object features and spatial location must be retained and integrated with saccade signals somewhere within the visual system. In order to successfully perform the task, information stored in memory must be remapped according to an egocentric measure of saccade metrics. The investigators confirmed that subjects' were able to successfully retain at least 3 objects in both the fixation and saccade task. When TMS was applied over bilateral PPC and FEF, this memory capacity was reduced.

The first of the aforementioned studies conducted by Prime (2008) investigated the role of PPC in trans-saccadic memory. The results, shown in **Figure 5** (page 44) were two-fold. First, TMS to right PPC disrupted performance in both the fixation and saccade tasks, with greatest effects in the saccade task,

during TMS at the 200ms interval. Secondly, analysis of saccade metrics revealed that TMS did not significantly alter the saccade trajectory, and was therefore not a candidate for the decrements in performance that were reported. Instead, TMS during the saccade (at the 200ms interval) likely interfered with the efference copy of the eye movement associated with the saccade. A perceptual copy of the object properties and spatial location must be retained and integrated across an eye movement. If the TMS pulse is delivered near the moment this signal is being updated, then a disruption in the remapping process could occur. The second study conducted by Prime (2010) examined the role of FEF in trans-saccadic memory. The same experimental design was implemented, and the results are shown in **Figure 6** (page 45). TMS to both left and right FEF significantly reduced performance in the saccade task at 100ms in the left hemisphere, and 100ms and 200ms in the right. These placed the timing of TMS pulses before or during a saccadic eye movement, which was in-line with the previous findings demonstrated by the same group. However, in this study, there was also a reduction in performance during TMS to right FEF in the fixation task. At first glance, this may seem counterintuitive if we are to take an approach that considers a disruption in remapping mechanisms responsible for reducing the memory capacity probed in these studies. The authors' suggest that this not need be a point of contention. It is still the function of a spatial updating system to inform visual processing that the eyes are fixating. If TMS is injecting neural

noise into the system, it may have similar effects whether the eyes have moved zero, two, or ten degrees.

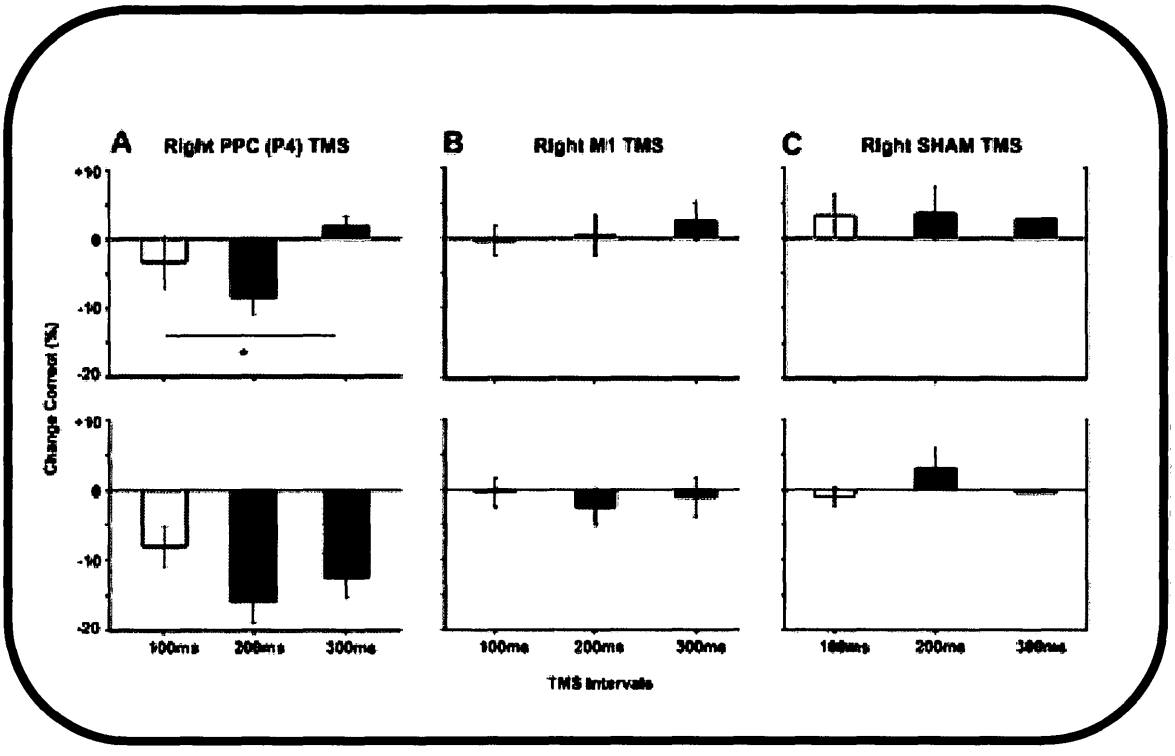

Figure 5. Results from Prime et al., 2008, TMS over PPC. The change in mean percent correct (TMS minus No-TMS baseline) for each TMS interval is shown for **A.** Right PPC **B.** Right M1 **C.** Right SHAM. The *Fixation Task* data is shown in the top panels, the *Saccade Task* data is shown in the bottom panels. Right PPC TMS displayed a significant reduction in performance at the 200ms time interval. M1 and SHAM TMS had no significant effect on performance. (Image taken from Prime et al., 2008).

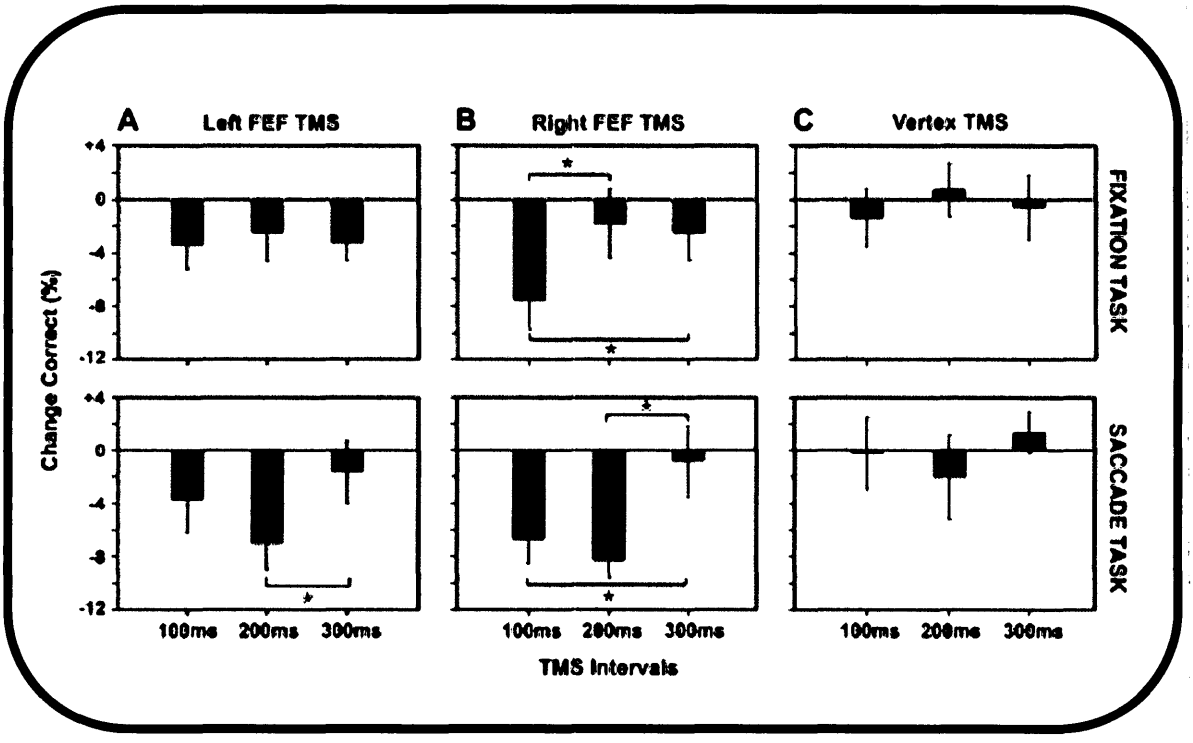

Figure 6. Results from Prime et al., 2010, TMS over FEF. The change in mean percent correct (TMS minus No-TMS baseline) for each TMS interval is shown for **A.** Left FEF **B.** Right FEF **C.** Vertex, CZ. In the *Fixation Task*, performance was disrupted during right FEF TMS at the 100ms time interval. In the *Saccade Task*, performance was disrupted during both left and right FEF TMS at 200ms. TMS to control site CZ had no significant effect on performance. (Image taken from Prime et al., 2008).

The trans-saccadic memory task in these studies requires that the spatial location and feature information of an object are updated across a saccade. The disruption of this process by TMS to PPC and FEF suggests that TMS may be injecting neural noise into the spatial updating system, that each of these areas subserve. These areas are both part of the network for visual object memory, which originates in the ventral stream of visual processing, and project to the frontal cortex. Both PPC and FEF have connections to the frontal cortex, with direct projections to DLPFC specifically (Goldman-Rakic & Schwartz, 1982; Ruff et al., 2008). Recall from **Figure 4** (page 40), the dorsal-ventral interactions mentioned, might differ depending on the requirements of the task at hand. The trans-saccadic memory task used here requires the features from multiple objects to be maintained, perhaps suggesting the use of higher order top-down control mechanisms of the frontal cortex (Miller & Cohen, 2001).

1.8 Present study

This project serves to determine whether the dorsolateral prefrontal cortex (DLPFC) plays a functional role in maintaining visual details in trans-saccadic memory, and allows for direct comparison to other cortical areas identified by Prime et al. (2008; 2010), by using the same experimental design. Using MRI-guided transcranial magnetic stimulation (TMS) to establish a causal role of DLPFC in trans-saccadic memory will elucidate the nature of ventral and dorsal

stream processing outlined in **Figure 4*b*** (Page 40). It was hypothesized that if DLPFC (in particular right DLPFC) is concerned with spatial working memory in general, performance in both the *fixation* and *saccade task* would be similarly affected, ie. TMS over DLPFC would reduce performance in both tasks. If however, TMS over DLPFC produces differential effects during saccades as observed in PPC and FEF, this could suggest a unique role for DLPFC in trans-saccadic memory.

2. Methods

2.1 Subjects

Ethical considerations were approved by the York Human Participants Review Subcommittee. All subjects had normal or correct-to-normal visual acuity, with no known contraindications to TMS. Pilot, and experimental sessions (2 or 3 sessions, approximately 2 hours each) were conducted on different days at least one week apart in order to minimize fatigue and TMS exposure. Eighteen subjects were recruited for participation in this study, after providing informed written consent. Seven subjects were excluded after psychophysical pilot data was collected, due to insufficient baseline performance. Three more subjects were excluded after TMS experiments for erroneous eye movements (see section 2.5 for details). A total of eight subjects were included in the final analysis (5 males, 3 females; mean age = 25.6).

2.2 Apparatus

Subjects were seated in a dark room with their head immobilized by a personalized dental impression bar. The customized experimental set-up is shown in **Figure 7** (page 50). A computer system of three personal computers was used for stimulus presentation and data recording. Visual stimuli were presented using a video projector that back-projected onto a display screen (1.9 X 1.4m, spanning 124.5° visual angle horizontally by 108.9° visual angle

vertically). Subjects sat 50cm in front of the screen, at 114cm eye-level. The experimental set-up was constructed to allow for the compatibility of the *Brainsight* and TMS system, and the display screen. *Brainsight* (Rogue Research, Montreal, Canada) co-registers scalp topography with MRI-based localization methods using an ultrasound based TMS-MRI system and software. Single-pulse TMS was administered using a Magstim 200 magnetic stimulator (*Magstim,* Whitland, *UK*) and a 70mm figure-eight coil. Right eye-position was monitored using an eye-tracking system mounted on the set-up (Applied Science Laboratories, Bedford, MA). Two-dimensional eye position was recorded at a sampling rate of 500 Hz using *Eyelink (*SR Research, Mississauga, Ontario, Canada*)*, and analyzed off-line.

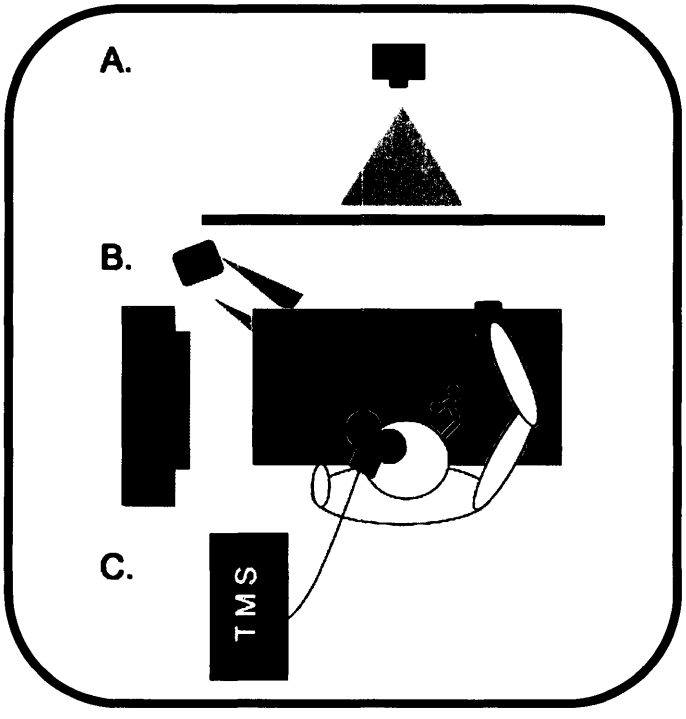

Figure 7. Representation of customized experimental set-up. **A.** The stimuli is back projected on a large display screen. **B.** The *Brainsight* system consists of a computer system and position sensor. The subject wears goggles with a tracking device. **C.** The *Mag-stim* TMS coil generates single-pulse TMS at 60%.

2.3 Localization of brain sites and TMS protocol

Each subject underwent anatomical MRI scanning at Sherman Health Science Research Centre, York University, prior to participation in the study. Stimulation sites (left and right DLPFC) were based on a T_1 weighted three-dimensional MPRAGE sequence scan of the entire head with an isotropic 1 mm^3 voxel (TR = 1900 ms, TE = 2.52 ms, 1 mm slice thickness, 256 x 256 matrix). To localize left and right DLPFC, stereotaxic coordinates (left DLPFC: *x = -35, y = 30, z = 38*; right DLPFC: *x = 35, y = 30, z = 38)* were selected based on a comprehensive review of 128 imaging studies that identified activation foci for DLPFC (Fitzgerald et al., 2006, Talairach & Tournoux, 1988). **Figure 8** (page 53) illustrates the stimulation sites for a representative subject. After identifying the anatomical location of left and right DLPFC, standardized stereotaxic space is translated to each subjects' native space (Fitzgerald et al., 2006), and marked at the correct stimulation location in *Brainsight.* Single-pulse TMS was administered at 60% fixed stimulation intensity. We chose a fixed stimulation output rather than tune the stimulation intensity to subjects' own motor threshold, as there is little evidence that cortical excitability correlates with motor thresholds outside of the motor cortex (Robertson, Theoret, & Pascual-Leone, 2003; Bermpohl et al., 2005). However, for comparison resting motor thresholds (RMT) were obtained from each subject, by stimulating left motor area (M1). This region was anatomically localized, and confirmed when a visible contraction of the first finger

of the right hand was observed. The RMT was defined as the lowest stimulation output required to illicit this movement. The average RMT for all subjects was (M = 52 SD =+/- 2.6). For each session, the TMS coil was placed tangentially against the scalp with the handle pointed backwards, in an antero-lateral position. This coil orientation was deemed the most effective in inducing a TMS effect in the prefrontal cortex (Hill, Davey & Kennard, 2000; Coubard & Kapoula, 2006). A control site was included to yield estimates of non-specific effects of TMS, the vertex of the head (electroencephalography coordinate, CZ).

Custom software triggered magnetic pulses at 100ms, 200ms, and 300ms following the onset of the saccade go-signal for the TMS trials, and at equivalent times in the fixation task. With respect to the normal latency distribution of saccades, this places the TMS pulse timing just before, during or after the saccade. The three discrete stimulation times were chosen on the basis of previous findings that isolated the effect of TMS at different times in different brain regions in a similar experimental design (Prime et al., 2008; 2010).

Figure 8. Location of left and right DLPFC for one representative subject, in *Brainsight.* The location is based on stereotaxic coordinates (left DLPFC: *x = -35, y = 30, z = 38*; right DLPFC: *x = 35, y = 30, z = 38).* From these coordinates, the middle portion of the anterior first third of the middle frontal gyrus was marked for each subject. The sagittal, coronal, and transverse sections of a T1-weighted MRI are shown here.

2.4 Experimental procedure

The task was the same used by Prime et al. (2007, 2008, 2010) illustrated in **Figure 9** (page 57)**.** In the control condition (*fixation task*) subjects fixate on a cross randomly presented at one of 29 possible spatial locations on the screen, within the display area spanning 18° X 18°. The target-display is briefly presented (100ms) consisting of a lone target, or a target plus a random number of distracters (1-3). The total set-size of the target display ranged from one to four items. The target and distracter items were randomly presented in the display area, without overlapping with one another or the fixation cross. When distracters are included in the target display, subjects do not know which item is the target, and thus are required to remember the details of as many items as possible. The targets and distracters consist of gabor patches 2.8° in diameter, with alternating black and white bars. Orientation is randomly selected from five possible starting orientations (25°, 35°, 45°, 55°, 65°), and rotated 10° clockwise or counterclockwise from the initial position.

Next, a mask (a uniform white field) was flashed (150ms) to reduce the possibility of visual after effects following the target-display. The fixation cross was then re-presented at the same initial location. TMS pulses are time-locked to the onset of the reappearance of the fixation cross and occur at 100ms, 200ms and 300ms. TMS trials were randomly intermingled with no-TMS trials.

After re-fixating at the fixation cross and a following a brief delay (750ms), a probe was presented (100ms) at the same spatial location as the target. The probe resembled the target, except that it had made a 10° rotation either clockwise or counterclockwise from its original position. This difference corresponds to the average discrimination threshold for 80% correct responses across subjects when comparing the orientation of two targets, as shown by Prime at al. (2007).

Subjects were required to indicate with their dominant hand whether the orientation of lines on the target had rotated clockwise (right mouseclick), or counterclockwise (left mouseclick) relative to the original target. This creates a baseline performance from which to compare our trans-saccadic data. In the *saccade task*, subjects were required to make an eye movement to a new fixation cross location, following the appearance of the first mask. The location of the second fixation cross was randomly selected. Here, subjects are required to compare probe orientation to the original, pre-saccadic target. This requires subjects to update the location of the target, relative to retinal position. This trans-saccadic data was compared with data where the targets and probes are presented within a single fixation.

Each experimental session began with a calibration sequence and practice block. Each trial type (0-3 distracters, No TMS, TMS at 100ms, 200ms,

300ms conditions) was repeated 16 times for left DLPFC, right DLPFC, and control site CZ. A total of at least 2,688 trials were performed per subject.

Before commencing the experimental sessions, subjects underwent behavioural pilot testing to ensure they were able to achieve ~80% accuracy with zero and one distracter. In total, 18 subjects were tested. Seven of these were deemed to exhibit insufficient performance, and were not asked to continue. Initially, subjects were tested using a set-size of up to 7 items. The results showed that performance reached chance level (~50%) after a set-size of four items, so the number of distracter conditions were reduced. The final analysis included only the trials where the set-size was from one to four items.

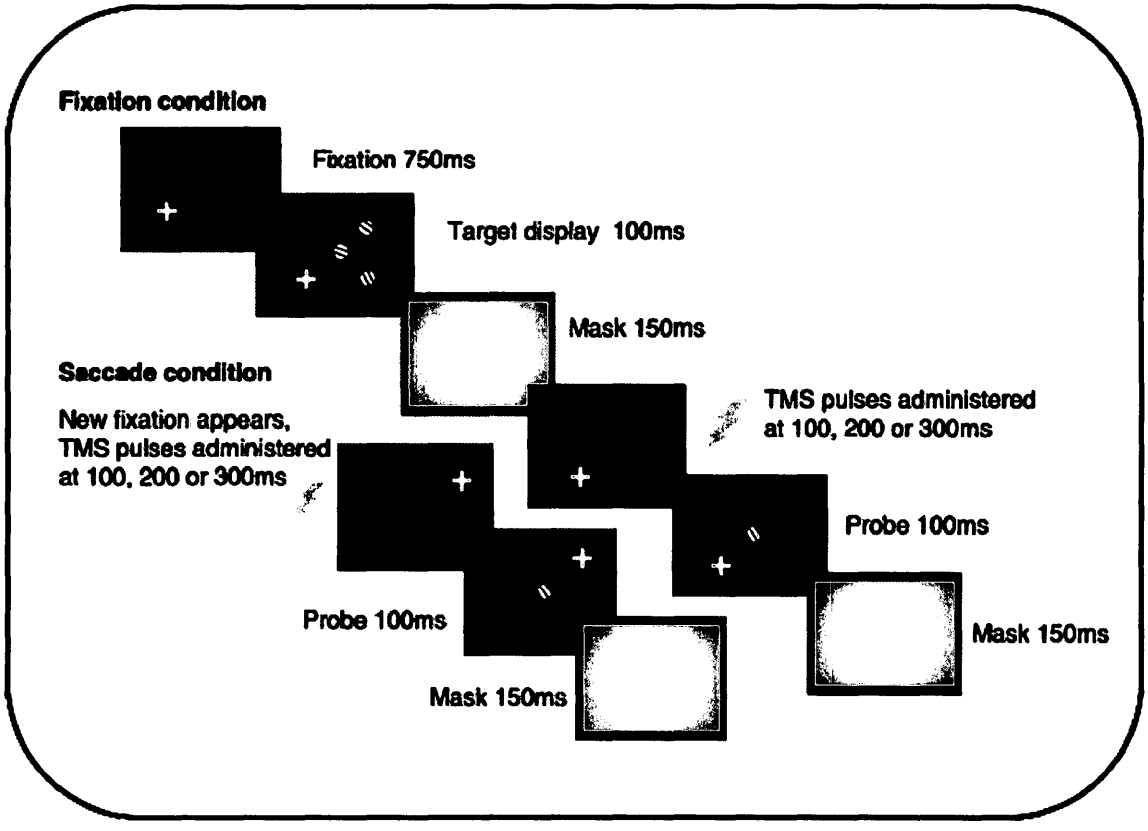

Figure 9. The experimental paradigm created by Prime et al. (2007). In both the *fixation* and *saccade task*, trials begin with a fixation period at one of 29 random spatial locations. A target and distracters (0-3) then appear, followed by a mask. In fixation trials, the fixation cross re-appears at the same spatial location. In saccade trials, the fixation cross re-appears at a randomly selected, new location. Subjects were required to make an eye movement to the new location. The probe is presented at the same spatial location as the target, but has made a 10° rotation clockwise, or counterclockwise. The subject is required to indicate whether the probe has rotated clockwise or counterclockwise from its original position.

2.5 Data analysis

The main experimental results for mean change correct responses will be examined using separate repeated measures ANOVAs to compare each of the three TMS time intervals to their No-TMS baseline.

To examine the magnitude of this effect of TMS, separate repeated measures ANOVAs will be conducted for: 1) baseline No-TMS data 2) TMS minus No-TMS data for each site independently 3) TMS minus No-TMS data, comparing each site 4) TMS minus No-TMS data, comparing between tasks. Where a significant main effect is found, post-hoc Tukey's test will be performed to correct for multiple comparisons.

2.6 Eye data analysis

Custom software was used to mark the eye position in all trials using *Human Browser* (Matlab, The MathWorks Inc., Natick, MA, USA). Each trial was inspected manually, to verify the validity of the eye position. For the fixation condition, a trial was considered valid (ie. kept for analysis) if the subject maintained stable fixation between two critical (100ms) windows, as shown in **Figure 10** (page 60), when the targets and probe were visible, and if no saccade greater than 2° occurred during the trial. For the saccade condition, trials were considered valid if the subject maintained stable fixation between the same two critical time windows, and a saccade, greater than 2° occurred sometime during

the memory delay (after the appearance of the second fixation point, and before the probe was presented). These criterions were chosen to avoid throwing away too many trials. With TMS to the frontal cortex, some subjects experienced a small degree of muscle twitching around the face and eye. On occasion, this would translate into blinking or microsaccades that were not associated with the actual eye movement itself. Three subjects were excluded on the basis of erroneous eye movements. The criteria described above resulted in less than five percent (5%) of trials per subject to be omitted from the final analysis, of the remaining eight subjects.

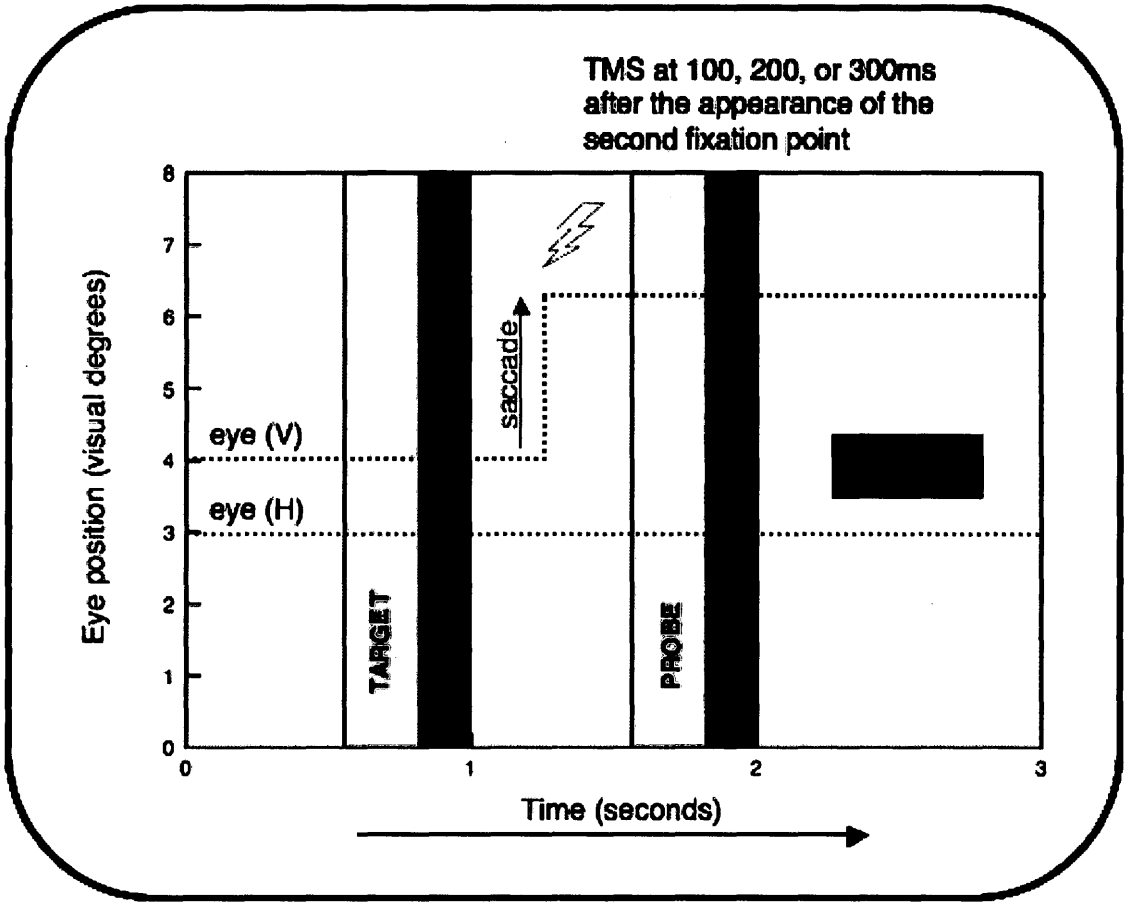

Figure 10. Schematic of an example trial in the saccade task. The new fixation point appears 2 degrees vertically of the original position. The subject is required to make a saccade to the new location. The dotted lines show the vertical and horizontal position of the right eye. In both the fixation and saccade conditions, a trial is considered valid if fixation is maintained during the target and probe presentation windows (with other criteria described above).

3. Results

3.1 Baseline performance – No TMS

Baseline performance, the No-TMS trials in both the *fixation task* and *saccade task,* is shown averaged across all subjects (n = 8) in **Figure 11** (page 62). Here, the percentage of correct responses is shown for each set-size, from one (the target is presented alone) to four (target plus three distracters). Performance without distracters (ie. a solitary target) begins at 86.5% in the *fixation task* and 79.5% in the *saccade task,* and declines steadily with the addition of one, two, or three distracters. In the *saccade task* performance declined more rapidly with the addition of one distracter, with a 17.5% drop in performance, compared to a 3.5% drop in the *fixation task.*

Baseline performance was evaluated using a two-way repeated measures ANOVA (task X set-size). This analysis revealed a significant difference in performance for task ($F_{1,7} = 12.48$; $P = 0.01$) and set-size ($F_{3,7} = 27.07$; $P = 0.001$). Performance dropped off fairly rapidly when distracters were added, and performance in the *saccade task* was lower than in the *fixation task.*

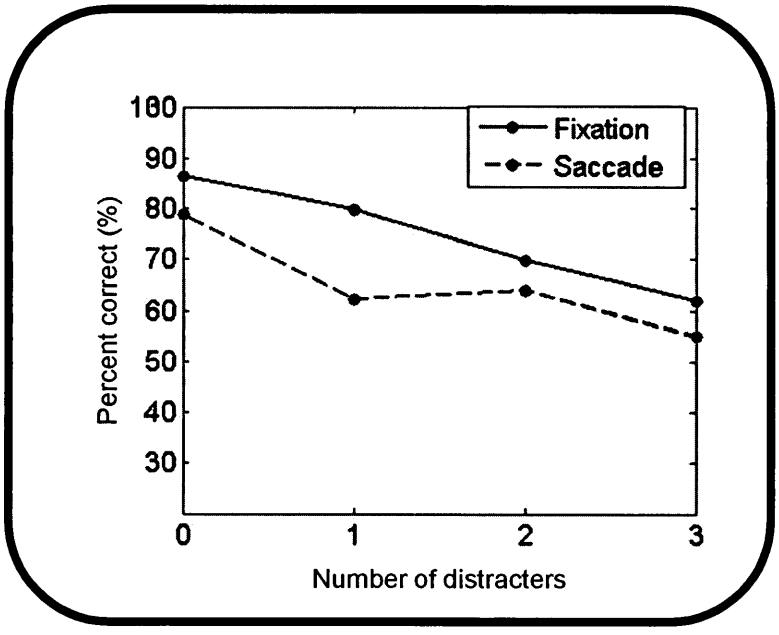

Figure 11. No TMS baseline performance in both the *fixation task* (solid black) and *saccade task* (dotted black). Performance is indicated as the percent correct response, as a function of set-size. Overall, better performance, or a higher percent correct responses, was exhibited in the *fixation task.*

3.2 TMS and saccade timing

Figure 12 (page 64) illustrates the frequency of saccade latency, for No-TMS and TMS trials in the *saccade task*. Discrete 20ms bins were created from 0-400 ms to illustrate the frequency of saccade initiation. The largest proportions of trials were initiated between 200-240ms. Mean latency for saccades in the TMS conditions were 223.61 (+/- 52.78) for left DLPFC and 221.27 (+/- 48.40) for right DLPFC. This confirms the 200ms TMS pulse coincides closely with saccade onset, while 100ms and 300ms occur just before, and after the eye movement is made.

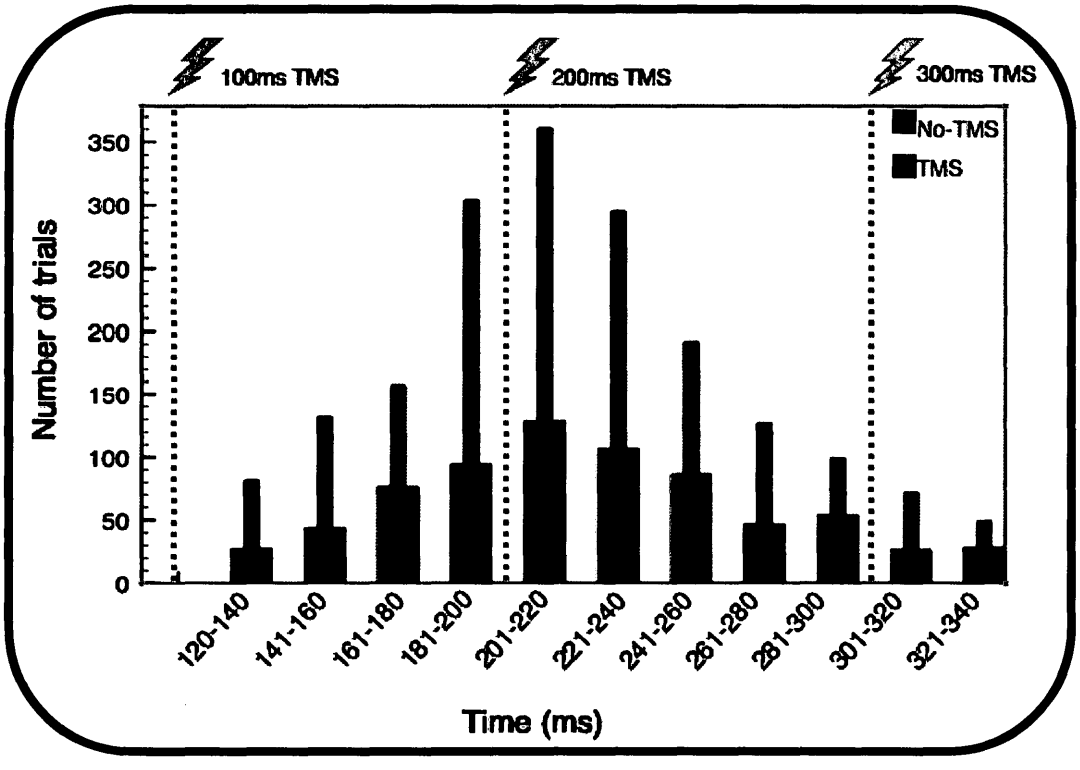

Figure 12. Frequency distribution of saccade latency. Discrete bins show the number of trials within each time slot, in 20ms increments. TMS trials are shown in black, No-TMS trials are shown in blue. The largest proportion of saccades are initiated between 200ms and 240ms.

3.3 TMS to left and right DLPFC and CZ

Figure 13 (page 68) shows the main results for mean percentage correct responses. The *fixation task* is shown in the left column, the *saccade task* is shown in the right column. The three sites are shown by row, beginning with the control site CZ on top, left DLPFC in the middle, and right DLPFC on the bottom. The four TMS conditions are shown in different colours: No-TMS in black, and 100ms, 200ms, 300ms TMS intervals in grey, blue and red, respectively. Similar tothe No-TMS baseline data described above, performance declined as the number of distracters was increased. The control site CZ exhibited the least amount of variability between No-TMS and the three TMS intervals, that is, the lines most closely overlap. The variability in performance between No-TMS and TMS trials was larger for each of the experimental sites, left and right DLPFC, and revealed a different pattern between the two tasks. Generally, performance in the *fixation task* is inhibited by TMS, the No-TMS curve is higher than the three TMS time intervals. In the *saccade task*, performance is enhanced with TMS, the No-TMS curve is lower than each of the three TMS intervals. This is an interesting finding, one that that is explored further in the discussion section (section 4). The statistical relationship between these overall trends in performance are described below.

Separate repeated-measures ANOVAs were conducted to compare the baseline No-TMS condition with each TMS time interval (100ms, 200ms, 300ms).

In the *fixation task*, no significant differences were found for left DLPFC comparing No-TMS to TMS at 100ms ($F_{1,7} = 0.87$; $P = 0.38$), 200ms ($F_{1,7} = 1.70$; $P = 0.23$), or 300ms ($F_{1,7} = 0.54$; $P = 0.49$). When comparing baseline No-TMS to the three TMS intervals for right DLPFC, a significant difference was found for 100ms ($F_{1,7} = 20.01$; $P = 0.003$), but not 200 ($F_{1,7} = 2.48$; $P = 0.16$), or 300 ($F_{1,7} = 0.43$; $P = 0.53$). No significant differences were found between No-TMS and TMS at 100 ($F_{1,7} = 0.03$; $P = 0.86$), 200 ($F_{1,7} = 0.26$; $P = 0.62$), or 300 ($F_{1,7} = 0.03$; $P = 0.87$) for the control site, CZ.

The same analysis comparing baseline No-TMS to each of the three TMS intervals (100ms, 200ms, 300ms) was conducted for the *saccade task*. For left DLPFC TMS, a significant difference in performance was observed for the 200ms interval ($F_{1,7} = 7.66$; $P = 0.03$) compared to No-TMS, but not 100ms ($F_{1,7} = 0.95$; $P = 0.36$), or 300ms ($F_{1,7} = 2.44$; $P = 0.16$). For right DLPFC TMS, a significant difference in performance was found for the 300ms interval ($F_{1,7} = 6.64$; $P = 0.04$, but not 100ms ($F_{1,7} = 1.66$; $P = 0.24$), or 200ms ($F_{1,7} = 0.39$; $P = 0.55$). Just as in the *fixation task*, no significant differences in performance were found for CZ between No-TMS trials and TMS at the 100ms ($F_{1,7} = 0.45$; $P = 0.53$), 200ms ($F_{1,7} = 0.04$; $P = 0.85$), or 300ms ($F_{1,7} = 0.03$; $P = 0.91$) interval.

Taken together, these results suggest there are differences in performance both between left and right DLPFC, and between tasks. There are

different patterns emerging from each of the two tasks, namely, suppression effects in the *fixation task,* and enhancement effects in the *saccade task*.

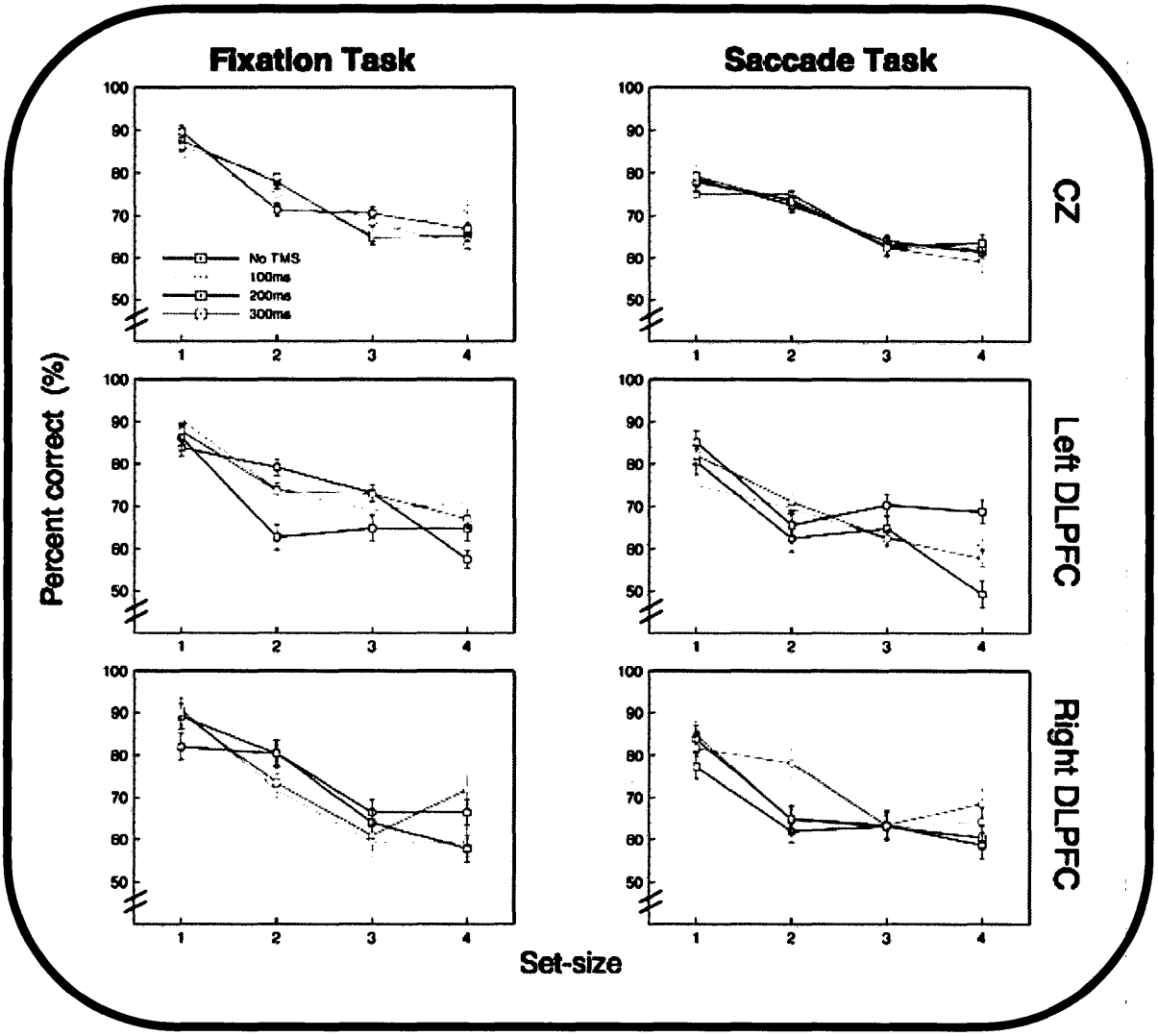

Figure 13. Results of average performance for No-TMS and TMS conditions. The *fixation task* and *saccade task* for the control site CZ (top panels), left (middle panels) and right (bottom panels) DLPFC. Mean percentage correct is plotted across all subjects (n = 8), for each set-size (0-3). The No-TMS data curve is plotted in black, while each of the three TMS intervals are plotted in grey (100ms), blue (200ms), and red (300ms). Error bars represent the standard error of the mean.

3.4 Magnitude of the TMS effect

Figure 14 (page 74) represents the magnitude of the TMS effect for each of the three TMS intervals (100ms, 200ms, 300ms). Here, the percent change correct is calculated by subtracting the No-TMS baseline data from each of the three TMS time intervals, for each site. A positive value indicates a facilitation of performance with TMS, a negative value indicates performance suppression. For simplification, the data is plotted for 100ms, 200ms, 300ms TMS intervals, after collapsing for set-size.

As expected, control site CZ subtractions showed values closest to zero, meaning TMS had little effect on performance. The subtractions for the experimental sites, left and right DLPFC showed a larger TMS effect, with differences across each of the two tasks. In the *fixation task*, negative values were exhibited during right DLPFC TMS in a consistent manner. TMS inhibited performance during each of the three TMS intervals. During left DLPFC TMS, performance was inhibited during TMS at 200ms, but facilitated during TMS at 100ms and 300ms. A consistent trend is visible in the *saccade task*, in that for both left and right DLPFC, each of the three TMS time intervals are positive values. This demonstrates that TMS to DLPFC facilitated performance when an eye movement was required.

TMS minus No-TMS data for each site independently

Each of the three TMS time intervals were compared to each other, within each site, for the *fixation task* and *saccade task* independently. This comparison was intended to highlight the temporal differences in TMS effects, for each site.

In the *fixation task*, comparisons of the mean change correct for the three TMS intervals yielded the following findings. There was a significant difference in performance for the three TMS intervals for left DLPFC TMS ($F_{2,7} = 5.35$; $P = 0.02$). Post-hoc Tukey tests indicated that accuracy for the 200ms interval was significantly lower than 100ms ($P = 0.047$), but not 300ms ($P = 0.09$), and no difference was found between 100ms and 300ms ($P = 1.00$). There were no significant differences between the three TMS time intervals for right DLPFC ($F_{2,7} = 1.56$; $P = 0.24$), or the control site CZ ($F_{2,7} = 0.07$; $P = 0.93$). In the *saccade task,* there were no significant differences in percent change correct for the three TMS time intervals for left DLPFC ($F_{2,7} = 1.69$; $P = 0.22$), right DLPFC ($F_{2,7} = 1.68$; $P = 0.22$), or control site CZ ($F_{2,7} = 0.45$; $P = 0.65$).

The limited number of significant statistics here should not be taken as meaningless. The three TMS intervals generally exhibit a similar direction of effect (ie. negative or positive), within each individual site. Only in the case of the left DLPFC during fixation trials, do the three TMS time intervals fall in different directions. The similarity of the pattern in the remaining three experimental conditions provided the rationale for additional analyses to be conducted,

namely, comparisons of the three TMS intervals between sites, and between tasks.

TMS minus No-TMS data comparing each site

A second comparison of the mean change correct values was conducted for each TMS interval, this time comparing between the experimental sites: left and right DLPFC. For example, left DLPFC TMS at 100ms was compared to right DLPFC TMS at 100ms, in the *fixation task*. These comparisons were conducted to examine if there were differences in the TMS effect, between the two hemispheres.

A repeated measures ANOVA was conducted to compare the percent change correct performance, between the left and right DLPFC for each of the three TMS intervals. In the *fixation task,* there was a significant difference in performance for TMS at 100ms, ($F_{1,7} = 6.20$; $P = 0.04$), but not at 200ms ($F_{1,7} = 0.04$; $P = 0.84$), or 300ms ($F_{1,7} = 1.10$; $P = 0.33$). In the *saccade task*, there was no significant difference in performance between left and right DLPFC at the 100ms ($F_{1,7} = 0.09$; $P = 0.78$), 200ms ($F_{1,7} = 2.70$; $P = 0.14$), or 300ms ($F_{1,7} = 0.58$; $P = 0.47$) intervals.

Again, this comparison failed to yield many significant results, as the pattern across the two experimental sites (within task), were so similar. The significant difference in the *fixation task* at the 100ms TMS interval was the result

of the directional difference of the percent change correct, ie. positive for left DLPFC and negative for right DLPFC. The possible explanations for hemispheric differences in the TMS effect will be explored further in the discussion section.

TMS minus No-TMS data comparing between tasks

The most striking effect in the magnitude of the TMS effect illustrated in **Figure 14** (page 74), is the difference in performance in the *fixation* and *saccade task*. Our original hypothesis stated a similar effect would be found in both tasks, that TMS would likely inhibit performance. The difference in the TMS effect in the *fixation* and *saccade tasks* was surprising, particularly due to the facilitatory effects that were observed in the *saccade task*. The possible interpretations of this finding will be explored in more detail in the discussion section.

A repeated measures ANOVA was conducted to compare performance between the *fixation task* and the *saccade task*, for each of the three TMS time intervals. For left DLPFC TMS, there was a significant difference between tasks for the 200ms interval ($F_{1,7} = 7.22$; $P = 0.03$), but not 100ms ($F_{1,7} = 0.001$; $P = 0.97$), or 300ms ($F_{1,7} = 0.33$; $P = 0.59$). For right DLPFC TMS, there was a significant difference in performance between tasks at the 100ms interval ($F_{1,7} = 8.08$; $P = 0.02$), and 300ms ($F_{1,7} = 8.56$; $P = 0.02$), but not 200ms ($F_{1,7} = 1.47$; $P = 0.27$).

These contrasts confirm the overall trend for performance suppression in the *fixation task* and performance enhancement in the *saccade task*. Subjects' ability to perform the task without TMS was better for fixation than saccade trials, but with the addition of TMS, the proportion of correct responses was altered in different ways. During saccade trials, baseline performance drops rapidly with the addition of even one distracter. When TMS is applied at 100ms, 200ms, or 300ms, the drop in performance is less drastic. It appears there is a quality of TMS that is unique to the saccade condition in the trans-saccadic memory task. Possible interpretations of this finding will be explored in the discussion (section 4).

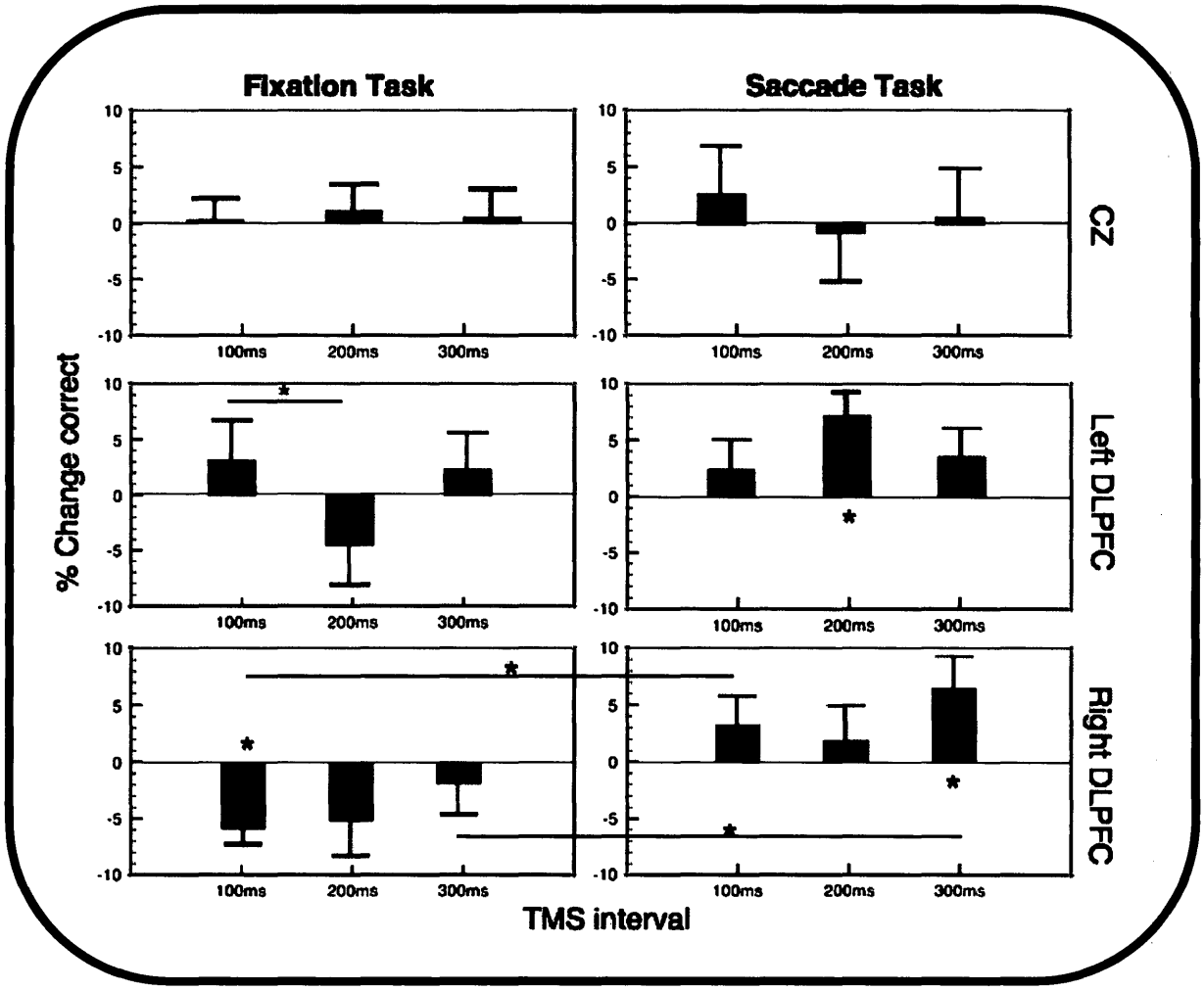

Figure 14. Magnitude of the TMS effect. The percent change correct is calculated as the difference of each of the three TMS time intervals from their respective No-TMS baseline, collapsed across set-size. The *fixation task* and *saccade task* data are shown for the control site CZ (top panels), left (middle panels) and right (bottom panels) DLPFC. Positive numbers represent a greater percentage correct and negative values represent a lesser percentage correct compared to the No-TMS baseline.

TMS minus No-TMS data with CZ subtracted

Figure 15 (page 77) illustrates the percent change correct for left and right DLPFC, after subtracting the CZ data. The same repeated measures ANOVAs were conducted as above (for time, site, and task). As the CZ data displayed no significant differences between TMS and No-TMS (ie. the percent change correct was close to zero), the comparisons here are similar to those listed above. In the *fixation task*, there was a significant difference in performance for the three TMS intervals for left DLPFC TMS ($F_{2,7} = 4.38$; $P = 0.03$). Pairwise comparisons revealed that performance during TMS at the 200ms was significantly lower than 100ms ($P = 0.05$), but not 300ms ($P = 0.11$). The effect of TMS time intervals for right DLPFC was not significant ($F_{2,7} = 1.58$; $P = 0.24$). In the *saccade task*, there were no significant differences in percent change correct for the three TMS time intervals for left DLPFC ($F_{2,7} = 1.44$; $P = 0.27$), or right DLPFC ($F_{2,7} = 1.26$; $P = 0.31$).

Paired-samples t-tests were conducted to compare performance during left and right DLPFC TMS for each time interval. In the *fixation task*, there was a significant difference between left and right DLPFC TMS at 100ms ($t_{(7)} = 2.50$; $P = 0.04$), but not 200ms ($t_{(7)} = 0.29$; $P = 0.84$), or 300ms ($t_{(7)} = 1.07$; $P = 0.33$). In the *saccade task*, there were no significant differences between left and right DLPFC TMS at 100ms ($t_{(7)} = -0.30$; $P = 0.78$), 200ms ($t_{(7)} = 1.66$; $P = 0.14$), or 300ms ($t_{(7)} = -0.76$; $P = 0.47$). For the between task comparison, there were no

significant differences found for left DLPFC TMS at 100ms ($t_{(7)}$ = 0.48; P = 0.64), 200ms ($t_{(7)}$ = -2.18; P = 0.07), or 300ms ($t_{(7)}$ = -0.45; P = 0.67). Similarly, there were no significant differences found for right DLPFC TMS at 100ms ($t_{(7)}$ = -1.41; P = 0.20), 200ms ($t_{(7)}$ = -1.15; P = 0.29), or 300ms ($t_{(7)}$ = -1.46; P = 0.19).

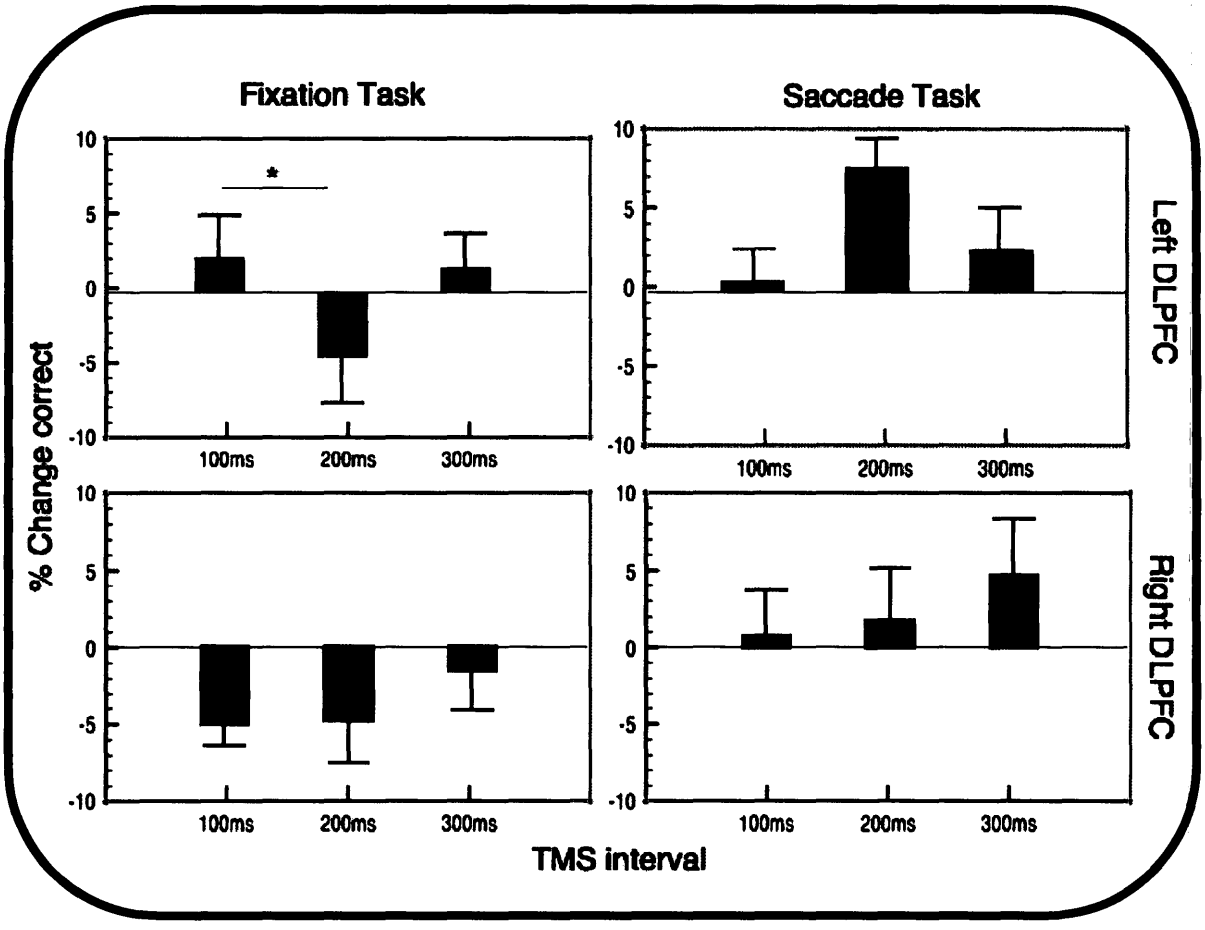

Figure 15. Magnitude of the TMS effect, with control site CZ subtracted. The *fixation task* and *saccade task* data are shown for left (top panels) and right (bottom panels) DLPFC. For Left DLPFC in *The Fixation* task, the TMS effect between100ms and 200ms is significantly different.

3.5 Effects of TMS on saccade metrics

The saccade metrics were examined in order to assess whether TMS had an effect on the amplitude and latency of the saccade, or whether gaze position or the visual hemifield of the target contributed to performance. No differences were found between TMS trials and No-TMS trials for saccade amplitude for left ($t_{(15)} = 1.32$; $P = 0.44$) or right ($t_{(15)} = 1.68$; $P = 0.62$) DLPFC. Similarly, no differences were found for average saccade latency for left ($t_{(15)} = 1.73$; $P = 0.28$) or right ($t_{(15)} = 1.10$; $P = 0.50$) DLPFC TMS, compared to the No-TMS baseline.

The visual field effect of TMS was also examined separately for both the fixation and saccade conditions. For the *fixation task*, no differences within either the left hemisphere: target presented in the left visual field ($t_{(7)} = -1.5$; $P = 0.19$), target presented in the right visual field ($t_{(7)} = 2.08$; $P = 0.45$), or the right hemisphere: target presented in the left visual field ($t_{(7)} = -0.82$; $P = 0.09$), target presented in the right visual field ($t_{(7)} = -0.41$; $P = 0.70$). For the *saccade task,* no differences within either the left hemisphere: target presented in the left visual field ($t_{(7)} = 0.05$; $P = 0.96$), target presented in the right visual field ($t_{(7)} = -0.27$; $P = 0.80$), or the right hemisphere: target presented in the left visual field ($t_{(7)} = 0.67$; $P = 0.525$), target presented in the right visual field ($t_{(7)} = -0.59$; $P = 0.58$).

Finally, saccade accuracy was assessed by calculating the mean saccade error, illustrated in **Figure 16** (page 80). Saccade error is defined by the distance

in horizontal and vertical coordinates between the saccade target (second fixation cross) and the post-saccadic eye position (saccade end-point). There were no statistical differences found in saccade error between left DLPFC TMS and No-TMS trials ($t_{(15)} = -0.43$; $P = 0.66$), or right DLPFC TMS and No-TMS trials ($t_{(15)} = -0.50$; $P = 0.62$).

As a result of these findings, we can conclude that TMS did not have any effect on the eye movement. Therefore, the results of the trans-saccadic memory task that were observed are not likely due to motor factors surrounding the saccade, rather a putative processing mechanism of the visual system.

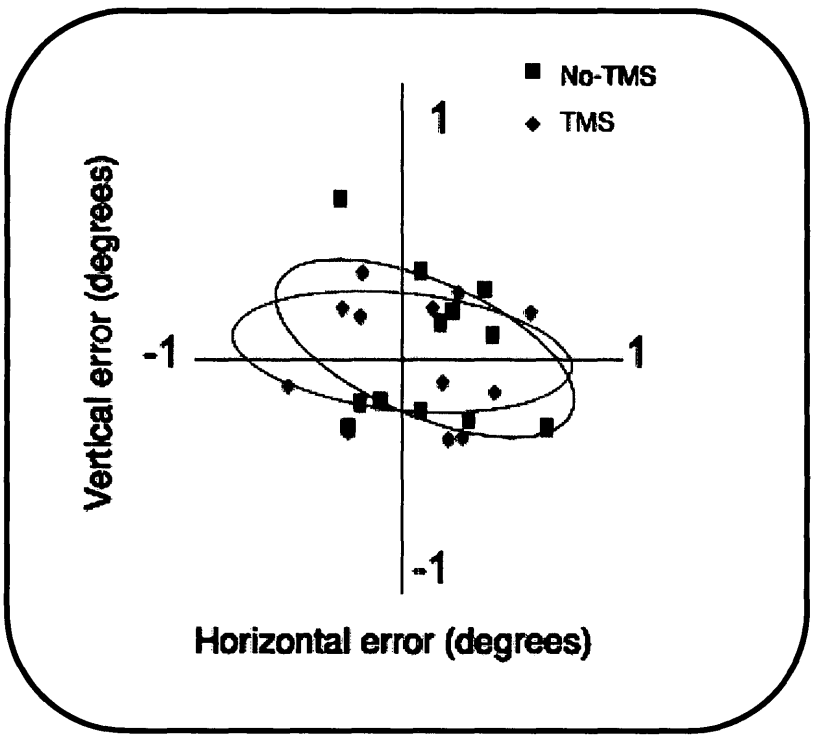

Figure 16. Saccade accuracy for right DLPFC. Each data point represents the mean saccade error for No-TMS (in red) and TMS trials (in blue) for one representative subject. Confidence ellipses are shown with the means centered.

3.6 Summary of TMS results

In an attempt to synthesize the TMS results, the percent change correct for each of the three TMS intervals were combined for each site, and each task. This is shown in **Figure 17** (page 82). This clearly illustrates the difference in performance between the *fixation* and *saccade task*, for the experimental sites. A two-way repeated measures ANOVA (site X task) was conducted, revealing a significant difference in performance between left and right DLPFC ($F_{1,7} = 5.48$; $P = 0.05$) but not task ($F_{1,7} = 1.68$; $P = 0.24$). The interaction was not significant ($F_{1,7} = 0.59$; $P = 0.47$).

T-tests were utilized to examine the differences between tasks within each hemisphere. There was no significant difference within left DLPFC ($t_{(7)} = -1.35$; $P = 0.22$). However, right DLPFC did exhibit a significant difference between performance in the *fixation* and *saccade tasks* ($t_{(7)} = -2.42$; $P = 0.04$). Right DLPFC plays a dominant role in spatial working memory, so the juxtaposition between performance in the two tasks is an interesting point which will be discussed below.

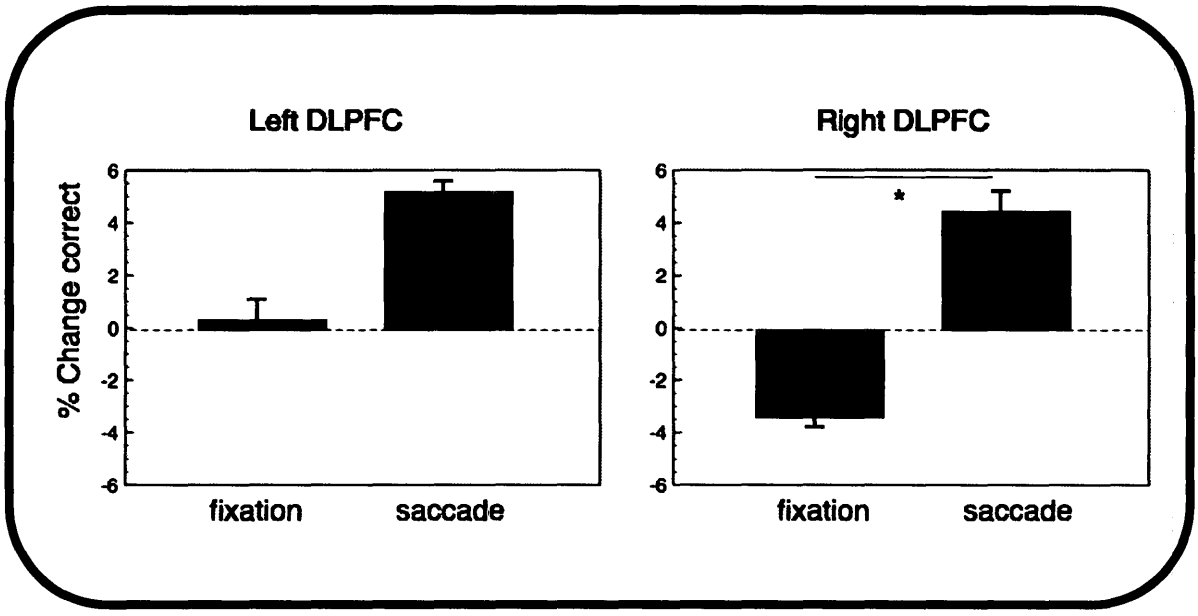

Figure 17. The percent change correct for left and right DLPFC, with each of the three TMS intervals in the *fixation* and *saccade task* combined. Right DLPFC exhibits a significant difference in performance for fixation and saccade trials.

4. Discussion

4.1 General Discussion

The main findings in this study are as follows. TMS over the control site CZ yielded no significant effect on performance during either the *fixation* or *saccade task*. However, TMS over left and right DLPFC had differential effects on performance during each of the two tasks, and at different TMS time intervals. Performance was significantly disrupted in the *fixation task*, when TMS was applied over right DLPFC at 100ms. In the *saccade task*, TMS over left DLPFC at 200ms, and right DLPFC at 300ms significantly *improved* performance. Overall, there was a general trend for TMS during the *fixation task* to produce performance deficits, while TMS during the *saccade task* facilitated performance. When the three TMS time intervals were pooled, right DLPFC showed a significant difference between the suppression and facilitation effect in the *fixation* and *saccade tasks,* respectively.

It has previously been hypothesized that trans-saccadic memory is a special case of visual working memory (Irwin, 1996), with the addition of signals related to spatial updating during saccades (Prime et al., 2008, 2010; Melcher & Colby, 2008). Based on this, and the assumption that DLPFC is an area involved in general working memory (Miller & Cohen, 2001), we hypothesised that performance would be suppressed with TMS in both the *fixation* and *saccade tasks* in a similar manner. Clearly the results did not agree with this hypothesis,

so the root assumption of this hypothesis, particularly the neural mechanism for trans-saccadic memory, needs to be re-evaluated.

4.2 Potential mechanisms of TMS action in this experiment

Before interpreting the results with respect to the trans-saccadic integration literature, I will re-consider the mechanisms of action for single-pulse TMS. Single-pulse TMS has been known to produce enhancement effects during stimulation to certain cortical areas, and under certain task parameters (see Luber & Lisanby, 2013 for a review). TMS to motor and visual cortex can produce muscle twitches and phosphenes, indicative of increasing the excitability of targeted neural populations (Barker et al., 1985). TMS has also been shown to facilitate performance during tasks related to motor learning (Butefisch et al., 2004), spatial working memory (Yamanaka et al., 2009), and visual awareness (Gosbras & Paus, 2003). Conditions under which TMS has facilitated performance (usually reduced RTs) vary considerably, but researchers have begun to converge on an understanding of how this may occur (Hamidi, Tononi & Postle, 2008; Kahn et al., 2005; Kirschen et al., 2006). One possibility is dis-inhibition of a given cognitive region. If there are two brain areas with a reciprocal inhibitory influence on each other, then disruption of one area via the application of TMS can result in hyperactivity of the second region (Theoret et al., 2003; Hamidi, Tononi & Postle, 2008). These studies lend support to the notion that

the view of TMS as a 'virtual lesion' is an incomplete one. TMS may suppress or facilitate physiological processing, which can alter both local states and that of the network.

TMS has also been described as injecting noise into the system, by inducing neural activity that is uncorrelated with cortical processing in a given region or network (Harris, Clifford & Miniussi, 2008). Here, the cortical signal that is associated with a given cognitive function is not reduced, but is masked by the increase in 'other' signals, or background noise. Recently, Fertonani et al. (2011) have made claims that this neural noise may serve a different function. They suggest that repeated stimulation (tRNS, random noise stimulation) can support temporal summation of neural activity, and may thwart homeostatic mechanisms of ion channels by providing a 'constant' electrical state, allowing membrane responses to return to resting state. An alternative hypothesis is outlined as a form of stochastic resonance. Adding neural noise into a non-linear system (such as the brain), can enhance the detection of sub-threshold, or weak stimuli, or enhance the information content of a neuronal signal (eg. action potentials; Moss, Ward & Sannita, 2004). It is still unclear however, exactly how TMS affects underlying neural populations. In the case of the trans-saccadic memory task used in our study, if noise were responsible for masking the memory signal in DLPFC, the results would be in line with our original hypothesis, that TMS would inhibit performance on a spatial memory task. If however, the noise produced by

TMS could enhance neural signal detection, the results could be quite different. By enhancing the memory signal, or top-down executive control system of DLPFC, performance on a spatial memory task might be improved. The addition of neural noise could also boost other sub-threshold signals that would otherwise go unnoticed, or reduce noise to relevant signals.

4.3 Comparing current results to previous PPC, FEF TMS experiments

Overall, we observed different TMS effects than that of Prime et al. (2008, 2010). In both of the previous studies, TMS over PPC and FEF inhibited performance in both the *fixation* and *saccade task*, with a greater effect in the *saccade task*. This effect was more prominent in the right hemisphere. In the current study, we observed consistent suppression of performance in the *fixation task* and facilitation of performance in the *saccade task*, during right DLPFC stimulation. We did not observe the consistent suppression of performance that Prime et al.(2008, 2010) reported, across tasks.

The time-specific effects we found were somewhat different than that of the previous PPC and FEF papers. Both of the previous studies demonstrated the greatest TMS effect at the 200ms interval. This is not surprising, given the role of these structures in spatial remapping and the temporal characteristics of saccades. The TMS effect was greatest when the pulse most closely coincided with that of the saccade. In the case of TMS to DLPFC, there were no such time-

specific effects; that is TMS affected performance at all three TMS time intervals.

In the *saccade task*, performance with TMS was the highest during the 200ms and 300ms interval. This could support the notion that TMS to DLPFC dis-inhibits the remapping network, and updated information is used by the fixation system to abolish old information. This may facilitate performance at the later TMS time intervals.

A key question raised by the present study is the difference in performance between the *fixation* and *saccade tasks,* and why these results fundamentally differ from the PPC and FEF study results. There are several possibilities for this finding, which will be discussed below.

4.4 Hemispheric asymmetry

It is not uncommon for TMS to produce different results for corresponding sites in the left and right hemispheres (Maeda, 2000; Yamanaka, 2009). For example, Prime et al. (2008) only found suppression of trans-saccadic memory during TMS over right PPC. We observed consistent suppression in performance during right DLPFC TMS in the *fixation task* across each of the three TMS intervals. This is consistent with known asymmetries of DLPFC function, with left hemisphere activity related to verbal and non-spatial working memory, and right hemisphere activity related to spatial working memory (D'Esposito et al., 1998; Muri et al., 2000). We observed less asymmetry in *saccade task.* Performance

for each of the three TMS intervals was consistently enhanced. Left DLPFC displayed similar results, but was not consistent across each of the three TMS intervals. This suggests a more complex relationship between DLPFC and trans-saccadic memory, which will be considered below.

4.5 Working memory vs. TSM

Our results suggest that visual working memory (*fixation task*) and trans-saccadic memory (*saccade task*) may not share the same cortical mechanisms. Previous work has drawn from similarities between visual working memory and trans-saccadic memory such as capacity (Luck & Vogel, 1997; Irwin, 1991) and representation ie. object-based rather than feature based (Irwin & Andrews, 1996), to infer that the two systems may be comprised of the same cortical network (Hollingworth, Richard & Luck, 2008). While it may be true that visual working memory and trans-saccadic memory exhibit similar properties, the manner by which they process information may be different.

The role of DLPFC in visual working memory has been well established (Miller & Cohen, 2001). This is further evidenced by the results of the current experiment, where TMS to right DLPFC disrupts performance on a visuo-spatial memory task. DLFPC is necessary for simple working memory during fixation, but when an eye movement is required, information may be shifted to other regions of the brain, as observed during spatial updating tasks (Medendorp et al.

2003; Merriam et al. 2003). In addition to those studies (which used memory of point stimuli) the trans-saccadic memory task utilized in this study requires that the spatial location of the target is updated in order to successfully discriminate the change in orientation of the probe. It is well established that both FEF and PPC are involved in updating this memory signal, which poses the question of how DLPFC may influence perceptual processing incurred by these two regions (Duhamel et al., 1992; Umeno & Goldberg, 1997). It is known that DLPFC has direct connections to both areas, but what is the significance?

DLPFC has anatomical and functional connections with parietal (PEF) and frontal regions (FEF, SEF) responsible for triggering intentional, reflexive, and memory-guided-saccades (Pierrot-Deseilligny et al., 1997), and sends extensive projections directly to SC (Goldman & Nauta, 1976; Johnson & Everling, 2006). DLPFC is thought to be essential in suppressing automatic responses during anti-saccade tasks and preparing predictive saccades (Pierrot-Deseilligny et al., 2005) and saccade sequences (Fujii & Graybiel, 2003), suggesting a decisional role in oculo-motor behaviour (Pierrot-Deseilligny et al., 2005). Disruption of DLPFC does not affect saccade metrics during visually-guided saccades and impairments during memory-guided tasks are not attributed to sensory or motor deficits (Pierrot-Deseilligny et al. 1991; Coubard & Kapoula, 2006). DLPFC likely functions as a modulator for saccade generation, via direct efferent connections to FEF and SC (Boxer et al., 2006).

Thus, while DLPFC has some influence over saccade generation, it is likely not required for remapping the eye movement signal. Consistent with this, our results failed to show any disruption of remapping during TMS over either side of DLPFC. Indeed, we even observed a significant facilitation. The following sections consider how this may have occurred and what this might mean for understanding the neural mechanisms of trans-saccadic memory.

4.6 TMS facilitation during the saccade task

We propose that the facilitation of working memory during TMS over DLPFC occurred through a process of dis-inhibition (Fierro, 2006; Cash et al., 2009). More specifically, we propose here that other areas of the brain involved in trans-saccadic memory are not only involved in driving the remapping of remembered stimuli (Prime et al. 2008, 2010; Melcher & Colby, 2008), but are also involved in the transient storage of this memory around the time of a saccade. During trials in the *saccade task*, TMS to DLPFC may affect the inhibitory inputs from DLPFC to the remapping network, resulting in a transient redistribution of visual information to areas associated with updating visual information. This could lead to improved performance during TMS in the *saccade task* by shifting cognitive processing from DLPFC to the remapping network. During saccades, this network would bear the brunt of the processing load,

rendering DLPFC less critical until the stored and updated information is re-transferred to the fixational memory system (Miller & Cohen, 2001).

TMS to DLPFC during saccades may facilitate remapping by effectively wiping out old fixation information in retinal coordinates that is no longer relevant for the new eye position. Around the time of a saccade, perceptual changes occur as visual information undergo spatial transformations (Hamker et al., 2011). Several lines of study have emerged to account for the transfer of information across a saccade, by examining changes in perception in light of the functional requirements for space constancy. Studies of psychophysics have shown that stimuli flashed shortly before or during a saccade are erroneously localized in the visual field, appearing displaced (Matin, Pearce & Pola, 1970; Honda, 1989, Morrone, Ross & Burr, 1997). A saccade can distort estimations on a temporal scale, where the separation of two peri-saccadic flashes is systematically underestimated, or the perceived order may be switched (Morrone et al., 2005). During stable fixation, object displacement in the visual environment is easily detectable; during a saccade however, displacement can go unnoticed (Burr et al., 1982). Saccades can cause significant shifts or suppression of perceptual processing with varying consequences that the visual system must resolve. We propose here that during saccades, TMS to DLPFC facilitates remapping by aiding the transfer of updated information to the fixation system, by helping to erase old information.

Visual information stored in fixed retinal coordinates is spatially invalid after a saccade. This can be corrected by remapping the retinal information into the appropriate position for the new eye position (Duhamel et al., 1992; Nakamura & Colby, 2002). This process must incorporate erasing or 'dumping' the original information, so that is does not interfere or compete with the remapped information. Such dumping could occur through the same signals that cause suppression of signals during saccades. For example, Sommer and Wurtz (2006) observed suppression of visual memory signals in cells in the frontal eye fields during saccades. In principle, TMS over DLPFC could enhance this process by helping to wipe clean irrelevant information in the fixation visual memory system.

4.7 Putative mechanisms for trans-saccadic memory

In order for subjects to perform the trans-saccadic memory task successfully, the spatial location and feature information of an object must be integrated with saccade-related signals within the visual system. In previous studies that used the same experimental task, it was shown that both FEF and PPC were involved in this process (Prime et al., 2008, 2010).

The results with TMS to DLPFC are more complex. DLPFC is involved with a number of functions related to perceptual processing including spatial working memory, executive function, and top-down control (Miller & Cohen,

2001). We propose that during stable fixation the role of right DLPFC in spatial working memory is crucial, evidenced by the consistent suppression of performance during TMS. However, as suggested in the previous section, when an eye movement is necessitated right DLPFC is no longer an essential processing area, as the memory signal is transferred to areas associated with the remapping network, and then transferred back into the fixational memory system after the saccade. This possibility is outlined in **Figure 18** (page 96).

What is this feature remapping network? There are several possibilities, which could include areas involved in both driving the remapping and/or the transient storage of the remapped signals. Both PPC and FEF are involved in processing for visual feature memory, with different contributions emerging at temporal and functional scales (Muggleton et al., 2011; Corbetta & Shulman, 2002). Using TMS to illustrate the time course of visual processing has shown that FEF disruption occurs earlier (40-80ms) than PPC disruption (120-160ms; Ashbridge et al., 1997; Kalla et al., 2008). In line with these temporal dynamics, FEF has demonstrated target discrimination independent of saccade planning, and may modulate extrastriate cortex target activity (Juan et al., 2004; Moore et al., 2003). PPC has been implicated in feature binding and spatial localization, consistent with a role in coordinate transformations and updating spatial information across eye movements (Treisman, 1996; van Donkelaar & Muri, 2002). Feature information (shape) has been found in area LIP of the monkey,

suggesting the PPC may be doing more than reconciling spatial information, and could affect visual feature storage as well (Sereno & Maunsell, 1998).

The early visual cortex (EVC) is another region that could be involved in trans-saccadic updating of visual feature memory. Spatial remapping has been observed in EVC (areas V1, V2, V3A), and the nature of such experiments suggests a close involvement with saccade related areas that provide access to CD signals (Merriam, Genovese, & Colby, 2003; Nakamura & Colby, 2002; Umeno & Goldberg, 1997; Ghandi et al., 1999; DeSouza et al., 2002). EVC receives re-entrant projections from higher-up visual processing pathways, making it a good candidate for integrating feature information with spatial updating signals (Prime et al., 2006; Moore et al., 1998). Recently, a study conducted by Malik et al. (in press), showed that TMS to EVC disrupted feature memory in a trans-saccadic integration task. Here, performance discriminating orientation change of a single object was degraded when a saccade caused a shift in visual hemifield bringing the EVC target site into the 'remapped' space.

Finally, Dunkley et al. (in press) have reported preliminary evidence for an area involved in trans-saccadic memory of visual orientation in posterior supramarginal gyrus in the inferior parietal lobule. If this is correct, then the study conducted by Prime et al. (2008), which involved TMS just posterior to this site, may have disrupted both saccade updating signals (as they proposed) and trans-saccadic storage.

Thus, it is likely that visual feature storage and information transfer occurs across a distributed network, which functions both to retain spatial information and uphold space constancy. Both PPC and FEF are likely involved in this network, and other contributing cortical regions are still being identified.

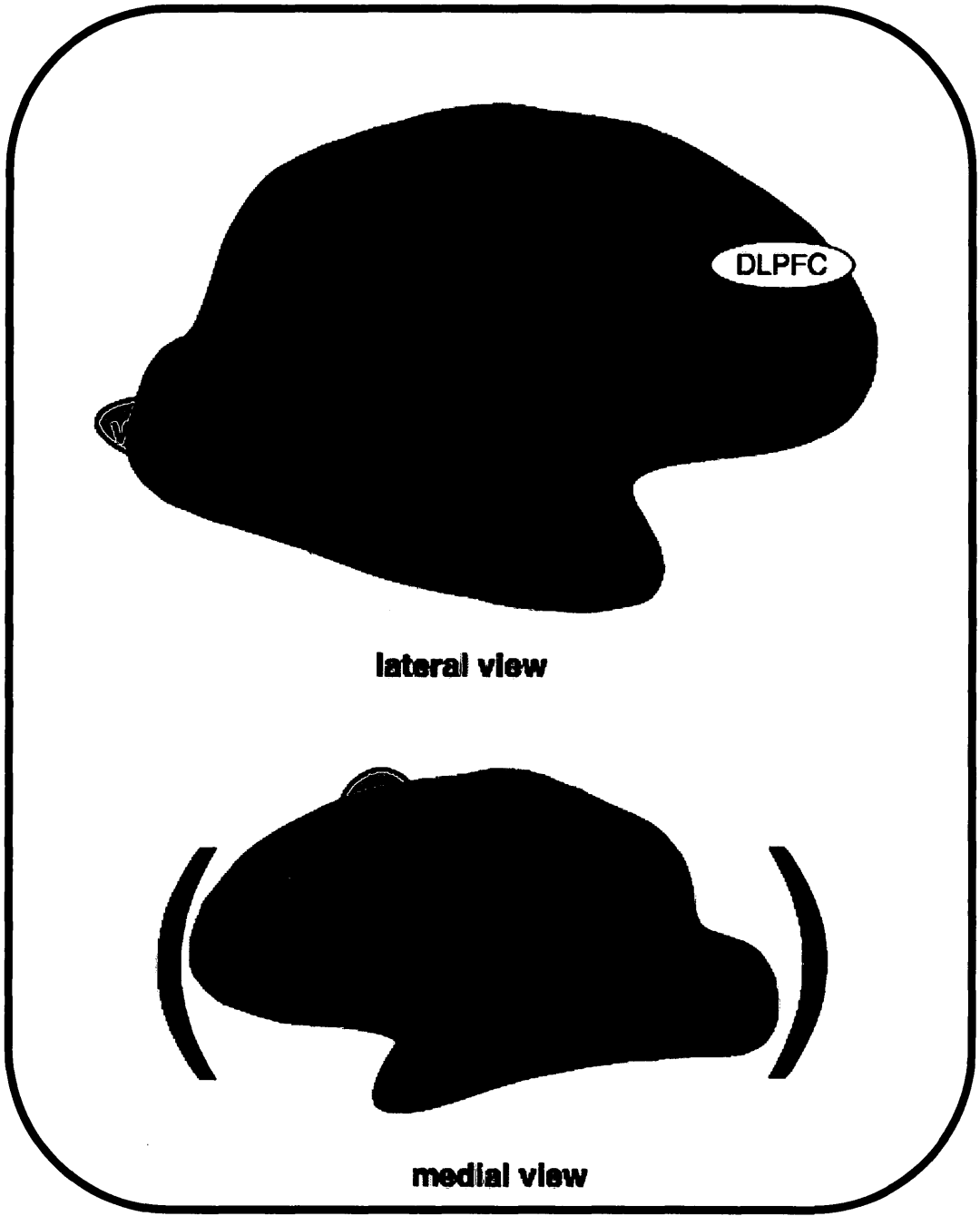

Figure 18. Possible mechanisms for visual perception during trans-saccadic memory. During trials in the *fixation task* DLPFC, an area responsible for spatial working memory, is important for processing visual information. During trials in the *saccade task*, processing is shifted to areas responsible for remapping visual information (indicated in blue). Dotted lines represent subcortical structures, illustrated in the medial view.

5. Conclusions

The work of Prime et al. (2008, 2010) demonstrated that single-pulse TMS to the PPC and FEF disrupts performance on a trans-saccadic memory task. The authors summate their findings in the context of trans-saccadic perception which reflects a two-stage process where stored representations in visual working memory are integrated with spatial updating processes that remap memory representations during an eye movement (Melcher & Colby, 2008; Prime et al., 2011). Reduced accuracy associated with TMS to PPC and FEF, may be attributed to a compromised efferent copy signal related to the saccade.

Results of the current study are more complex than that of Prime et al. (2008, 2010). We found an overall trend for both performance suppression and facilitation, during the *fixation* and *saccade task*, respectively. The differences in performance in these two tasks suggest that the role of DLPFC in processing spatial working memory changes when the requirements of the task are altered. Our original hypothesis stated that DLPFC, in particular right DLPFC, would be equally important for both visual working memory (*fixation task*) and trans-saccadic memory (*saccade task*). Our data does not fully support this hypothesis. Right DLPFC does show consistent suppression of performance in the *fixation task*, but shows a different effect during the *saccade task*. The facilitated performance exhibited during right DLPFC TMS in the *saccade task*, could indicate that this particular cortical area is not critical for trans-saccadic

integration. With TMS, facilitations in performance may suggest a dis-inhibition of trans-saccadic processing, and thus aiding the transfer of updated information to the fixation system by helping to erase old information. Studies conducted by Prime et al. (2008, 2010) support the view that working memory and trans-saccadic memory comprise similar cortical networks. The data presented here may draw a distinction between these two cortical networks. Here, the different TMS effects, and different memory load capabilities (significant differences between baseline performance in the two tasks), suggest that working memory and trans-saccadic memory may operate in a unique fashion.

The results of this project build upon the work previously conducted by Prime et al (2008, 2010) and contribute to the understanding of trans-saccadic memory and DLPFC function. We propose that there may not be a single network for trans-saccadic integration, and that visual working memory and trans-saccadic memory may involve distinct, interacting cortical mechanisms. Based on the data of the current experiment, the current working model of trans-saccadic memory should be revised in a manner that is consistent with the previous PPC and FEF papers (Prime et al., 2008, 2010). The current data also necessitates further research in the future.

Recall from **Figure 4** (page 40), the four-panel prediction of how trans-saccadic memory may involve the ventral and dorsal visual processing streams. We have shown that it is not likely that visual processing for trans-saccadic

memory occurs via feed-forward connections to DLPFC (**Figure 4*b***). It would be useful however to examine this process using fMRI or concurrent fMRI-TMS to validate our results. Using the same, or similar event-related task design, fMRI could be used to examine whether the behavioural effects of TMS to DLPFC is correlated with an increase in BOLD (blood-oxygen level dependent) in areas of the remapping network.

Recent evidence has implicated other areas involved in working memory, including the medial temporal lobe (Jeneson et al., 2012) and the hippocampus (Baddeley, 2011). It could be useful to examine these regions in an attempt to localize the memory component of trans-saccadic memory. Also still to test, are the bottom-up processing influences of early visual areas and automatic visual integration. V1 neurons have exhibited long latency responses that have been associated with top-down cognitive processing by higher visual areas (Motter, 1994; Hupe et al., 1998). These effects likely are mediated by recurrent feedback to early visual cortex. This illustrates the re-entrant hypothesis outline in **Figure 4*d*** (page 40), where signals from the visual processing streams are integrated through re-entrant pathways to earlier visual areas. Whether early visual areas play a role in integrating visual information from higher cortical areas and are involved in trans-saccadic memory beyond simple image processing remains to be formally tested. This could provide insight to the cortical mechanisms necessary for successful visual integration across eye movements, and

consolidate both the results presented here and that of Prime et al., (2008, 2010) into a coherent model of trans-saccadic memory.

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