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On the normal use of oculomotor reflexes

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On the Normal Use of Oculomotor Reflexes

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Summary

The experiments reported in this thesis aimed at investigating how voluntary control is exerted through the modulation of neural circuitry mediating reflexive behaviours. Eye movements were used as a model system to study how two primitive collicular reflexes, the fixation reflex and inhibition of return are integrated, for use in visual cognition. I observed that automaticity and control independently influence the FOE (Chapter 2). Automaticity was studied by systematically varying the foreperiods within a block of trials. Voluntary control was examined by inducing different task sets (either pro-, or anti-saccades). I showed that both influence the FOE independently. In chapter 3, I examine whether patients with PD can voluntarily control their oculomotor reflexes. I showed that dopamine deficiency due to Parkinson's disease impairs voluntary control of the FOE (Chapter 3). I explain this in terms of the role of the basal ganglia in oculomotor behaviour. In Chapter 4 and 5, I asked how inhibitory tags (IOR), which are used by visual cognition to aid visual search, are remapped and represented by the parietal cortex. In order to investigate this, Transcranial Magnetic Stimulations (TMS) was applied over the parietal cortex just after the onset of an eye movement. I found that when subjects were required to make horizontal eye movements to the right or left, TMS over the right parietal cortex prevented remapping of IOR for both saccade directions (Chapter 4). However, TMS over the left parietal cortex did not influence remapping of IOR. When subjects were required to make vertical eye movements (Chapter 5), TMS over the right parietal cortex prevented remapping of IOR in both the right and left visual field. However, TMS over the left parietal cortex prevented remapping of IOR in only the right visual field. These findings suggest a different role for the right and left parietal cortex. More precisely, the findings suggest that the right hemisphere does not only remap the inhibitory tag, but also maintains a stable representation across eye movements. The reported findings provide further support for the theoretical models which were discussed in the introduction.

Chapter 1: Introduction

In his 1972 essay published in the *American Scientist* titled 'On the normal use of reflexes', Easton argued that the neural circuits that subserve reflexes are the building blocks for more complex behaviour; and that the nervous system routinely goes about its business through an orchestration of those circuits by cortical processes that activate or inhibit them (Easton, 1972). Easton reasoned that voluntary motor coordination based on the reflexes would be simpler and more economical for organisms, i.e. if the basic units of the motor control are reflexes fewer commands and resources are required. According to Easton, there is a hierarchy with simple reflexes at the bottom of the hierarchy, and more complex, but sill stereotyped reflexes higher in the hierarchy. Volitional control is at the top of the hierarchy. In addition, higher levels of the CNS are becoming more important with increasing complexity and development of the brain. This is, for example, apparent in the course of the development of the mammalian foetus, where first simple reflexive movements emerge, which are later integrated into more complex movements.

A similar framework has been developed by Rozin (1976) who argued that, in the course of evolution, reflexes became the organism's response to specific environmental challenges, i.e. they are "adaptive specializations". For example, all types of eye movements employ the same muscles and motor neurons. In the course of vertebrate evolution, specific brain areas have appeared for each motor function (Delgado-Garcia, 2000). At the time of their origin, these reflexes are not accessible, i.e. they are completely autonomous. According to Rozin, higher systems gained access to these reflexes during evolution, and ultimately consciousness control can be applied. Moreover, the evolution of more complex behaviour required brain mechanisms to regulate reflexes in the service of goal directed action.

In summary, our visual orienting behaviour is influenced by our evolutionary history; every eye movement is the result of an interaction between higher cortical areas and reflexive sub cortical areas, and can

therefore be used as a model to study how cognition influences reflexive behaviour. The goal of the research conducted in this thesis was to develop a framework for understanding the psychobiology of automaticity and control from this evolutionary perspective. It focuses on oculomotor behaviour as a model system to investigate this. More precisely, two reflexive processes that involve the phylo-genetically older midbrain visual system of the superior colliculi were studied. Since an eye movement to a visual signal is simple and natural, oculomotor behaviour can be studied in infants, brain injured patients, non-human primates, as well as healthy adults. As a result, much is known about its development, neurophysiology, and pathology. In chapter 2, in which healthy adults were studied, and 3, which studied patients with Parkinson's disease, I report research on the control of the visual grasp and fixation reflex. In chapters 4 and 5, dual pulse TMS was employed to examine the role of the intraparietal cortex in the remapping of visual saliency maps. These experiments explored the hypothesis that an inhibitory tag (Inhibition of Return, or IOR), which involves the superior colliculi, is utilized by the oculomotor cortex to encode a visual saliency map which is employed in visual cognition.

The visual grasp and fixation reflex

A salient stimulus in the periphery automatically elicits an orienting response in most animals. Foveate animals can make saccadic eye movements independent of head movements, and in them the automatic orienting response evolved into a reflexive saccade towards the suddenly appearing target (Delgado-Garcia, 2000). According to Hess, the purpose of this visual grasp reflex (VGR) is to change the line of sight of eccentric targets towards the central foveal region where it can be analyzed in more detail. In Rozin's framework (Rozin, 1976), the VGR can be considered as an adaptive specialization, since it enables a quick analyses of the stimulus by foveating it, and thereby maximizing the time to respond to it. Once a target is fixated, it has to be kept stable on the fovea to be analyzed. A foveated stimulus therefore elicits a fixation reflex, i.e. a period of oculomotor immobility. Normal oculomotor

behaviour consists of a saccade-fixation sequence, repeated over and over again (Findlay & Walker, 1999). Behavioural studies have shown that a stimulus at fixation suppresses the VGR. Saslow (1967) discovered that the latencies of saccadic eye movements towards peripheral targets are shorter when a fixation stimulus disappears before the target onset, compared to when the fixation point remains visible. This effect is referred to as the GAP effect. Pratt et al. (Pratt, Bekkering, & Leung, 2000) also found that increasing the size of the fixation point 200 ms before the appearance of a visual target resulted in slower reaction times towards the target compared to when the fixation point remained the same size.

Neurophysiological studies of the gap effect have implicated the SC Ablation of the SC in monkeys, cats, gerbils, and rats results in a loss of the orienting response (Delgado-Garcia, 2000). In addition, humans who suffer from progressive nuclear palsy, a progressive neurological disease which affects the SC, no longer show a VGR (Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988). This evidence indicates that the SC is important for this reflexive behaviour. The SC is a laminated structure. It receives direct retinal input in its superficial layers, and generates motor output in the intermediate layers, which is sent to the saccade burst generator circuits of the brainstem (Moschovakis, 1996). The receptive fields of the sensory superficial layer neurons are retinotopically organized (Munoz & Guitton, 1989; Munoz & Wurtz, 1993a, 1993b; Peck, 1989). Neurons in the rostral part have receptive fields in the foveal region, whereas the contralateral visual field is represented by the remaining neurons. More precisely, the upper and lower visual field are coded in medial and lateral direction respectively, whereas the periphery is coded in a caudal direction, with more caudal neurons representing increasingly peripheral loci in the visual field. The intermediate layers of the superior colliculus also respond to visual stimuli with the same retinotopic mapping as the overlying superficial layers. There neurons, however, also respond at the onset of a saccades, and have 'movement fields' as well as visual

receptive fields. That is, electrical stimulation of these neurons elicits a saccade to the same location as its receptive visual field.

The output neurons of the intermediate layer consist of different types of neurons, two output types give rise to the GAP effect: the fixation neurons (FN) and saccade neurons (SN). The FN are located in the rostral part of the intermediate layer, and lie directly underneath the neurons in the superficial layers with a foveal receptive field. The FN are tonically active during fixation, even in darkness, and stop firing during a saccade. The movement fields of SN follow a similar retinotopic as the receptive fields of the superficial layer neurons. The SN are active just before and during saccades to their movement field. The neurons of the intermediate layers receive input from the superficial layers, substania nigra, cerebellum, and cortical areas. It has therefore been posited to be the final common pathway for saccade generation, in which all input from the different structures interact, and where competition for saccade generation from these different sources is resolved to send a motor command to brainstem saccade generators and, thence, to the oculomotor nuclei.

Munoz and Fecteau (2002) have developed a theoretical model referred to as the dynamic interactions model in order to explain how the intermediate layer processes this external input. They have argued that saccade initiation and fixation can be viewed as independent motor plans which compete with each other in the intermediate layer. According to this model, a saccade is initiated only when a SN reaches a certain threshold of activity, and that disengagement of fixation is needed before a saccade can be initiated. Furthermore, neuronal activity in the intermediate layer neurons leads to local excitation and remote inhibition. The model also proposes that the total neuronal activity of the intermediate layer is relatively constant, but the location of the activity on the retinotopic motor map can change.

Based on these rules, FN activity leads to local excitation of other nearby FN, whereas distant SN are inhibited. However, when a SN becomes more active, both FN, and other remote SN are suppressed. In other words, FN and SN mutually inhibit one another. The model can

explain the GAP effect by assuming that active fixation leads to bilateral tonic FN activity, resulting in inhibited SN, since FN and SN mutually inhibit one another. However, when the fixation point disappears before the target onset, the tonic activity FN start to decrease, resulting in relatively disinhibited SN; i.e. less external activity is needed to reach the saccade threshold in this situation. This results in faster saccadic latencies during gap trials.

The model is based on neurophysiological findings. First of all, it has been demonstrated that fixating on a central fixation point is correlated with bilateral tonic activity of rostral FN. Munoz and Wurtz (1993a) measured from rostral pole collicular cells in three monkeys. They found that when the monkeys were actively fixating, the FN were tonically active. The same neurons paused during saccades. In a subsequent study, they directly tested whether the FN are needed for maintaining active fixation and suppressing saccades (Munoz & Wurtz, 1993b). They demonstrated that by increasing the FN activity via electrical stimulation resulted in slower visually guided saccades in all three monkeys. More precisely, no saccades were initiated before the stimulation stopped. Interestingly, only the reaction time was affected, not the accuracy or amplitude. Inhibition of the FN by locally injecting muscimol (GABA agonist) revealed the opposite pattern; reducing saccade latencies and leading to instable fixation behaviour. Munoz and Istvan (1998) recorded from SN and FN while electrically stimulating different collicular neurons. They found that electrical stimulation of FN, which renders them more active, leads to a reduced activity of SN. This finding provides direct evidence that by increasing the FN activity not only the saccadic latencies are longer, but the SN are also reduced. It has therefore been hypothesized that the FN and SN inhibit each other (Munoz & Fecteau, 2002). However, there are no direct connection between these two pools of neurons, suggesting that the inhibition is likely to happen outside of the SC (Isa, 2002; Isa & Saito, 2001).

Dorris and Munoz (1995) examined what happens during the gap period in the monkey SC. They recorded from the FN of the intermediate layer. The monkey started maintaining gaze at a centrally presented

fixation point before the point disappeared. Next, a visually target was presented after a variable delay, ranging between 0 and 800 ms (steps of 100 ms). The monkey was trained to make an eye movement as fast as possible to the visual target, but to keep his gaze if there was no target, i.e. the only difference with the initial fixation period was the absence of a visual stimulus at fixation. The activity level of 53 FN was recorded for each gap duration, and this was averaged in order to calculate the population response. The tonic activity of the FN started to reduce immediately. However, the activity decreased only up to 250 ms, and started to increase again after this. Interestingly, the neuronal population response correlated with the monkey's saccade behaviour. The correlation between normalized fixation cell activity and saccade reaction time was .98, when the time it takes for visual stimuli to reach the SC, which has been estimated to take 40-50 ms (Goldberg & Wurtz, 1972), was taken into account. In other words, the saccadic reaction times were also fastest for gaps around 200-300 ms. This behavioural pattern is in agreement with human subjects studies (Saslow, 1967).

It has been argued that the gap effect is a result of two processes. Firstly, the offset of the fixation point can be considered as a warning signal, which results in an increased general readiness to respond (Kingstone & Klein, 1993; Reuter-Lorenz, Oonk, Barnes, & Hughes, 1995; Saslow, 1967). Additionally, the offset of the fixation point is thought to lead to a disengagement of fixation (Fischer, Weber, Biscaldi, Aiple, Otto, & Stuhr, 1993; Forbes & Klein, 1996; Kingstone & Klein, 1993; Munoz & Wurtz, 1992). Fendrich, Demirel and Danziger (1999) investigated the contribution of these processes to the GAP-effect in more detail. In their experiment they varied the gap duration. A gap period of 200 ms, 0 ms GAP, or a fixation point overlap was used. In an attempt to have the same amount of general readiness for all conditions, a warning sound was presented in all gap conditions in the 200 ms period prior to the target appearance. The saccadic latencies were 14 ms shorter for the 200 ms gap condition than the 0 ms gap, whereas the latencies of the 0ms gap were 18 ms shorter than the fixation point overlap. This indicates that, assuming that an auditory

signal and visual signal provide the same kind of warning signal, general readiness alone cannot account for the GAP-effect. The authors also investigated whether foveal visual input was required for the GAP effect to occur. They presented 4 small circles on the edges of an imaginary 4 degree square. Subjects were required to keep their eye fixated at the centre of this imaginary square, i.e. there was no direct visual input to the fovea. The same three gap durations were presented as in their previous study; 200 ms gap, 0 ms gap, and an overlap. Interestingly, there was still a significant gap-effect; saccadic reaction times were 20 ms faster in the 200 ms gap condition than in the 0 ms gap condition. However, there was no significant difference between the 0 ms gap and the overlap condition. The size of the imaginary square was varied in a subsequent study to determine how much input is required for the fovea. The four circles were presented at either the edges of an 0,1,2, or 4 degree circle. As expected, a significant gap effect was observed for in all conditions. However, the difference between 0 ms gap and overlap trials was only significant for 0 and 1 degree squares, i.e. there was no significant difference between 0 ms gap and overlap trials for 2 and 4 degree squares. The authors argue that their data supports that hypothesis that the benefit in saccadic reaction times between overlap and 0 ms gap is the result of the decreased rostral FN activity in the 0 ms gap. They hypothesize that only visual signals in the fovea have an influence on the activity of FN. This difference in reaction time between fixation point offset trials (0 ms gap duration) and overlap trials is referred to as the Fixation Offset Effect (FOE) (Kingstone & Klein, 1993). In summary, it seems that more than one process contributes to the gap effect. For example, Kingstone & Klein (1993) have argued that it consists of both an increased general readiness to respond, and a disengagement of FN. The GAP effect is not only restricted to the oculomotor domain. For example, Pratt et al (Pratt, Bekkering, & Leung, 2000) found a gap effect for both saccades and directional key presses. However, the FOE requires direct foveal visual input, and has only been reported for saccadic responses. In other words, the FOE can be considered to be an oculomotor reflex. Therefore, the FOE was used in

this thesis to investigate how voluntary control makes use of this subcortical reflex.

Input to the the SC

The interaction that can be observed between FN and SN in the intermediate layer of the SC is the result of external input. The neurons in the intermediate layers receive input from the superficial layers of the SC (Isa, 2002; Isa & Saito, 2001), in addition they also receive input from the cerebellum, substantia nigra pars reticulate, and cortical structures. Or, in other words, although the SC is crucially involved in controlling eye movements, it has become part of a cortically modulated system in the course of evolution.

An important connection to the SC is from the FEF. The FEF has both direct connections to the SC, and indirect connection via the basal ganglia. In addition, the FEF has also direct connection to the brainstem saccade generators (Keller, Lee, & Lee, 2008). The FEF have three different types of cells: visual cells that respond to visual stimuli, motor cells which are correlated with saccadic eye movements, and visuo-motor cells which show both (Brooks & List). There are visual FEF cells with foveal receptive field, and cells with receptive fields outside the fovea (Segraves & Goldberg, 1987). Electrical stimulation of the monkey FEF can elicit saccades. For example, Golberg, Bushnell and Bruce (1986) electrically stimulated different FEF cells. Most of the stimulation sites elicited contralateral saccades. Interestingly, when the monkey was actively fixating, saccades were more difficult to elicit, i.e. a higher electrical current was required. Burman and Bruce (1997) investigated the effect of electrical stimulation in the vicinity of visual cells with foveal receptive fields which lie deeper in the monkey's arcuate sulcus. They discovered that stimulation in that area resulted in a prolonged saccadic latency; although latencies were affected bi-laterally, the effect of stimulation was the biggest for contra-lateral directed saccades. Moreover, the eyes remained fixated at the current locus, even during the presentation of loud noises that under normal circumstances elicit saccades. The authors also note that conflicting motor plans, fixation

and saccades, could be locally suppressed within the FEF. Dias and Bruce (1994) recorded from neurons in the FEF. The SC receives also input from other oculomotor areas like the supplementary eye fields, parietal eye fields, dorso-lateral prefrontal cortex, suggesting that a distributed oculomotor network is involved in controlling the SC.

Rozin (1976) argued that higher levels of the CNS are becoming more important with increasing complexity and development of the brain. This can be observed in the development of humans, in which the reflexive eye movements come under voluntary control with the maturation of the frontal-basal ganglia-collicular circuitry. The fixation reflex, which inhibits the VGR, is extremely powerful in babies. After around 2 months the SNr starts to exert inhibitory control over the SC, leading to 'sticky fixations', i.e. infants can hardly move their eyes (Hood, Atkinson, Braddick, & Wattam-Bell, 1992; Johnson, 1990). McConnell and Bryson (2005) tested 25 infants at 2, 4, and 6 months of age. They presented a bright visual target in the centre, and started the trial when the subjects were looking at the bright target. A peripheral target was presented either after a GAP of 1000 ms, or while the central target was still. The saccadic latencies towards the peripheral target were measured. The results demonstrated that the latencies for overlap trials showed a massive decline between 2 and 4 months. Further more it has been suggested that the voluntary control over the VGR and fixation reflex improves up to 20 years of age (Fischer, Biscaldi, & Gezeck, 1997). In other words, the maturation of fronto-nigral-collicular pathways results in voluntary control over this reflex. Damage to these circuits may lead to a reduction, or even loss of this voluntary control. This will be studied in more detail in chapter 3.

Voluntary Control over the oculomotor reflexes

In summary, although the FOE reflects a reflexive response of fixation neurons, the circuitry for this reflex appears to involve other cortical and subcortical structures. In other words, cognitive control can influence this reflexive circuitry. This has often been investigated by employing the anti-saccade paradigm (Hallett, 1978). In this paradigm, subjects are

instructed to make a saccade in the opposite direction of a suddenly appearing visual target, i.e. the mirror location. Correct performance depends on the combined ability to suppress an automatic saccade towards the sudden visual onset, and ability to initiate a voluntary saccade in the mirror direction (Hallett, 1978). How might participants accomplish this and how does this influence the reflexive processes underlying the FOE?

It has been suggested that subjects adopt a different strategic set during anti-saccades than during pro-saccades in order to suppress the VGR. Subjects prepare with the purpose of inhibiting the VGR by actively fixating. Since active fixation is correlated with a bilateral increase of FN activity, and resulting in a suppression of SN, this active fixation results in an increased internal control over the fixation reflex, i.e. the reflex is less influenced by an external fixation point. This should lead to a reduced size of the FOE. Several studies have found smaller or non-significant effects of fixation point offsets in anti-saccades (Abrams, Oonk, & Pratt, 1998; Craig, Stelmach, & Tam, 1999; Machado & Rafal, 2000a; Reuter-Lorenz, Hughes, & Fendrich, 1991). This supports the hypothesis that cognitive control can influence the reflexive processes underlying the FOE.

Other experiments have provided converging evidence that the FOE can be used as a model task to study how cognitive control makes use of oculomotor reflexes. Machado and Rafal (2000b) asked whether advanced motor preparation could influence the size of the FOE. In their experiment, subjects received either informative, or uninformative cues about the direction of an upcoming target, i.e. they could prepare for an upcoming eye movement if they received an informative cue. The results showed that saccadic latencies were faster for informatively cued saccades. Crucially, the size of the FOE was also reduced for these informatively cued trials. The authors argued that increasing oculomotor readiness is associated with reduced influence of the fixation stimulus on the fixation reflex.

In previous experiments manipulating oculomotor set, it has been shown that normal adults can modulate the magnitude of the FOE (Machado & Rafal, 2000c, 2000d; Rafal, Machado, Ro, & Ingle, 2000). For example, the FOE decreased when oculomotor readiness was increased by reducing the proportion of catch trials (i.e. in which no target was presented and no eye movement was made) (Machado & Rafal, 2000b). In another study the subjects received either informative cues so they could prepare for an upcoming endogenous saccade, or uninformative cues (Rafal, Machado, Ro, & Ingle, 2000). Preparation of a voluntary saccade, prior to the appearance of a peripheral saccade target, not only reduced saccade latencies, but also reduced the FOE.

Everling, Dorris, and Munoz (1998) have examined the neurophysiological correlates of this cognitive control over the SC. They discovered that while the activity level of FN neurons increased, the SN activity was inhibited during anti-saccades. Additionally, the activity level of saccade neurons was also reduced in the FEF. This will be discussed in more detail in chapter 2 and 3.

Automaticity and voluntary control

In Chapter 2, I have investigated whether automaticity has an influence on oculomotor control. I also investigated whether automaticity and control interact, or are capable of independently influencing oculomotor reflexes. Using an aging foreperiod paradigm, and the FOE as a marker for cortical control of reflexive fixation, I showed that, for both prosaccades and antisaccades, increasing preparation across the foreperiod reduced both saccade latency and the FOE. Consistent with Los's trace conditioning account (Los, 1996; Los & Heslenfeld, 2005; Los, Knol, & Boers, 2001), these effects reflected greater preparation for trials when the current short foreperiod was preceded by a trial with a short foreperiod. The FOE was also smaller for antisaccades than for prosaccades demonstrating strategic modulation. However, the effects of trace conditioning were comparable in the two tasks, demonstrating that strategic and unconscious priming effects both independently modulate the control of ocular fixation.

The role of the Basal Ganglia in the voluntary control of oculomotor reflexes

In Chapter 3 the role of the basal ganglia in controlling oculomotor reflexes was studied. We studied patients with Parkinson's disease (PD). PD leads to a dysfunctional basal ganglia. PD can therefore be used as a model to study the role of the basal ganglia in the voluntarily control of oculomotor reflexes. The size of the FOE was measured during a block of pro- and a block of anti-saccades. As expected, the healthy controls showed a reduced FOE during the anti-saccades, which is the result of an increase in voluntary control over oculomotor reflexes. However, there was no difference in size of the FOE between the pro- and anti-saccade tasks for PD patients. This indicates that they are impaired in controlling their oculomotor reflexes.

Inhibition of Return

As previously discussed in the context of the VGR, a salient stimulus in the periphery automatically elicits an orienting response in most animals. However, although there is a great inclination for fixating a salient stimulus, a stimulus can be attended without looking at it. Or, in other words, attention , which is the process that selects information for further processing while ignoring other pieces of information, can independently 'move' from the fixated location. This is often referred to as covert orienting. Once could argue that the ability to attend to the most salient stimuli is an evolutionary advantage. However, once a stimulus has been attended and analyzed in more detail, it is important that other stimuli are also investigated, i.e. attention should be stopped from returning to previously inspected locations. For example, while foraging for food, an animal should not keep looking for food in the same place once the animal discovered that there is nothing to eat. A reflexive behaviour that might help guide foraging and visual search is inhibition of return (IOR).

Posner and Cohen (1984) were the first to study this exogenous orienting behaviour. Subjects were required to press a button as fast as possible once they detected a target which appeared either on the right

or left of fixation. The target appeared in one of two peripheral marker boxes, or place holders, that were presented throughout the experiment. The target was always preceded by a cue, which was a brief brightening of one of the two boxes. Although the cue did not give the subjects any information about the location of the upcoming target, it still affected subsequent target reaction times. It was found that both the location of the cue, and the time between the cue and target has an effect. At first, there is a advantage for targets at the cued location, which is reflected in faster reaction times for cued relatively to uncued targets. This benefit has been attributed to an automatic orienting towards the target. However, for longer cue target intervals, typically longer than 200-300 ms, the pattern reverses; i.e. reaction times for cued targets are longer than for uncued targets. This detriment for cued locations is referred to as IOR, and is thought to reflect a bias against returning to a previously attended location (Klein, 1988)

It has been hypothesized that this inhibitory tag helps efficient visual search. Klein (1988) investigated whether subjects were less likely to return to a previously attended location. Subjects were required complete a serial and parallel search task. The search tasks were immediately followed by a luminance detection task. There is converging evidence that subject can complete the parallel search 'pre-attentively', since the target pops out, i.e. there is no need to attend to each location. However, serial search requires the allocation of attention to each item in the display(Klein, 1988). In order to test whether subjects were biased against return to a previously attended location, the luminance signal was presented on a location which was occupied by a distracter of the previous visual search task, or in an empty part of the previously presented search array. On average, subjects were around 50 ms slower to detect the luminance signal when it was presented on a location that had been occupied by a probe of the visual search array. However, this was only true during the serial visual search task. Interestingly, there was significant difference during the pre-attentive parallel search task. These results indicate that this reflexive IOR can help efficient visual search. Recent evidence has replicated and

extended the view that IOR is a foraging facilitator in visual search (Klein & MacInnes, 1999). They investigated more natural search behaviour by presenting subjects with complex images from the 'Where is Waldo?' books. Subjects were instructed to find Waldo. After a random period of time, a small round black circle would suddenly appear. The subjects were instructed to fixate this circle as fast as possible. The location of the circle was either on the previously fixated location, or another location. Subjects were slower to detect the circle at a previously fixated location. Interestingly, the authors also studied the visual search behaviour prior to the circle presentation. It was found that subjects were the least likely to make a saccade in the direction of the previously fixated location. These findings provide further evidence that IOR guides efficient visual search.

The role of the SC in IOR

There is ample evidence that the SC is involved in the generation of IOR. Rafal, Calabresi, Brennan, and Sciolto (1989) made use of a then recent discovery that there is a nasal-temporal asymmetry in the projections within the retino-tectal pathway, but not in the retino-cortical pathway (Perry & Cowey, 1984; Sylvester, Josephs, Driver, & Rees, 2007). As a result, each colliculus receives relatively more input from the temporal than the nasal hemifield. Subjects were tested under monocular conditions on a standard IOR paradigm. Rafal, Calabresi, Brennan, and Sciolto (1989) showed that the IOR was larger in the temporal hemifield compared to the nasal hemifield, indicating that the retino-tectal pathway is involved.

Further supported for collicular involvement in IOR comes from developmental studies. The retino-tectal pathway is more evolved in infants, but the retino-cortical pathway is not yet fully developed. It has therefore been argued that visual behaviour in newborns is predominately subcortically mediated. It has been demonstrated that infants have IOR as well. For example, Valenza, Simion, and Umilta (1994) demonstrated that newborns (mean age 72 hours) demonstrate IOR. They measured the eye movements and found that they occurred

quicker and more frequently towards the uncued targets. In a subsequent study, Simion et al. (1995) demonstrated that in newborns the IOR is also greater in the temporal hemifield than in the nasal hemifield.

Danziger, Fendrich and Rafal (1997) asked whether patients with a lesion to the primary visual cortex still show IOR. Patients with a lesion to the primary visual cortex are clinically blind in the contra-lesional field. However, it has been reported that there is some visual processing left in this blind field. This effect is referred to as blindsight, since subject are not aware of visual stimuli in their damaged visual field (Weiskrantz, 2002). It has been hypothesized that this residual visual processing is mediated by the retino-tectal pathway, i.e. the SC. Danziger, Fendrich, and Rafal (1997) presented two vertically aligned marker boxes in the patient's blind field. A cue was presented in either the lower or upper box. After the cue, the patient made an eye movement towards a fixation point in the centre of the two boxes. Next, a target was presented in the cued or uncued box. The patient still showed IOR. This provides further evidence that the collicular pathway is important for the generation of IOR. They also tested another hemianopic patient. This patient did not show IOR in his blind field. However, this patient had an additional lesion in the thalamus. It is therefore likely, that an inhibitory tag was generated in this patient, but not remapped due to the thalamic lesion (Sommer & Wurtz, 2006). This will be discussed in more detail later on.

Direct evidence for the involvement of the SC is provided by a single case study of a patient with a unilateral SC lesion. Sapir, Soroker, Berger, and Henik (1999) tested a 46 year old patient who suffered a hemorrhage in the right SC. In order to assess the effects of the lesion in more detail, the stimuli were presented monocularly. It was found that IOR was only present in the hemifield that projected to the left SC. As expected, the IOR was bigger in the temporal hemifield of the right than in the nasal hemifield of the left eye. More importantly, there was no IOR in the temporal hemifield of the left eye, and the nasal

hemifield of the right, both of which project to the lesioned SC, providing direct evidence that the colliculus is involved in IOR.

A recent study by Sumner, Nachev, Vora, Husain, and Kennard (2004), using S-cone stimuli that are invisible to the retino-tectal pathway, revealed that IOR was still present for manual responses, but not for saccadic responses. This indicates mechanisms underlying IOR might be more complex than outlined above.

Cortical Involvement in IOR

For IOR to be useful in guiding efficient visual search, it has to be stable across eye movements, and exists for a longer period of time. Samuel and Kat (2003) provided evidence that IOR is relatively constant for at least 3 seconds. Maylor and Hockey (1985) demonstrated that IOR is coded in an environmental reference frame, rather than retinotopic frame of reference. They required subjects to make a saccade between the presentation of the cue and target. They demonstrated that IOR was present at the previously cued location, i.e. it was spatially updated. In addition, Tipper, Driver, and Weaver (1991) showed that IOR can be associated with an object, i.e. object based. Moreover, they demonstrated that as an object moves through space, the inhibitory tag associated with the object can move with the object. Based on these findings, it has been hypothesized that IOR is generated through the retinotectal pathway, but is further controlled by collicular-cortical interactions.

There is converging evidence for the involvement of cortical structures. First of all, several fMRI studies have reported the involvement of different cortical areas in a standard IOR task (Mayer, Seidenberg, Dorflinger, & Rao, 2004; Peelen, Heslenfeld, & Theeuwes, 2004). More relevant for the research reported in this thesis, two studies in neuropsychological patients provided supportive evidence for the view that cortical structures make use of this reflexive inhibitory tag. Tipper et al (1997) tested two split-brain patients. Three black boxes were presented on the screen, one in the centre, one on the the right, and one on the left (6.6 degree). Next one of the two boxes was cued, after a

subsequent central cue, the peripheral boxes started to move. The boxes moved either within each hemi-field, or they crossed the midline, i.e. between hemi-fields. Once the boxes stopped moving, the target was presented in the cued or uncued box. Healthy controls showed an IOR in both conditions. However, both patients showed an IOR only for within hemifield movements. Interestingly, they showed a facilitation for between hemifield conditions. These findings provide evidence that object-based IOR is mediated by cortical structures. Another study by Sapir, Hayes, Henik, Danziger, and Rafal (2004) provides evidence that a parietal cortex lesion impairs the updating of IOR in environmental locations. Their experiment has been the foundation of chapter 3 and 4. In these chapters, I have studied how dual pulse TMS over the parietal cortex affects the updating of this inhibitory tags. The Sapir et al. study, and the spatial updating literature will be discussed in more detail in chapter 3 and 4. Therefore, I will only give a short summary below.

Updating of saliency maps

The visual image on the retina is shifted after each eye movement. However, visual world is perceived as being stable. It has been proposed that the brain employs a mechanism which incorporates the information about an upcoming eye movement to in order to keep a stable percept of the world. There is now sufficient evidence that suggests that the SC do not only sent out a motor command to the brainstem saccade generating circuits, a signal which carries information about the upcoming eye movement is sent upstream travelling via the thalamus to the cortex at the same time (Sommer & Wurtz, 2006). This signal is referred to as corollary discharge. Duhamel, Colby, and Goldberg (1992) discovered that neurons in the parietal cortex use this corollary discharge to update their receptive fields. In a subsequent study, it was demonstrated that patients with lesions to the frontal and parietal cortex are impaired in updating saccade motor vectors (Duhamel, Goldberg, Fitzgibbon, Sirigu, & Grafman, 1992). The patients were tested on a double step saccade. In this task, subjects are required to make an eye movement towards two briefly flashed targets

locations, which disappear before the subjects starts. Therefore, the first saccade can be based on the remembered retinotopic location, whereas the location of the second saccade has to be remapped in environmental locations. Patients were impaired when the first saccade was made towards the contralesional hemifield, and the second towards the ipsilesional hemifield, implying that each hemisphere generates a signal used for remapping towards the contralesional hemifield.

Sapir et al. (2004) used IOR as a way to investigate whether the parietal cortex is involved in updating visual saliency maps. The patients were tested on an adjusted version of the Maylor and Hockey paradigm (1985) in which an eye movement between the cue and target separates the retinal and environmental location of the tag. They discovered that a lesion to the parietal cortex causes an impairment in the ability to remap this inhibitory tag. Interestingly, the deficit was independent of the direction of the eye movement between the cue and target presentation, i.e. the effect was bi-lateral. The authors explained their findings by proposing that the parietal cortex is not only involved in the remapping of saliency maps, but that it might also be involved in encoding this remapped inhibitory tag. More precisely, a saccade towards the contralesional field will not be accompanied by a remapping of the saliency maps, since the lesioned parietal cortex can no longer do this task. An ipsilesional saccade would probably be remapped. However, the remapped signal would be send to the damaged hemisphere, and as a result it will be lost.

The patients studied by Sapir et al. (2004) all had chronic lesions. It is not clear whether the effects reported in those patients reflect the normal function of parietal cortex, or are the consequence of brain reorganization. Moreover, Sapir et al studied only two patients with left parietal lesions and three with right parietal lesions, and could therefore not draw any conclusions about possible hemispheric asymmetries for maintaining salience maps.

In summary, the IOR, which is likely to be generated by the SC, is transferred to the parietal cortex to help guided efficient visual search. In chapter 4, I have used an adapted version of the Sapir et al study in

which subjects made horizontal saccades between the cue and target. I applied dual pulse TMS to transiently disrupt the function of parietal cortex, and to compare the effects of right and left parietal TMS in order to test for a hemispheric asymmetry. In chapter 5, I studied the remapping of saliency maps for laterally presented cues and targets after vertical saccades.

Chapter 2: Control of subcortical oculomotor reflexes: independent effects of strategic and automatic preparation[1]

Abstract

The reduction in saccade latency when the fixation point is removed (fixation offset effect – FOE) reflects the degree to which fixation neurons are influenced by a stimulus at fixation. Strategic manipulations of oculomotor readiness that bring these neurons under endogenous control reduce the magnitude of the FOE. Using an aging foreperiod paradigm, and the FOE as a marker for cortical control of reflexive fixation, we showed that, for both prosaccades and antisaccades, increasing preparation across the foreperiod reduced both saccade latency and the FOE. Consistent with Los's trace conditioning account, these effects reflected greater preparation for trials when the current short foreperiod was preceded by a trial with a short foreperiod. The FOE was also smaller for antisaccades than for prosaccades demonstrating strategic modulation. However, the effects of trace conditioning were comparable in the two tasks, demonstrating that strategic and unconscious priming effects both independently modulate the control of ocular fixation.

[1] A version of this chapter has been published in Experimental Brain Research: Van Koningsbruggen, M.G. & Rafal, R.D. (2009). Control of oculomotor reflexes: independent effects of strategic and automatic preparation. *Experimental Brain Research, 192(4), 761-8.*

Easton (1972) argued that the neural circuits that subserve reflexes are the building blocks for more complex behaviour; and that the nervous system routinely goes about its business through an orchestration of those circuits by cortical processes that activate or inhibit them (Easton, 1972). The evolution of more complex behaviour required cortico-subcortical integration to regulate reflexes in the service of goal directed action (Ingle, 1973; Rozin, 1976). Eye movements provide an attractive model to study how preparatory states influence reflexive behaviour. The current investigation employs the Fixation Offset Effect (FOE) in order to investigate the effects of strategic control and more automatic, non-specific preparation on oculomotor reflexes.

The fixation offset effect

In the rostral pole of each superior colliculus (SC) are cells that are active during fixation, even in the dark, and whose activity is further increased by a visual signal at fixation (Munoz & Wurtz, 1992, 1993a). These fixation neurons help anchor the eyes at fixation. Caudal to the fixation neurons, and inhibited (either directly or indirectly) by them, are neurons (movement cells) whose activity moves the eyes to a new position (Munoz & Istvan, 1998). Eye movements toward a peripheral target, then, are controlled by an opponent process: there is mutual inhibition between the visual grasp reflex (VGR), activated by abrupt signals in the visual periphery and mediated by movement neurons, and the fixation reflex, activated by visual signals at fixation and mediated by fixation neurons. Together, the activity of these two types of cells determines when and where the eyes will move (Connolly, Goodale, Menon, & Munoz, 2002; Findlay & Walker, 1999).

The offset of a fixated stimulus prior to, or simultaneous with, the onset of a peripheral target disinhibits the VGR and reduces the latency to initiate an eye movement to the target (Saslow, 1967). This benefit of fixation offset on

saccadic latencies has been termed the fixation offset effect (FOE) (Klein & Kingstone, 1993), and has been shown to reflect neural activity within the colliculus. When a fixated stimulus offsets, the activity of fixation neurons decreases, and inhibition of movement cells is reduced resulting in shorter saccade latency (Dorris & Munoz, 1995; Munoz & Wurtz, 1992). Conversely, electrical stimulation of fixation neurons just prior to or during an eye movement can delay or arrest the eye movement (Munoz & Wurtz, 1993a). When fixation cell activity decreases in response to fixation offset, movement cells are disinhibited and more quickly reach threshold for saccade initiation thereby reducing saccade latency. The difference in saccade latency between fixation offset and fixation overlap conditions (the FOE) is a measure of the degree to which fixation neurons are under external control by the fixation stimulus.

Strategic Control of Ocular Fixation during the Visual Grasp Reflex

The SC receives visual input both directly from the retina and from visual cortex, as well as input from oculomotor cortex of frontal and parietal lobes. Competition between the competing demands of voluntary and reflexive eye movement signals are resolved in the SC by their interacting influences on fixation and movement neurons. The emerging evidence indicates that the opponent interactions between collicular fixation and movement neurons are not sequestered in a simple intra-collicular circuit. There seems to be no direct inhibitory connections between the rostral pole fixation neurons and the movement neurons of the SC (Isa, 2002; Lee & Hall, 2006). In addition, direct retinotectal input to fixation neurons in the rostral pole of the colliculus is not necessary for an FOE to occur (Sumner, Tsai, Yu, & Nachev, 2006), suggesting that visual cortex is part of the circuitry of the FOE. Lesions of the

human pulvinar abolish the FOE (Rafal, McGrath, Machado, & Hindle, 2004), indicating that it, too, is part of the circuitry.

Thus, although the FOE reflects a reflexive response of fixation neurons, the circuitry for this reflex appears to involve other cortical and subcortical structures; and this reflex circuit can be modulated by cognitive control. Manipulations of strategic set can bring the fixation neurons under endogenous control, reducing the influence of the external stimulus at fixation and, thereby, the size of the FOE. The logic here is straightforward. If endogenous control is exercised over fixation neurons before a target appears – either by tonically increasing their activity (for example to prevent errors in an antisaccade task), or by reducing their activity because of an increased readiness to make an eye movement – then the fixation point will have less effect on these neurons, and the FOE will be reduced. It should be noted that any endogenous control of fixation neurons, regardless of whether the exercise of this control increases or decreases fixation neuron activity, may render them less responsive to the exogenous influence of a fixation stimulus and reduce the FOE. The size of the FOE then is not an index of fixation cell activity but, rather, an index of the degree to which they are susceptible to reflexive activation.

In previous experiments manipulating oculomotor set, it has been shown that normal adults can modulate the magnitude of the FOE. For example, the FOE decreased when oculomotor readiness was increased by reducing the proportion of catch trials (i.e. in which no target was presented and no eye movement was made) (Machado & Rafal, 2000b). In another study the subjects received either informative cues so they could prepare for an upcoming endogenous saccade, or uninformative cues (Rafal, Machado, Tony, & Ingle, 2000). Preparation of a voluntary saccade, prior to the appearance of a peripheral saccade target, not only reduced saccade latencies, but also reduced the FOE. These observations suggest that increasing oculomotor

readiness is normally associated with reduced influence of the fixation stimulus on the fixation reflex.

The FOE is also smaller for anti-saccades than for pro-saccades (Machado & Rafal, 2000a; Reuter-Lorenz, Oonk, Barnes, & Hughes, 1995). To prevent errors in a block of anti-saccades, the VGR needs to be suppressed, which is achieved by adopting a strategic oculomotor set that increases fixation cell activity (Everling & Munoz, 2000; Munoz & Everling, 2004). This strategic manipulation causes longer saccade reaction times (RT), since more movement cell activity is necessary to reach the saccade threshold. However, since the fixation cells are endogenously activated by the strategic set required in the anti-saccade task, they are less influenced by the *removal* of an external visual fixation point. This results in a smaller difference in RT between overlap and offset trial, i.e. a reduced FOE.

Priming effects in the aging foreperiod paradigm

The research summarized above demonstrates that strategic preparation can regulate and modulate the circuitry of oculomotor reflexes. However, it is unknown whether more automatic and unconscious cognitive processes, which occur without intention, can influence these reflexes. Here our focus is on non-specific response readiness over time. The effect of non-specific preparation on RT has been studied by varying the foreperiod, which is the time between the onset of a neutral warning stimulus and the onset of the target stimulus, on a trial by trial basis. In experiments with a variable foreperiod duration, a longer foreperiod is associated with a reduction in RT. This is referred to as the variable foreperiod effect, and it is thought to be the result of a higher non-specific preparation for the longer foreperiod (Niemi & Näätänen, 1981). In addition to the variable foreperiod effect, there are also

sequential effects; the reaction times on a trial are influenced by the length of the foreperiod of the preceding trial. Sequential effects are asymmetric, i.e. the effect of the preceding trial depends on the length of the foreperiod of the current trial. The RT for long foreperiods are generally not affected by the foreperiod of the previous trial, but the RT for short foreperiods are shorter if the foreperiod of the previous trial is short, compared to when the previous foreperiod is long.

It has recently been proposed that preparatory effects across the foreperiod result from priming in which the length of the foreperiod of the *previous* trial influences the RT of the next trial (Los, 1996; Los & Heslenfeld, 2005; Los, Knol, & Boers, 2001). According to their trace-conditioning model, the RT associated with a foreperiod depends on the conditioning strength that is associated with it. The way in which the foreperiod of the previous trial influences the conditioning strength for specific foreperiods on the current trial follows a set of rules. Firstly, the conditioning strength corresponding to a certain foreperiod is reinforced if the stimulus is presented at that foreperiod. Secondly, it is suppressed if the stimulus is presented at a later foreperiod. Thirdly, there is no change if the stimulus is presented at a shorter foreperiod. According to these rules, priming by the previous trials is only present for events with short foreperiods, because on the previous trial these conditioning strength are either reinforced (foreperiod previous trial is short) or suppressed (foreperiod previous trial is long). Importantly, because the conditioning strength of the long foreperiod is never suppressed, i.e. it is not bypassed in time, it approaches some asymptotic value in the course of a few trials, resulting in no priming effect of the foreperiod of the previous trial for the long foreperiod. Los and Heslenfeld (2005) provided empirical evidence for this model in an experiment in which they presented the stimulus after either a short (400 ms) or a long foreperiod (1200 ms).. In addition, they demonstrated

that subjects had no intentional control over this process. Other, dual-process theories, have been proposed to explain the a symmetric sequential effects (Niemi & Näätänen, 1981; Vallesi, Shallice, & Walsh, 2007).

In two experiments, the present study investigated the effect of non-specific preparation on the cognitive control of oculomotor reflexes by measuring the size of the FOE, while manipulating the amount of non-specific preparation by systematically varying sequences of the foreperiod of the previous trial and current trial. In addition, we manipulated the strategic set using a pro-saccade task in experiment 1 and an anti-saccade task in experiment 2 to determine if non-specific preparation and strategic preparation are independent processes.

Experiment 1

Methods

Participants

Fifteen undergraduate psychology students at the University of Wales, Bangor participated for course credits.

Stimuli and Procedure

Horizontal eye position was recorded with an Eye Trac 210 scleral reflectance device (ASL) at a sampling rate of 1000 Hz. A 50 deg/s velocity criterion was used to compute the latency of saccade onset. Presentation software (Neurobehavioral Systems) was used for stimulus presentation, and recording of saccade RT.

Throughout the experiment, two white marker boxes (1.5°) on a black background were presented at 9° to the left and right of the centre of the screen. After an inter-trial interval of 2500 ms, each trial began with the onset of a Fixation point, a 0.4° white circle, in the centre of the screen. After either 500, or 1500 ms, the left (50%), or right (50%) marker box turned white. Participants were instructed to make an eye movement to the centre of this box as fast as possible. On half of the trials, the fixation point remained visible (overlap condition), while on the other half it disappeared simultaneously with the onset of the visual target (offset condition). The target remained on the screen until subjects made a response. A total of 384 trials were presented in 6 blocks. An algorithm was used to ensure that each previous-current trial condition combination had an equal probability within each block of trials. The algorithm randomized the sequence, and checked whether all combinations had an equal probability. The randomized sequence was only used when all the combinations had an equal probability, else the procedure was repeated.

Since the onset of the fixation point signalled the start of the trial, and it is crucial that subjects are aware of the start of the trial in a foreperiod paradigm, subjects were instructed to look at the centre of the screen at the start of the trial, and keep their eyes at the centre throughout the whole foreperiod. This was monitored online, and if the subject failed to do this, the trial was ended and an error sound was presented for 100 ms. An error sound was also presented if subjects blinked during the foreperiod, moved their eyes in the wrong direction, or responded too fast (<50 ms), or too slow (>800 ms).

Results and Discussion

Errors

An analysis of variance (ANOVA) with the foreperiod of the current trial ($Foreperiod_{(current)}$), the foreperiod of the previous trial ($Foreperiod_{(previous)}$), and Fixation point condition as factors, showed a significant main effect of $Foreperiod_{(current)}$, $F(1, 14) = 6.81$, $p < 0.05$, $\square_p^2 = 0.33$, indicating that subjects made more errors if the current trial had a long foreperiod (5.3%) compared to if the current trial had a short foreperiod (3.6%). In addition, there was a significant main effect of $Foreperiod_{(previous)}$, $F(1,14) = 4.96$, $p < 0.05$, $\square_p^2 = 0.26$, reflecting that less errors were made in trials that were preceded by a short foreperiod (4.0%) than in trials that were preceded by a long foreperiod (5%). No other effects were found to be significant (see Table 2.1).

Table 2.1. Mean error rates (SD in parentheses) for each condition in Experiment 1.

FP Current Trial	Short		Long	
FP Previous Trial	Short	Long	Short	Long
Offset	2.8% (1.7)	4.1% (3.6)	4.6% (4.1)	5.9% (5.1)
Overlap	3.4% (3.9)	4.1% (3.4)	4.6% (4.9)	5.9% (4.6)

Saccadic RT

Trials on which an error was made were excluded from the Saccadic RT analyses. Since preliminary analyses showed no difference in saccade RT for left and right eye movements ($P>0.1$) data for left and right eye movements were pooled. Mean saccade latency for correct responses were calculated in each condition for each participant and subjected to a repeated measures ANOVA with the foreperiod of the current trial ($Foreperiod_{(current)}$), the foreperiod of the previous trial ($Foreperiod_{(previous)}$), and Fixation point condition (offset and overlap) as factors. Figure 1 (top panel) depicts the mean saccadic RT of Experiment 1. Saccade RT was shorter (FOE) for trials on which the fixation point offset (283 ms) than when it overlapped (331 ms) the target [$F(1,14) = 35.88$, $p<0.01$, $\square_p^2 = 0.72$]. Saccade RT was shorter for trials with a long (295 ms) than for those with a short foreperiod (319 ms), $F(1, 14) = 20.11$, $p < 0.01$, $\square_p^2 = 0.59$, demonstrating that the variable foreperiod effect (Sollers & Hackley, 1997) is manifest for saccadic responses. As expected, the effect of the preceding trial was asymmetrical and, as shown in Figure 2.1 (top panel), was only present for trials on which the current foreperiod was short (Los,

1996; Los, Knol, & Boers, 2001; Los & van den Heuvel, 2001; Niemi & Näätänen, 1981). This was confirmed by a highly significant interaction between $Foreperiod_{(current)}$ * $Foreperiod_{(previous)}$, $F(1, 14) = 55.02$, $p < 0.01$, $\square_p^2 = 0.78$. Pair wise comparisons (Bonferroni corrected) revealed that saccade RT was longer ($p<0.001$) if a short foreperiod was preceded by a long foreperiod on the previous trial (334 ms) compared to all other $Foreperiod_{(previous)}$ * $Foreperiod_{(current)}$ conditions (short-short 305 ms; long-long 296 ms; short-long 293 ms). None of the other conditions differed significantly from each other.

The key finding of the experiment was that the FOE was modulated by the preparatory state over the foreperiod, and that this modulation also reflected the asymmetric influence of priming on preparatory state by the preceding trial. As shown in Figure 2.1 (top panel), the FOE was larger on trials with a short foreperiod when preceded by a trial with a long foreperiod: $Foreperiod_{(current)}$ * $Foreperiod_{(previous)}$ * Fixation Point Condition, ($F [1, 14] = 5.04$, $p = 0.04$, $\square_p^2 = 0.27$). Six pair-wise comparisons of the magnitude of the FOE for each $Foreperiod_{(current)}$ * $Foreperiod_{(previous)}$ condition (Bonferroni corrected) were conducted. The FOE was significantly smaller in the $Foreperiod_{(current=short)}$ - $Foreperiod_{(previous=short)}$ condition (40 ms) than the $Foreperiod_{(current=short)}$ - $Foreperiod_{(previous=long)}$ condition (56 ms), $t(14) = 3.94$, $p < 0.01$. None of the other pair-wise comparisons were significant.

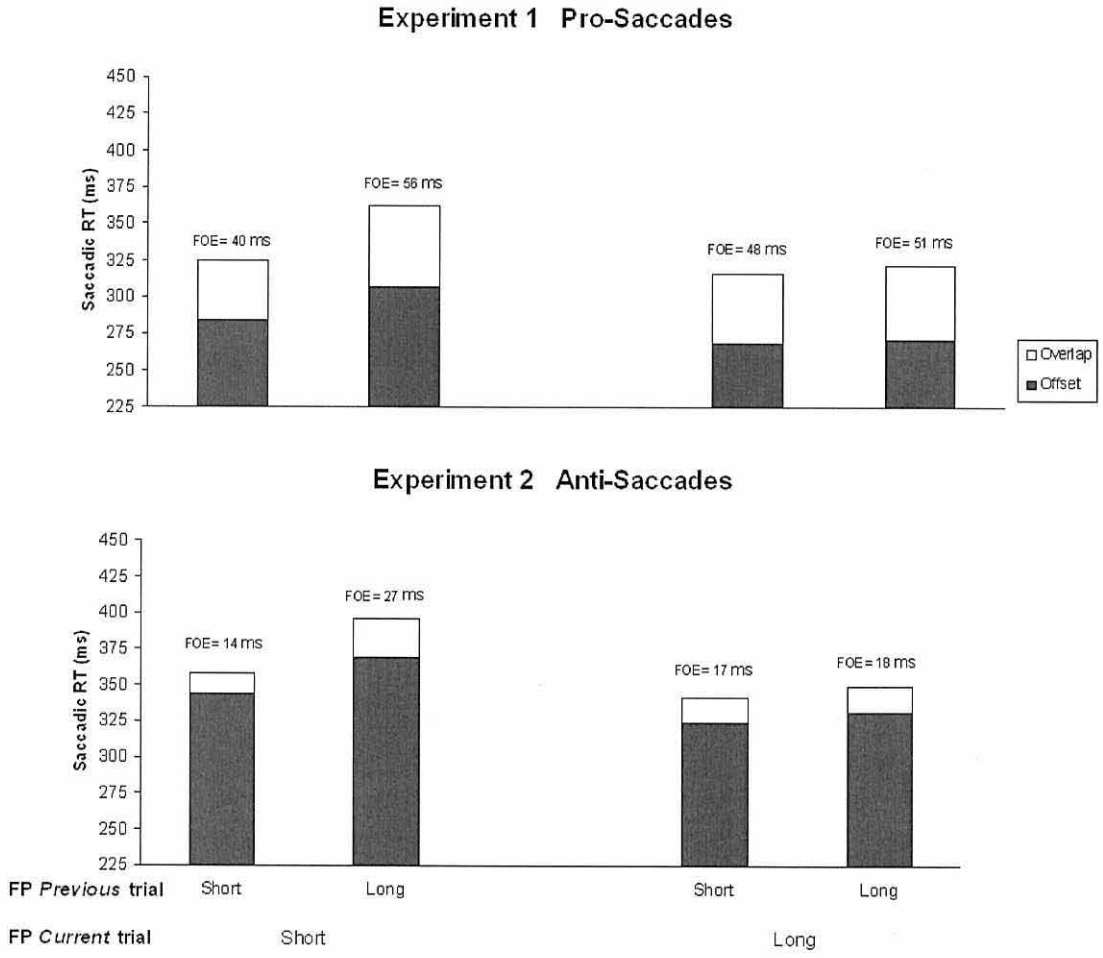

Figure 2.1 *Mean saccade reaction times and size of the Fixation Offset Effect for pro saccades (top panel), and anti-saccades (bottom panel).*

The results revealed that when the conditioning strength of the current trial was reinforced on the previous trial ($Foreperiod_{(current=short)}$ - $Foreperiod_{(previous=short)}$), the Saccadic RT were faster compared to when the condition strength was not reinforced ($Foreperiod_{(current=short)}$ - $Foreperiod_{(previous =long)}$); critically the FOE was also reduced, indicating that non-specific preparation influences the responsiveness of fixation neurons to visual signals. To examine whether strategic modulation and non-specific preparation engage independent mechanisms, an anti-saccade paradigm was employed in Experiment 2 to induce an inhibitory strategic set.

Experiment 2

In Experiment 2, the display and stimuli were identical to those used in Experiment 1, except that participants were required to perform an antisaccade task in which they had to inhibit the prepotent response of making a saccade to the target and, instead, to execute a voluntary saccade to the marker box in the visual field opposite the target. Previous research in humans has shown that the FOE is smaller in the antisaccade than the prosaccade task (Machado & Rafal, 2004), and that in non-human primates, an instruction to execute an antisaccade is associated with an increase in neural activity in fixation neurons in the rostral pole of the SC (Middleton & Strick, 2000b). Thus, the strategic oculomotor set required to inhibit prosaccades results in a top-down facilitation of fixation neurons activity and reduces the influence of an external stimulus at the fovea on them. This experiment examined whether non-specific preparatory effects also exert an effect on fixation cell responsiveness to visual stimuli that is independent from those engendered by a strategic oculomotor set. Twenty one undergraduate psychology students at the University of Wales, Bangor participated for course credit.

Results and Discussion

Errors

Trials where subjects did not look at the centre of the screen at the start, blinked during the foreperiod, or moved their eyes before target onset, were scored as fixation errors. Only a low number of fixation errors were made (3.30%), and were therefore not further analyzed. If a reflexive eye movement was not successfully suppressed and subjects made an eye movement towards the target, the trial was scored as a direction error. An ANOVA of the direction error data revealed only a significant main effect of Fixation Point, $F(1, 20) = 5.91$, $p = 0.03$, $\square_p^2 = 0.23$: Participants had more difficulties suppressing the VGR towards the visual target on trials with a fixation offset (4.2%) than when the fixation stimulus overlapped (3.0%) the target (see Table 2.2). All errors were excluded from the Saccadic RT analyses.

Table 2.2*. Mean direction error (SD in parentheses) for each condition in Experiment 2.*

FP Current Trial	Short		Long	
FP Previous Trial	Short	Long	Short	Long
Offset	4.0% (4.6)	3.9% (3.5)	4.6% (4.4)	4.4% (4.2)
Overlap	3.2% (3.1)	1.8% (1.9)	2.5% (2.7)	4.6% (4.5)

Saccadic RT

An initial analysis demonstrated that there was no significant difference between eye movements to the right and left (P>0.5), and saccade RTs for leftward and rightward saccades were therefore pooled. The resulting mean saccadic RTs are shown in the bottom panel of Figure 2.1. An ANOVA with $Foreperiod_{(current)}$, $Foreperiod_{(previous)}$, and Fixation Point Condition as within-subject factors, revealed the same main effects and interactions that were observed in Experiment 1. Saccade RT was shorter (i.e. FOE) on trials with a fixation point offset (342 ms), than on trials with a fixation point overlap (361 ms) [$F (1, 20) = 29.95$, $p < 0.001$, $\square_p^2 = 0.60$]. The effect of foreperiod ($Foreperiod_{(current)}$) was also reliable: saccade RT was longer for trials with a short foreperiod (367 ms), compared to trials with a long foreperiod (336 ms), $F (1, 20) = 102.91$, $p < 0.001$, $\square_p^2 = 0.84$. In addition, there was a significant main effect of $Foreperiod_{(previous)}$,. Saccade RT of trials which were preceded by a trial with a long foreperiod were longer (361 ms) than trials preceded by a short foreperiod (342 ms) [$F (1, 20) = 143.28$, $p < 0.001$, $\square_p^2 = 0.88$)]. There was an asymmetric effect of priming from the previous trial for short and long foreperiods: $Foreperiod_{(current)} * Foreperiod_{(previous)}$, $F (1, 20) = 50.88$, $p < 0.001$, $\square_p^2 = 0.72$. As was the case in for prosaccades (Experiment 1) the FOE was modulated by preparatory state over the foreperiod ($Foreperiod_{(previous)} *$ Fixation Point Condition, [$F (1, 20) = 7.45$, $p = 0.01$, $\square_p^2 = 0.27$]), and this modulation also reflected the asymmetric influence of priming by the preceding trial on preparatory state ($Foreperiod_{(current)} * Foreperiod_{(previous)} *$ Fixation Point Condition, [$F (1, 20) = 9.40$, $p < 0.01$, $\square_p^2 = 0.32$].) Six pair wise comparisons (adjusted for Bonferroni) compared the size of the FOE for each $Foreperiod_{(current)} * Foreperiod_{(previous)}$ combination. The FOE was significantly smaller for trials with a short foreperiod that were preceded by a short

foreperiod (14 ms), compared to trials with a short foreperiod that were preceded by a long foreperiod (27 ms). None of the other pair wise comparisons were significant.

An 2x2x2x2 mixed AVOVA compared performance for prosaccades (Experiment 1) and antisaccades (Experiment 2) with Task as between subject factor, and $Foreperiod_{(current)}$, $Foreperiod_{(previous)}$, and Fixation Point Condition as within-subject factors. Saccade RT was longer for antisaccades (351 ms) than for prosaccades (306 ms) ($F[1,34]=12.5$, $p =.001$, $\square_p = .26$). The FOE was smaller for the antisaccade (19ms) than for the prosaccade (49ms) task ($F(1, 34) =13.64$, $p < 0.01$, $\square_p^2 = 0.29$) demonstrating that the more inhibitory oculomotor strategic set required for antisaccades modulated the FOE. However, the influence of non-specific preparation on the size of the FOE was comparable (Task * $Foreperiod_{(current)}$, $Foreperiod_{(previous)}$, and Fixation Point Condition, $F[1, 34] <1$, $p > 0.9$, $\square_p^2 < 0.01$) in the two experiments (16 ms for prosaccades and 13 ms for antisaccades).

In addition to the ANOVA, six independent samples t-tests were conducted with task as a grouping factor, and priming effect as testing variable. The priming effects were calculated by computing the difference in size of the FOE for all the six different $Foreperiod_{(current)}$ * $Foreperiod_{(previous)}$ pairs. For example, an independent samples t-test examined whether the priming effect $FOE_{(current=short)(previous=short)}$ - $FOE_{(current=short)(previous=long)}$ was different for pro and anti saccades. None of these t-tests were significant (all $p>0.36$), confirming the results of the 2x2x2x2 mixed AVOVA that the influence of non-specific preparation on the fixation reflex were the same for pro and anti saccades.

Subjects were slower for anti saccades than prosaccades. As expected, the size of the FOE was smaller in Experiment 2 (anti-saccades) than in Experiment 1 (pro-saccades). The results revealed that asymmetrical sequential effects were also present for the more voluntary anti-saccades. More interestingly, the size of the FOE was influenced by the amount of non-specific preparation. Like Experiment 1, the size of the FOE was the smallest when the non-specific preparation was the highest, i.e. for $Foreperiod_{(current=short)}$ - $Foreperiod_{(previous=short)}$ combinations.

Additional statistical tests found no significant difference in the effect of non-specific preparation on the size of the FOE between Experiment 1 and 2. This suggests that strategic modulation and non-specific preparation reflect independent processes.

General Discussion:

For both prosaccades and for antisaccades we observed a non-specific preparatory effect of priming from the previous trial. Consistent with Los's (Los, 1996; Los & Heslenfeld, 2005; Los, Knol, & Boers, 2001) trace conditioning account of non-specific preparation on response latency during an aging foreperiod, this priming effect was asymmetric: it occurred only for the short foreperiod. In addition to extending Los's model to oculomotor preparation, we showed that the effect of non-specific preparation was comparable for reflexive prosaccades and for more voluntarily controlled antisaccades, indicating that this is a general mechanism that operates independently of the task that has to be performed. Sollers and Hackley (1997) have shown that the effect of an aging foreperiod on response latency is greater for voluntary (manual) than for reflexive (acoustic startle) blink responses. While prosaccades are not as reflexive as eye blinks – subjects are, after all, instructed to make a saccade to the target – they are clearly more reflexive than antisaccades. Our observations suggest that there is not a systematic relationship between the degree of automaticity of a response and the degree to which it is influenced by non-specific preparation. However, the foreperiod effects examined in the current investigation were quite different from those reported by Sollers and Hackley (1997): their study examined foreperiods of several seconds, whereas the foreperiod range in the current investigation was much earlier and narrower.

By manipulating offset of the fixation point, it was possible to study the effect of both strategic set and non-specific readiness on reflexive fixation. We confirmed previous studies showing that the strategic set required to suppress the VGR in the antisaccade task reduces the FOE. We also showed that the

non-specific effect of response readiness across an aging foreperiod induced by priming from the preceding trial modulated the size of the FOE. Specifically, the FOE was smallest when readiness to respond was the lowest. Critically, we also showed that the effect of trace conditioning in modulating the FOE was comparable for the two saccade tasks.

Thus, both non-specific and strategic preparatory cognitive processes are capable of independently influencing oculomotor reflexes prior to target onset. The observation that non-specific and strategic preparatory processes do not interact suggests that different neural processes may be involved.

The FEF have been shown to be important in the strategic control of eye movements in the context of the anti-saccades tasks, and has been shown to have a role in oculomotor fixation. A critical role for the control of strategic preparatory processes has been attributed to the FEF (Connolly, Goodale, Goltz, & Munoz, 2005; Connolly, Goodale, Menon, & Munoz, 2002). A study of chronic unilateral frontal eye fields (FEF) lesions in humans has implicated the FEF in strategic regulation of fixation neurons (Machado & Rafal, 2004). The patients showed a reduced saccadic RT when cued to prepare a voluntary saccade to a specified location compared to when they received non-informative cues. Although the RT was reduced, there was no reduction in the FOE. This suggests that they could prepare an eye movement prior to the target onset, but that they lost the ability to modulate the activity of fixation neurons.

The role of the FEF in controlling the SC is also supported by neurophysiological data. Everling and Munoz (1999) studied set-related activity for saccadic eye movements of neurons in the frontal eye field with direct projections to the SC (identified by antidromic stimulation of SC neurons with receptive fields of 10°, 20° or < 2°). Monkeys were trained on a task in which they were cued on each trial to execute either a prosaccade or an antisaccade.

The activity of set-related FEF neurons was higher for prosaccades than for antisaccades. Also, the lower prestimulus and stimulus-related activity on anti-saccade trials compared with pro-saccade trials correlated with RT, express saccade occurrence, and errors in the anti-saccade task. These observations further support the view that the FEF exert strategic control over eye movements by reducing the excitatory drive from saccade-related FEF neurons to the SC during anti-saccade trials.

FEF neurons with projections to collicular fixation neurons were not identified or studied in this experiment. It remains to be determined whether decreased activity of presaccadic burst neurons in an antisaccade task set is implemented by the FEF modulation through direct projections to fixation neurons, or whether fixation neuron responsiveness is controlled by indirect projections of the FEF through the basal ganglia (Everling, Dorris, Klein, & Munoz, 1999).

In conclusion, the current research has examined automaticity and control in the oculomotor system and has demonstrated that both strategic and automatic preparation independently regulate oculomotor reflexes.

Chapter 3: Parkinson's disease leads to impaired control of the oculomotor reflexes[2]

Abstract

The current study investigated the ability of patients with Parkinson's disease to voluntarily control oculomotor reflexes. We measured the size of the Fixation Offset Effect, which is the difference in saccade reaction time between Fixation Overlap and Offset trials, during a block of pro- and a block of anti-saccades. As expected, the healthy controls showed a reduced FOE during the anti-saccades, which reflects voluntary control over oculomotor reflexes. It is assumed that in order to suppress reflexive saccades in a block of anti-saccades, the preparatory set increase fixation related activity. Due to this increase in activity of fixation related process, the oculomotor system is less influenced by the presence or absence of an external fixation point. However, there was no difference in size of the FOE between the pro- and anti-saccade task for PD patients, indicating that they are impaired in exerting control over oculomotor reflexes.

[2] A version of this chapter has been submitted for publication: Van Koningsbruggen, M.G., Pender, T., Machado, L., & Rafal, R.D. (submitted). Parkinson's disease leads to impaired control of the oculomotor reflexes.

Tom Pender assisted with the data collection. Liana Machado provided useful discussion points.

In the previous chapter, the effect of automatic preparation on the size of the FOE was studied. The results provided evidence for an independent modulation of oculomotor reflexes by automatic and strategic preparatory processes. In the current chapter the neural systems involved in strategic preparation are considered. The role of the basal ganglia was studied. We tested patients with Parkinson's disease (PD), which have dysfunctional basal ganglia due to a loss of dopaminergic cells in the substantia nigra pars compacta. The patients were tested on a block of pro-, and a block of anti-saccades. In order to measure the FOE, the fixation point disappeared simultaneously with the target onset in half of the trials (offset condition), while it remained present in the other half (overlap conditions).

Parkinson's disease (PD) is caused by a loss of dopaminergic neurons in the substantia nigra pars compacta, resulting in a dysfunctional basal ganglia. The cardinal signs are a set of movement disorders, like akinesia, bradykinesia, rigidity, and tremor at rest (Galvan & Wichmann, 2008). In addition to the motor signs, a wide variety of cognitive impairments have been reported, which have been assumed to be caused by decreased levels of dopamine in the non-motor parts of the striatum or cortex (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000a, 2000b). In the current study, we have examined the ability of PD patients to control oculomotor reflexes.

A frequently used paradigm to study the ability of healthy individuals and different patient groups to control oculomotor reflexes is the anti-saccade paradigm (Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002; Hutton & Ettinger, 2006; Munoz & Everling, 2004). In this paradigm, subjects are instructed to make a saccade in the opposite direction of a suddenly appearing visual target, i.e. the mirror location. Correct performance depends on the combined ability to suppress an automatic saccade towards the sudden visual onset, and ability to initiate a voluntary saccade in the mirror direction (Hallett, 1978).

The suppression of saccades towards visual targets is achieved by voluntary control of two primitive oculomotor reflexes; the visual grasp reflex, which moves the eyes towards a suddenly appearing target, and the fixation reflex, which anchors they eyes on a foveated stimulus. The SC, which is considered to be the final common pathway for the different cortical and subcortical

oculomotor areas (Moschovakis, Scudder, & Highstein, 1996), has been demonstrated to be involved in these two reflexes. There are two different types of neurons in the intermediate layers of the SC: fixation neurons, which give rise to the fixation reflex, and saccade neurons, which give rise to the VGR. The two reflexes mutually inhibit each other: more fixation related activity leads to less saccade activity, and vice versa for a review see (Munoz & Fecteau, 2002). Since there are no direct connections between these fixation and saccade neurons of the SC (Isa, 2002; Isa & Saito, 2001; Lee & Hall, 2006), the inhibitory interactions between these two reflexes could occur either downstream in the brainstem (Takahashi, Sugiuchi, Izawa, & Shinoda, 2005), upstream in the oculomotor cortex (Dias & Bruce, 1994; Hanes, Patterson, & Schall, 1998), or substantia nigra *pars reticulata* (SNpr) (Basso & Liu, 2007; Hikosaka & Wurtz, 1983a, 1983b).

Neurophysiological studies have found that, compared to pro-saccades, the activity level of fixation neurons is enhanced, while the activity level of saccade neurons is reduced, in the both the SC and FEF during anti-saccades (Everling, Dorris, Klein, & Munoz, 1999; Everling & Munoz, 2000). This suggests that by endogenously increasing the activity level of fixation cells before the target appears, one is capable of suppressing the VGR. Evidence for the direct involvement of these two types of neurons in an anti-saccade task has been demonstrated in monkeys. Everling, Dorris, and Munoz (1998) measured from saccade neurons in the SC. They found that errors in the anti-saccade task, i.e. unsuppressed saccades towards the target, could be predicted by the amount of pre-target activity in saccade neurons; higher activity was correlated with more errors.

A way to probe the amount of voluntary control over these two reflexes in humans is to use a fixation offset (FOE) paradigm (Kingstone & Klein, 1993; Saslow, 1967). The FOE refers to the reduction in saccadic reaction times when the fixation point disappears simultaneously with the target onset, compared to when the fixation point remains visible (overlap). This disappearance of the fixation point results in a decrease of activity of the fixation neurons (Munoz & Wurtz, 1992, 1993a), which results in a relative disinhibition of the saccade neurons (Dorris & Munoz, 1995), i.e. less activity is needed to reach the saccade threshold. However, as stated above, the preparatory set that is adopted during a block of anti-saccades can bring these

neurons under endogenous control. This increased endogenous control not only results in longer reaction times during anti-saccades; since more saccadic activity is required, it also leads to a smaller FOE during a block of anti-saccades, compared to a block of pro-saccades (Forbes & Klein, 1996; Machado & Rafal, 2000a; Reuter-Lorenz, Hughes, & Fendrich, 1991). The smaller FOE is a result of the increased internal control over the fixation neurons during anti-saccades, rendering them less susceptible to external signals at fixation. In other words, their activity levels are less influenced by visual signals since their activity level is already endogenously increased. The difference between the size of the FOE during pro-saccades and anti-saccades can therefore be used to measure the amount of cortical control over these two oculomotor reflexes, i.e. more voluntary control leads to a bigger difference between the size of the FOE for anti- and pro-saccades.

Another paradigm to measure the amount of cortical control has been developed by Rafal, Machado, Ro and Ingle (2000). They showed that saccadic reaction times are shorter when informative cues are presented about the location of an upcoming target, compared to when subjects receive an uninformative cue. In addition, the FOE is also reduced for saccades to cued locations. They argued that subjects utilize a different strategic set than during an anti-saccade task. In this case, subjects endogenously decrease the level of fixation neurons when they know the location of an upcoming target in order to be as fast as possible, resulting in a smaller FOE.
In a subsequent study, Machado and Rafal (2004) tested patients with either a lesion to the FEF, or parietal cortex. Both groups of patients were able to use the informative cues to prepare an upcoming saccade resulting in shorter reaction times. However, FEF patients were not able to reduce the size of the FOE, indicating that the FEF are important in the voluntary control of these oculomotor reflexes.

There is evidence that there are at least 9 different loops from the basal ganglia, which is dysfunctional in PD patients, to different cortical areas, including primary motor, pre-motor, frontal eye fields, prefrontal, and inferotemporal cortex. One such a loop is referred to as the oculomotor loop (Alexander, DeLong, & Strick, 1986; Galvan & Wichmann, 2008; Middleton & Strick, 2000a, 2000b). The input area of the oculomotor loop is the caudate nucleus, which receives input from different areas of the oculomotor cortex:

FEF, dlPFC, supplementary eye fields and parietal cortex. The caudate nucleus is connected to the Substantia Nigra pars reticulate (SNpr) via direct inhibitory projections, and indirect net excitatory projections. The SNpr have direct inhibitory projections to the intermediate layers of the SC (Hikosaka & Wurtz, 1983b). Hikosaka and Wurtz (1983a) showed that neurons in the SNpr responded to stimuli in their receptive field with a decrease in spike frequency. Hikosaka and Wurtz (1983a) also examined the effect of a central fixation target, which was presented centrally and not in their receptive field. They found that the neuronal response was reduced when the monkeys were fixating, indicating that this pathway is involved in fixation related processes. Further evidence for this involvement has been provided by a recent study that used electrical stimulation to disrupt SNpr cells (Basso & Liu, 2007). Short bursts of electrical stimulation decreased the latency of visually guided saccades, whereas the latencies of memory guided saccades increased. In addition, the SNpr not only projects to the SNpr, it is also connected to thalamic nuclei, which projects back to the FEF. SNpr can therefore inhibit the activity of saccade neurons of the SC, and the FEF (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000b; Munoz & Everling, 2004). Therefore, the loss of dopamine in the striatum might influence PD patient's ability to control oculomotor reflexes.

Chan, Armstrong, Pari, Riopelle, and Munoz (2005) tested 18 PD patients on a block of pro-saccades, and anti-saccades. A gap manipulation, in which the fixation point disappears 200 ms before the target onset, or remains visible (overlap), was included in both blocks (Saslow, 1967). It has been proposed that the gap effect, which is bigger than the FOE, is a combination of the effect of a general warning signal, and a FOE (Forbes & Klein, 1996; Kingstone & Klein, 1993). PD patients made more express saccades in the immediate pro-saccade task during both the overlap and gap trials compared to healthy controls. PD patients also made more directional errors in the anti-saccades, and were slower to initiate a saccade in the opposite direction. In addition, they also tested the patients on a delayed pro- and delayed anti-saccades. In the delayed tasks the fixation point remained visible for a variable period after the target onset. Subjects were instructed to initiate an eye movement when the fixation point disappeared. This task manipulation allowed the measurement of the ability to suppress responses, since both pro- and anti-saccades had to be suppressed. PD patients made more timing errors, that is initiating an eye

movement before the fixation point disappeared, during both delayed pro-, and anti-saccades. Their results suggest that PD patients have more difficulties suppressing automatic responses, and are slower generating subsequent saccade in the mirror direction. The authors did not test whether the size of the gap-effect was influenced by the strategic set (i.e. pro- versus anti-saccades).

Crevits, Vandierendonck, Stuyven, Verschaete, and Wildenbeest (2004) studied the influence of PD on the control of oculomotor reflexes. The measured the size of the gap effect during either reflexive pro-saccades, or voluntary pro-saccades in which an eye movement had to be generated in the direction of an arrow. Healthy control subject showed a reliable gap effect in both types of saccades, whereas PD patients only had a reliable gap effect for the reflexive pro-saccades. However, the interpretation of these results is difficult since a non-traditional manipulation was used to measure the gap effect in voluntary pro-saccades. During gap trials, in which the fixation point disappeared 200 ms before the target onset, there was an abrupt onset of an arrow at central fixation to indicate the direction of the saccade after the gap period. It is known that an abrupt onset captures the attention, and especially influence eye movement latencies when it is presented in the centre (Walker, Deubel, Schneider, & Findlay, 1997). Another difference is that the gap and overlap trials were presented in different blocks. A recent study by Rafal, McGrath, Machado, and Hindle (2004) studied the size of FOE for both reflexive and voluntary saccades in PD patients. Fixation offset and overlap trials were randomized within blocks. More importantly, to avoid presenting central arrows auditory cues were used in the voluntary task. PD patients had reliable FOE in both voluntary and reflexive saccade tasks. Saccade latencies and FOE magnitudes were comparable to healthy controls for both type of saccade.

Amador, Hood, Schiess, Izor, and Sereno (2006) tested PD patients on anti-saccades, delayed anti-saccades, and remembered anti-saccades. The patients were, compared to controls, slower to initiate saccades on all tasks, and had more difficulties inhibiting automatic responses. These results were predicted on the basis of their theoretical model, the tonic inhibition model of orienting (Sereno, 1992). The tonic inhibition model argues that there is a voluntary and reflexive attentional system. The voluntary system, which consists of the prefrontal cortex and basal ganglia, has a tonic inhibition over

the reflexive system (brainstem and colliculi). The model further predicts that an impaired voluntary system would lead to a disinhibited reflexive system. In a recent study by the same group, the effect of the dopamine pre-cursor levodopa, an often prescribed medication for PD patients, was examined on saccade performance (Hood, Amador, Cain, Briand, Al-Refai, Schiess, & Sereno, 2007). Patients were tested on two occasions. Patients were tested at least 12 hours after their last levodopa medication during the first session, i.e. the off state. Next, they were tested in the on state, i.e. when medicated. They were tested on a block of pro-, and a block of anti-saccades, both with a gap manipulation. Interestingly, levodopa medication resulted in longer latency pro-saccades, and less errors during the anti-saccade task. However, the authors did not report any statistical values considering the size of the gap effect.

To summarize, PD patients, compared to controls, appear to make more direction errors on the anti-saccade task (Amador, Hood, Schiess, Izor, & Sereno, 2006; Briand, Strallow, Hening, Poizner, & Sereno, 1999; Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Hood et al., 2007), which could be caused by a general impairment of saccade suppression (Chan, Armstrong, Pari, Riopelle, & Munoz, 2005). In addition many studies have reported longer saccade latencies during the anti-saccade task for PD patients. However, no studies have directly studied whether PD patients can endogenously control the size of the FOE. Therefore, the goal of the current study was to investigate the ability of PD Patients in controlling oculomotor reflexes.

Methods

Participants

Nineteen patients with PD (mean age = 66.56; sd = 6.71) and twenty age matched controls (mean age = 66.10; sd = 5.09) were tested. The patients were diagnosed with PD on average 7.06 years (sd = 4.95) ago. The Unified Parkinson's Rating Scale was administered to all patients, their mean score was 15.28 (sd = 7.81). All patients were tested while on medication.

Stimuli and Procedure

Presentation software (Neurobehavioral Systems) was used for stimulus presentation, and were presented on a Mitsibuthsi Super Bright CRT Monitor (240 Hz) which was 57 cm in front of the subjects. Horizontal eye position was recorded with an Eye Trac 210 scleral reflectance device (ASL) at a sampling rate of 1000 Hz. The analogue output of the right eye was recorded by a Powerlab data acquisition unit (ADInstruments) and stored for off-line analyses.

Throughout the experiment, two white marker boxes (1.5°) on a black background were presented at 9° to the left and right of the centre of the screen. After an inter-trial interval of 2500 ms, each trial began with the onset of a Fixation point, a 0.4° white circle, in the centre of the screen. After the fixation point onset, the experimenter, who was present throughout the whole experiment, started the trial only when the participant was looking at the central fixation point (+/- 0.5 degree). If the participant was not looking at the fixation point, the experimenter would ask the participant to look at the fixation point. A 1000 Hz sound (100 ms) was presented as soon as the experimenter initiated the trial, and served as a general warning signal for the participants. After a randomized delay between 250 and 750 ms (in steps of 25 ms), the target was presented. On half of the trials, the fixation point remained visible (overlap condition), while on the other half it disappeared simultaneously with

the onset of the visual target (offset condition). The target remained on the screen for 750 ms. Participants were instructed to make an eye movement to the centre of this box as fast as possible during the pro-saccade task, and instructed to make an eye movement towards the centre of the opposite box during anti-saccades. The experimenter constantly monitored the performance, and provided feedback to the participant on every trial.

Every session started with 10 practice trials. The main experiment was only started if the participant understood the task, and made less than 50 % errors. Else additional practice trials were presented. A total of 100 trials were presented for each task, with a three point calibration every 10 trials, and after every significant head movement. Each task took approximately 45 minutes to complete. The patients completed the pro-saccades and anti-saccades on different days due to the length of the experiment. In addition regular breaks were interspersed to ensure good task performance. The healthy controls were tested on only one session. The task order was counterbalanced across subjects.

Data Analyses

Matlab was used to analyze the eye movement data. First the horizontal position signal was filtered with a 3-ms FWHM (full width at half maximum) Gaussian kernelfilter to remove noise. Next, the velocity profile was calculated. The first sample with a velocity greater than 30 degrees per second, if followed by an elevated velocity over the next 10 samples, was marked as the saccade onset. The saccade offset was determined based on similar criterion: the first sample with a velocity smaller than 30 degrees per second, and a diminished velocity profile in the preceding 10 samples. All eye movement traces were visually inspected by the experimenter to determine whether the algorithm had identified the onset and offset correctly, and whether the eye movements were not contaminated by blinks. Trials were rejected by the experimenter for further analyses if the algorithm was incorrect, or the eye movement was contaminated by blinks. In addition, trials with a reaction time shorter than 75

ms, or longer than 750 ms, which did not start within +/- 1 degree of central fixation, and those with amplitudes of less than 6 degrees or more than 14 degrees were also rejected. Based on these criteria, significantly more trials were rejected for PD patients (16 %) than for healthy controls (8 %), $F(1,37) = 11.23$, $p < 0.01$, $\square_p^2 = 0.23$. However, the amount of rejected trials did not differ for pro- and anti-saccades ($p = 0.17$), nor was there a significant interaction between task and the group ($F<1$).

Reaction Time Analyses

Trials on which a direction error was made were excluded from the Saccadic RT analyses. Since preliminary analyses showed no difference in saccade RT for left and right eye movements ($P>0.2$) data for left and right eye movements were pooled. Kolmorgorov-Smirnov tests indicated that most variables deviated from normal distribution, which was resolved by a LOG-transformation. Therefore, all statistical tests are based on the LOG-transformed data. However, graphs and reported reaction times are based on the mean reaction times. Log mean saccade latency for correct responses were calculated in each condition for each participant and subjected to a repeated measures analyses of variance (ANOVA) with the task (Pro-saccades vs. Anti-saccades), and Fixation point condition (offset and overlap) as within subject factors, and Group (PD patients vs. Healthy controls) as between subject factors. There was no significant difference between the two Groups, $F(1,37) < 1$). The main effect for Task was significant, $F(1,37) = 57.78$, $p < 0.001$, $\square_p^2 = 0.61$, indicating that reaction times for anti-saccades (307 ms) were longer than for pro-saccades (262 ms). In addition, the main effect of Fixation Point Condition was significant, $F(1,37) = 30.93$, $p < 0.001$, $\square_p^2 = 0.46$, caused by shorter saccadic latencies for fixation point offset trials (277 ms) compared to overlap trials (292 ms). The interactions between Task x Fixation Point Condition, and between Task x Group were not significant (both $F < 1$). More important, the three-way interaction between Task x Fixation Point Condition x Group was significant, $F(1,37) = 6.03$, $p < 0.05$, $\square_p^2 = 0.14$.

The mean saccade latencies and the size of the FOE are displayed in Figure 3,1. As expected, the size of the FOE is smaller for anti-saccades, than pro-saccades for the control group. This seems not to be the case for PD patients. Therefore, two paired samples t-tests were conducted to further investigate the three-way interaction. The size of the FOE during anti-saccades (FOE = 9 ms) was significantly smaller than during pro-saccades (FOE = 17 ms) for the control group, t (19) = 2.41, p = 0.01. However, for PD patients, the size of the FOE was not significantly smaller during anti-saccades (FOE = 23 ms) than during pro-saccades (FOE = 12 ms), t (18) = -1.17, p = 0.87.

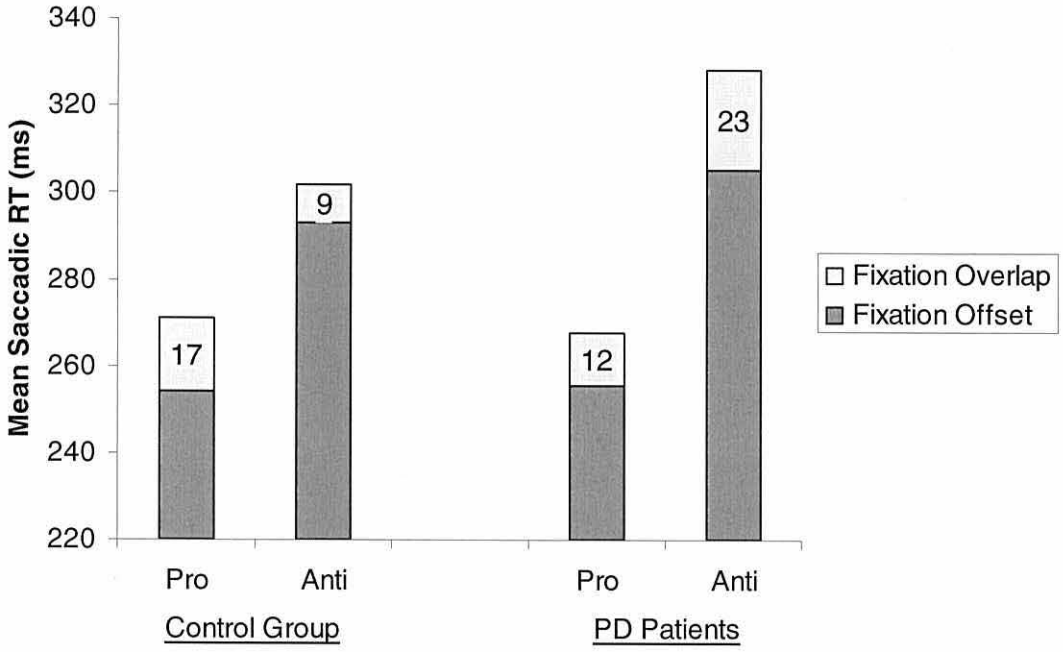

Figure 3.1 *Mean Saccadic Reaction times for both groups, with the size of the FOE*

The amount of cortical control can be estimated by calculating the difference between the size of the FOE during pro- and anti-saccades: Control = $FOE_{(Pro-Saccades)} - FOE_{(Anti-Saccades)}$, a larger value reflects more control. The 95 % confidence interval for the amount of control for both PD patients and healthy controls is shown in Figure 3.2. A t-test confirmed that healthy controls had more control (Control = 9 ms) than PD patients (Control = - 11 ms), $t(37) = 2.5$, $p < 0.05$.

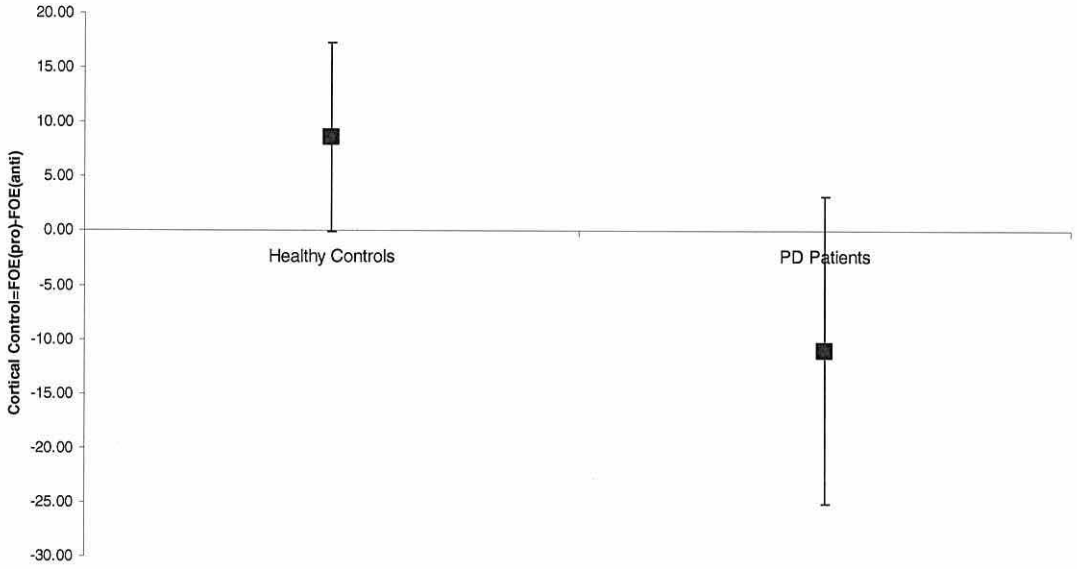

Figure3.2 *The 95%CI of the mean amount of control over oculomotor reflexes (= $FOE_{(pro-saccades)} - FOE_{(anti-saccades)}$) for both PD patients and healthy controls.*

The interaction between Task and Group was not significant, which was not expected since it has been frequently reported that PD patients are slower to initiate anti-saccades compared to healthy controls. To further investigate whether PD patients were slower during the anti-saccade task, two independent samples t-tests were conducted to compare the saccade latencies for both overlap and offset trials between PD patients and healthy controls. However, there were no significant difference between PD patients and controls for either the anti-saccade overlap trials (p=0.15), or the anti-saccade offset trials (p=0.27).

Saccade Amplitude Analyses

Similar to the reaction time analyses, trials on which a direction error was made were excluded from the Amplitude analyses. Since preliminary analyses showed no difference in saccade RT for left and right eye movements (P>0.4) data for left and right eye movements were pooled. Mean saccade amplitudes for correct responses were calculated in each condition for each participant and subjected to a repeated measures ANOVA with the task (Pro-saccades vs. Anti-saccades), and Fixation point condition (offset and overlap) as within subject factors, and Group (PD patients vs. Healthy controls) as between subject factors. The saccadic amplitude was significantly smaller for PD patients (9.81 degree) than for healthy controls (10.46 degree), $F(1,37) = 6.78$, $p = 0.01$, $\square_p^2 = 0.16$. The main effect of task was not significant, $F(1,37) = 1.05$, $p = 0.31$, $\square_p^2 = 0.03$, indicating that there was no difference between the amplitude of pro- and anti-saccades. There was no amplitude difference between offset and overlap trials $F(1,37) = 1.05$, $p = 0.31$, $\square_p^2 = 0.03$. There were no significant interactions between Task x Group, Fixation Point Condition x Group, and Task x Group x Fixation Point Condition (all F's < 1). However, the interaction between Task and Fixation Point Condition was significant, $F(1,37) = 4.53$, $p = 0.04$, $\square_p^2 = 0.11$. Paired wise comparisons revealed no significant differences. The mean saccade amplitudes are shown in Figure 3.3.

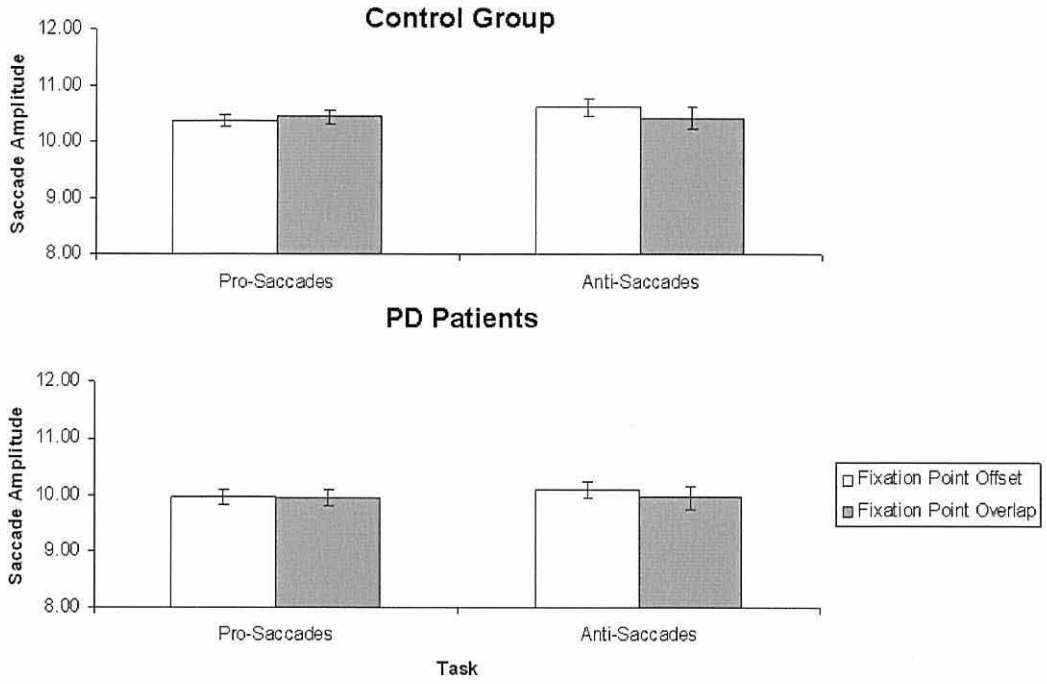

Figure 3.3 *Mean saccade amplitude for each condition (+/- 1 SE) for both the healthy controls (top panel) and PD patients (bottom panel)*

Error Analyses

Direction Error Analyses

As expected, most subjects did not make any direction errors during the pro-saccades task. Since, one average, both PD patients and healthy controls never made more than 1 % direction errors during the pro-saccade task, this condition was not further analysed.

Therefore, only the direction errors during anti-saccades were analyzed (see Figure 3.4). Data for both right and left eye movements were pooled, since a preliminary analyses showed no difference (P>0.5). Mean direction errors were calculated in each condition for each participant and subjected to a repeated measures ANOVA with Fixation point condition (offset and overlap) as within subject factors, and Group (PD patients vs. Healthy controls) as between subject factors. PD patients made significantly more direction errors (8.8 %) than healthy controls (4.8 %), $F(1,37) = 4.29$, $p < 0.05$, $\square_p^2 = 0.10$. The main effect of Fixation Point condition was also significant, $F(1,37) = 18.87$, $p < 0.01$, $\square_p^2 = 0.34$. This was caused by the fact that subjects made more errors during the fixation point offset condition (9.1%) compared to the fixation point overlap condition (4.6 %). However, the two-way interaction between fixation point condition x group was not significant ($F < 1$).

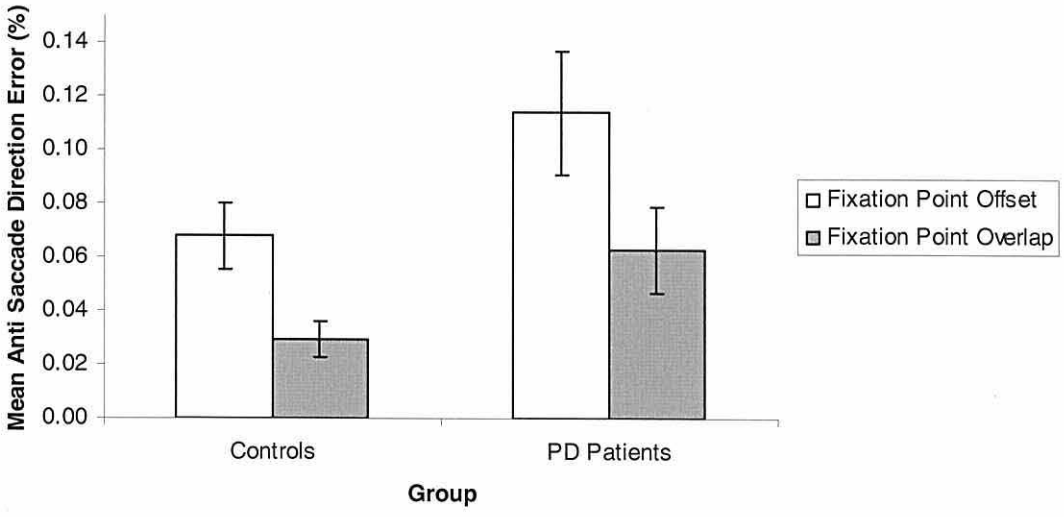

Figure 3.4 *Mean amount of direction errors during the anti-saccade task (+/- 1 SE)*

Discussion

The current study investigated whether PD patients have a normal control over their oculomotor reflexes. The size of the FOE, i.e. the difference in saccadic RT between overlap and offset trial, was measured during both a pro-saccade task, and an anti-saccade task. Healthy controls were able to endogenously control oculomotor reflexes, as reflected by a decrease in the size of FOE during anti-saccades compared to pro-saccades. It is suggested that the strategic set employed during anti-saccades endogenously increased the level of fixation neuron activity in order to suppress the visual grasp reflex. This not only causes longer reaction times, but also results in less influence of a visual signal at fixation. However, this form of cognitive control was absent in the PD patients: although anti-saccade latencies were longer, the size of the FOE was of the same size during pro-saccades and anti-saccades. This indicates that PD patients cannot employ the same preparatory set in regulating the responsiveness of fixation neurons to visual signals.

Another finding of the current study was that the amplitude was smaller for PD patients, but this was not affected by the task. This significant difference was caused by the fact that controls had a tendency to overshoot the centre of the target, whereas the PD patients had shorter saccades that undershoot the target.

Consistent with previous research (Briand, Strallow, Hening, Poizner, & Sereno, 1999; Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002), PD patients made significantly more direction errors. In addition, both patients and controls made more errors in the fixation point offset condition. It has been shown in monkeys, that although the saccade neuron activity is reduced in a block of anti-saccades, the pre-target activity level of saccades neuron in the monkey FEF and SEC predicts direction errors on the anti-saccade task. (Everling, Dorris, & Munoz, 1998; Everling & Munoz, 2000). In other words, although the activity level of those neurons is reduced on average, there is a trial by trial variation; on some trials monkeys are less prepared. Humans are hypothesized to engage the same form of strategic control, which is reflected by a reduced FOE. However, on some trials a suboptimal level of preparation might have been reached, resulting in more errors, especially in fixation offset trials.

A difference with previous research is that reaction times were not longer for PD patients than for healthy controls during the anti-saccade task. This could be due to fact that a warning signal was presented at the start of the trial. Also, we only selected trials which started at fixation, and within a preset amplitude range. However, a recent review highlights the fact that there is contradictory evidence regarding PD performance on the anti-saccade task (Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002). They hypothesize that this difference could be caused by the fact that PD patients form a heterogeneous group. It has been reported that some PD patients show similar impairments on cognitive tasks as patients with a lesion to frontal lobe (Dubois & Pillon, 1997), which could be caused by a depletion of dopamine in the prefrontal cortex (Crawford, Bennett, Lekwuwa, Shaunak, & Deakin, 2002; Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983). To test their hypothesis, Crawford, Haeger, Kennard, Reveley, and Henderson (1995a; , 1995b) tested PD patients on an anti-saccades task, and tested their frontal lobe function on the Wisconsin Card Sort Test. They discovered that the performance on the anti-saccade was highly correlated with preservative errors on the Wisconsin Card Sort Test.

The findings of the current study, that PD patients cannot endogenously control FOE, indicates that the basal ganglia is involved in exercising this control. As discussed in the introduction, the basal ganglia participated in different cortical loops, one of which is referred to as the oculomotor loop (Alexander, DeLong, & Strick, 1986; Galvan & Wichmann, 2008; Middleton & Strick, 2000a). Patients with a lesion to the FEF are also impaired in controlling the same kind of oculomotor reflexes (Machado & Rafal, 2004), suggesting that the FEF are needed for this control. Additional evidence for the involvement of the FEF is provided by Connolly, Goodale, Menon, and Munoz (2002). They studied preparatory set in the human oculomotor cortex using fMRI. The BOLD activity in both the FEF and intraparietal sulcus was measured during a response preparation period (i.e. no actual response was generated). The results showed that the FEF showed greater preparatory activity for anti-saccades than for pro-saccades. In an additional study, the authors showed that the pre-target FEF activation correlated with subsequent anti-saccade RT. Further evidence is provided by a TMS study. Olk, Chang, Kingstone, and Ro (2006) tested subjects on a modified anti-saccade task, in which pro- and anti-saccades are mixed within a block, and inhibition was

required for both pro- and anti-saccades. Ipsilateral directed anti-saccade latencies were longer; whereas the latencies of pro-saccades was not influenced by the TMS. The FEF have direct connections to the SC, and indirect connections to the SC via the SNpr of the basal ganglia (Moschovakis, Scudder, & Highstein, 1996). The reduced control over the FOE could be the result of the disrupted basal ganglia route. However, the basal ganglia also project back to the FEF, which could be resulting in a relative dysfunctional FEF.

However, recent evidence has suggested that the DLPFC are also involved in anti-saccade task. Johnston and Everling (2006) measured from a subset of neurons in the monkey a DLPFC, which had direct connection with the SC. Like FEF and SC neurons, the DLPFC neurons showed higher pre-target activity during anti- than during pro-saccades, and presaccadic activity that correlated with anti-saccade reaction times. A TMS study found evidence that the DLPFC is also involved in the anti-saccades task (Nyffeler, Muri, Bucher-Ottiger, Pierrot-Deseilligny, Gaymard, & Rivaud-Pechoux, 2007). They reported that TMS over the DLPFC 100 ms before the target resulted in more erroneous reflexive saccades towards the target. In addition, patients with lesions involving the DLPFC have an increased error rate on the anti-saccade task. As discussed before, it has been hypothesized that the basal ganglia participates in at least 9 different loops. One such a loop includes the DLPFC, indicating that this might be involved as well. Additionally, it has been reported that in PD disease, which is caused by a degeneration of dopamine cells in the SNpc, can also lead to a reduction of dopamine in the prefrontal cortex (Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983).

In summary, the findings of the present study is that PD patient have an impaired ability to control oculomotor reflexes, indicating that the basal ganglia is important for oculomotor control.

Chapter 4: Hemispheric asymmetry in the remapping and maintenance of visual saliency maps; A TMS study[3]

Abstract

Parietal cortex has been implicated in the maintenance and updating of a salience map after eye movement, a mechanism that is required for coherent visual experience and for the control of visually guided behaviour. Using TMS over anterior intraparietal cortex (AIPCx), we demonstrate different hemispheric contributions to the updating of visual salience maps across saccadic eye movements. An uninformative visual cue was presented at one object in a display to generate a salience map with an inhibitory tag at the location of the cued object. After making a saccade to either left or right, we probed for updating of the location of the inhibitory tag by measuring manual reaction time to targets at the cued location compared to an uncued location. Between the time of saccade initiation and target appearance, dual pulse TMS was targeted over the right or left AIPCx. TMS of a vertex control site confirmed remapping of the inhibitory tag after a saccade. Updating of the location of the inhibitory tag was eliminated by right, but not the left, AIPCx, suggesting that the right parietal cortex is involved in the remapping of inhibitory tags. There was no updating of the inhibitory tag for both eye movements to the left (contralateral) and to the right (ipsilateral) visual fields. I conclude that AIPCx is involved not only in generating the efference copy necessary for updating, but is also the neural substrate for maintaining a salience map across saccades.

[3] A verion of this chapter has been submitted for publication: Van Koningsbruggen, M.G., Gabay, S., Sapir, A., Henik, A., & Rafal, R.D. (submitted). Hemispheric asymmetry in the remapping and maintenance of visual saliency maps: A TMS study Shai Gabay, Ayelet Sapir and Avishai Henik assited with discussion about the experimental design. Shai Gabay helped with collecting pilot data. Tony Bedson helped with acquiring the MRI scans.

As previously discussed in the introduction, Easton (1972) argued that the neural circuits that sub serve reflexes are the building blocks for more complex behaviour. I also discussed in the context of the VGR, that an automatic orienting response is elicited by salient peripheral stimuli. However, the current experiments investigate how a stimulus can be attended without looking at it. It has been argued that argue that the ability to covertly attend to the most salient stimuli is an adaptive specialization (Rozin, 1976). An important feature of such an adaptive specialization is that attention should be stopped from returning to locations that have already been further analysed. For example, animals should look at more than one place when looking for food. A reflexive behaviour that might help guide foraging and visual search is inhibition of return (IOR). These experiments explored the hypothesis that an inhibitory tag (Inhibition of Return, or IOR), which involves the superior colliculi, is utilized by the oculomotor cortex to encode a visual saliency map which is employed in visual cognition.

Although the retinal input changes dramatically with every eye movement, our visual experience is coherent. Information across successive fixations is integrated into a spatially consistent percept. This spatial consistency is hypothesized to be achieved by a remapping mechanism that uses corollary discharge as an 'extra-retinal signal' to compensate for each saccade (Sommer & Wurtz, 2008). One example for the importance of corollary discharge in maintaining spatial consistency is provided by Stevens et al. (1976) who temporarily paralyzed the eye muscles of human observers using anaesthesia. The subjects reported that an intention to move the eyes displaced their perception of the world although they could not physically move their eyes. However, the intention to move their eyes generated a corollary discharge which was used to remap the visual world. Haarmeier, Thier, Repnow, and Petersen (1997) describe a patient with an extensive bi-lateral parietal-occipital lesion, the patient's main complaint was that the world moved every time he made an eye movement. The lesions impaired the patient ability to use the corollary discharge signal to integrate information from consecutive fixations.

Duhamel, Colby and Golberg (1992) reported the first neurophysiological evidence of neurons in monkey's Lateral Intra-Parietal (LIP) cortex that remapped their receptive fields either before or after eye

movements. During a task requiring continuous fixation, neurons in LIP only respond to visual stimuli presented within their retinotopic receptive field. However, in an experiment that involved eye movements, in which a stimulus was presented outside a neuron's receptive field, and the monkey was instructed to make a saccade which would bring the stimulus into the receptive field, a subset of the LIP neurons responded to stimuli at the location of the future receptive field before saccade initiation. The authors postulated that LIP made use of the corollary discharge from the saccade command to represent a stable perceptual map of the visual environment. Duhamel, Colby, and Goldberg (1992) also observed LIP neurons that responded to 'remembered' targets. When a briefly flashed stimulus was presented outside their receptive fields before a saccade, the neurons responded after the saccade brought this location into their receptive field, even though this location no longer contained the stimulus. Duhamel, Colby, and Goldberg (1992) concluded that visual memory has a retinotopic representation which is updated after every saccade. Subsequent studies have reported neurons with similar properties in the monkey's SC (Walker, Fitzgibbon, & Goldberg, 1995), FEF (Umeno & Goldberg, 1997, 2001), striate and extra-striate cortex (Nakamura & Colby, 2002)

More recently, it has been shown that LIP neurons do not simply remap visual stimuli but, more specifically, remap the saliency of the visual stimulus (Gottlieb, Kusunoki, & Goldberg, 1998). In their experiment, a saccade always brought the same visual stimulus within the neuron's receptive field while the salience of the stimulus was manipulated. In one experimental condition, the stimulus had been visible throughout the experiment, resulting in a relatively low response rate of the neuron after the saccade. However, when the same visual target had an abrupt onset just before the saccade, making the stimulus more salient, the discharge rate was much higher.

There is converging evidence, from neuropsychological, TMS and fMRI investigations, that similar mechanisms exist in humans. Patients with lesions in the parietal cortex have impaired performance on the double step saccade task. In this task, two saccades are made to sequentially flashed targets, each of which disappears before the first eye movement. The first saccade can be made on the basis of retinotopic coordinates. However, an accurate second saccade requires updating of the location of the second target based on the motor vector of the first saccade. Failure to update the location faithfully results

in inaccurate saccades to the second target or, if no extra-retinal signal is generated at all, the second saccade either cannot be executed at all, or will be made to the retinal location of the target. For example, infants less than four months old make saccades to the retinal locus of the second target in this paradigm, with accuracy of the second saccade improving with cortical maturation thereafter (Gilmore & Johnson, 1997).

Duhamel, Goldberg, Fitzgibbon, Sirigu, and Grafman (1992) studied a patient with a right fronto-parietal lesion in the double step saccade paradigm. The patient's performance was unimpaired when the first saccade was directed towards the ipsilesional field, and the second directed contralesionally. However, when the first saccade was directed to the contralesional field, the patient failed to make a correct second saccade to the ipsilesional field. In a subsequent group study, the parietal cortex was confirmed as the critical site for updating the environment after a saccade (Heide, Blankenburg, Zimmermann, & Kompf, 1995). In a task in which the two targets were presented in opposite visual fields, patients with both left and right parietal lesions were impaired in the second saccade when the first was directed contralesionally (Heide, Blankenburg, Zimmermann, & Kompf, 1995).

Recent fMRI and TMS studies have confirmed and extended the involvement of the parietal cortex in spatial updating. Merriam, Genovese, and Colby (2003) studied remapping processes in the parietal cortex in an fMRI experiment. They presented a lateralized visual stimulus in either the left or right visual field. As expected, based on the retinotopic receptive field of neurons in the parietal lobe, the stimulus elicited a BOLD response in the opposite hemisphere. Two seconds after the stimulus had disappeared subjects made a saccade which brought the extinguished stimulus location into the opposite visual hemifield. After the saccade there was a significant BOLD response in the opposite parietal lobe, which could not be simply explained by the saccade execution. This result indicates that the human parietal cortex also maintains a representation of space which is remapped with every eye movement. Van Donkelaar and Muri (2002) found that right parietal TMS stimulation 150 ms, but not earlier, after the onset of the first saccade of a double step paradigm impaired accuracy of the second saccade. Right TMS stimulation only impaired performance if the first saccade was to the left and the second saccade to the right. Morris, Chambers and Mattingley (2007) used a more focal figure of eight coil and found that a posterior part of the IPS, close

to the transverse occipital sulcus, and not a more anterior part, was involved in updating in a variant of the double step paradigm.

Other TMS studies have found that remapping signals are not only used to update motor vectors, but also internal maps of visual features. Chang and Ro (2007) studied the effect of parietal TMS stimulation on the detection of displacement of visual targets that moved during a saccade. They stimulated only the right PPC, and observed that TMS stimulation just before the onset of a leftward, but not a rightward saccade, resulted in a reduction of displacement detection. Chang and Ro postulated that TMS introduces noise into the PPC representation, and thereby reducing sensitivity to displacement. Prime, Vesia and Crawford (2008) studied transsacadic memory of visual features, which they defined as the maintenance of visual information used to integrate information across saccades. They stimulated over the mid-IPS on both left (P3) and right (P4) electrode sites. Only TMS stimulation over right parietal lobe impaired memory performance. The TMS induced deficit was greater when trans-saccadic memory was required than in a control fixation task.

In an experiment motivating the current research, Sapir, Hayes, Henik, Danziger, and Rafal (2004) demonstrated that the human parietal cortex is not only involved in remapping motor vectors, but also in updating visual saliency maps across eye movements. Their experiment used an exogenous cueing paradigm that elicits an inhibitory tag at a location that was previously cued resulting in slower responses to targets at cued location (inhibition of return – IOR (Posner, Rafal, Choate, & Vaughn, 1985). IOR has been hypothesized to contribute to the elaboration of a salience map that can guide efficient visual exploration by favouring novel locations(Klein, 1988, 2000; Posner & Cohen, 1984). Sapir et al. exploited the fact that the location of this inhibitory tag is updated after a saccade (Danziger, Fendrich, & Rafal, 1997; Maylor & Hockey, 1985; Posner, Rafal, Choate, & Vaughn, 1985; Tipper, Grison, & Kessler, 2003).

In the IOR paradigm employed by Sapir et al. (2004), one of four boxes was briefly cued to generate an inhibitory tag and, after a saccade was made to a new location, a target requiring a manual detection response was presented at either the retinal location of the cue, the environmental location of the cue, or at corresponding uncued locations. They tested 5 patients with a unilateral lesion involving the superior IPCx and healthy controls. Healthy

control participants showed inhibitory tagging (IOR) at the remapped, environmental location of the cue, as well as a smaller inhibitory effect at the retinal location. The patients' results revealed no evidence of updating the location of the inhibitory tag: i.e. IOR was observed only at the retinal location of the cue. In contrast to the results of double-step saccade paradigms summarised above, the deficit in remapping was bilateral; that is, it occurred for targets in both the ipsilesional and contralesional visual field, and after both ipsilesional and contralesional saccades. Interestingly, abolished remapping of the inhibitory tag was found in the three patients with a right hemisphere lesion but not in the two left hemisphere patients. Sapir et al. (2004) interpreted their results to indicate that parietal cortex was not simply the source of the corollary discharge that provides the extra-retinal signal for saccade remapping, but that it may also provide the neural substrate for maintaining a salience map across saccades.

The patients studied by Sapir et al. (2004) all had chronic lesions. It is not clear whether the effects reported in those patients reflect the normal function of parietal cortex, or are the consequence of brain reorganisation. Moreover, Sapir et al studied only two patients with left parietal lesions and three with right parietal lesions, and therefore could not draw any conclusions about possible hemispheric asymmetries for maintaining salience maps. Here we employed dual pulse TMS to transiently disrupt the function of parietal cortex, and to compare the effects of right and left parietal TMS in order to test for a hemispheric asymmetry. The parietal stimulation site, over the rostral IPCx, corresponded to the area of lesion overlap in the patients studied by Sapir et al. (2004). A TMS vertex control site was also stimulated. The timing of the TMS pulses, 150 ms and 250 ms after saccade onset was based on the observations of Van Donkelaar and Muri (2002).

Methods

Participants

Twenty-eight subjects (16 Female) participated in Experiment 1. Their mean age was 24 (SD = 4.47). Subjects were divided into two equal groups: a right and a left parietal TMS group. Six subjects of the 28 subjects participated also in a control experiment in which inhibitory tagging without eye movement was tested. Written informed consent was obtained from each participant. In addition, subjects filled in a safety screening questionnaire for TMS (Keel, Smith, & Wassermann, 2001). Ethics approval was obtained from the School of Psychology at the University of Wales, Bangor, United Kingdom. Participants received £10/hour for their participation.

Apparatus

A limbus tracker (ASL 210, Bedford, MA) was used to monitor horizontal eye position at a rate of 1000 Hz. The eye movement recording device was calibrated by a three point calibration every twenty trials. A chin and cheek rest was used to reduce head movements. The analogue output of the eye tracker was processed online to determine the onset of saccades. When the velocity of saccades reached 50°/s, a TTL pulse was sent to stimulus PC which recorded the saccadic latency and direction. Next, the stimulus PC sent out two TTL pulses to the TMS stimulator to trigger two TMS pulses 150 and 250 ms after the onset of the eye movement. Presentation software (Neurobehavioural systems) was used for stimulus presentation and triggering of the TMS machine. Stimuli were presented on an Ilyama vision master pro 512 monitor (200 Hz). A response device connected to the gameport was used to record manual reaction times.

TMS stimulation

A magstim super rapid with a 70mm figure eight coil was used for the TMS stimulation. First, the hand area of the motor cortex was localized in the left hemisphere. Next, the motor threshold was determined, by finding the minimum amount of TMS stimulation that was required to elicit a visible hand twitch in the right hand. Stimulation was set to 120% of the MT. Each group participated in two sessions, separated by at least one week. The right parietal group received TMS over either the vertex (control site) or a right parietal location that was 3 cm to the right and 4 cm posterior relative to the vertex.

The left parietal group received TMS over either the vertex, or a similar left parietal site. A similar criterion for parietal cortex stimulation has been used in previous investigations (Chang & Ro, 2007; Kapoula, Yang, Coubard, Daunys, & Orssaud, 2004, 2005; van Donkelaar & Muri, 2002)

Procedure

The experiment was conducted in a dimly lit room. The distance between the monitor and the subjects was 57 cm. The stimulus display consisted of three small white fixation points (0.1 x 0.1 degree) on a black background, one presented in the centre, and the other two presented 10 degrees to the right or left of the centre. A white unfilled box (3 x 3 degree) was presented 5 degree above and below each fixation point. The six boxes and the two peripheral fixation points were presented throughout the experiment.

Each trial began with the onset of a central fixation point. If fixation did not obtain within 250 ms, the trial was aborted and an error sound was presented. After 1000 ms, a non-informative cue was presented in one of the midline boxes, either above or below the central fixation. The cue was a thickening of the line for 200 ms. A right or left arrow (1 degree) was presented at central fixation 300 ms after cue offset. The arrow was presented for 200 ms. Subjects were instructed to move their eyes as fast as possible in the direction of the arrow towards either the left or right peripheral fixation point. If subjects made a saccade in the wrong direction, or did not make a saccade within 500 ms, the trial was aborted and an error sound was presented. Following the eye movement, subjects were required to keep fixation at the indicated peripheral fixation point. After 700, or 900 ms, a target was presented either above or below the central fixation point. The target was presented until the subject responded by pressing a button with their right index finger, or for 1000 ms. See figure 4.1 for a graphical illustration of the trial structure. Following a training session of 20 trials, a total of 176 trials were presented, with 10% catch trials. Catch trials were exactly the same as the other trials (i.e. including TMS stimulation), except that no target was presented.

All subjects participated in two sessions: depending on the group one session with either left or right parietal TMS, and one with TMS stimulation over the vertex. Each session took around 60 minutes, and the order of sessions was counterbalanced across subjects. The inter trial interval was set to 4000 ms, to make sure that the time between two successive TMS trains was never shorter than 5000 ms (Wassermann, 1998). Sapir et al.'s (2004) probed for IOR at

both retinal and environmental locations. However, because of the long inter-trial interval required, in the current study the TMS sessions were 60 minutes long, and it was not practical to test for both retinal and environmental IOR.

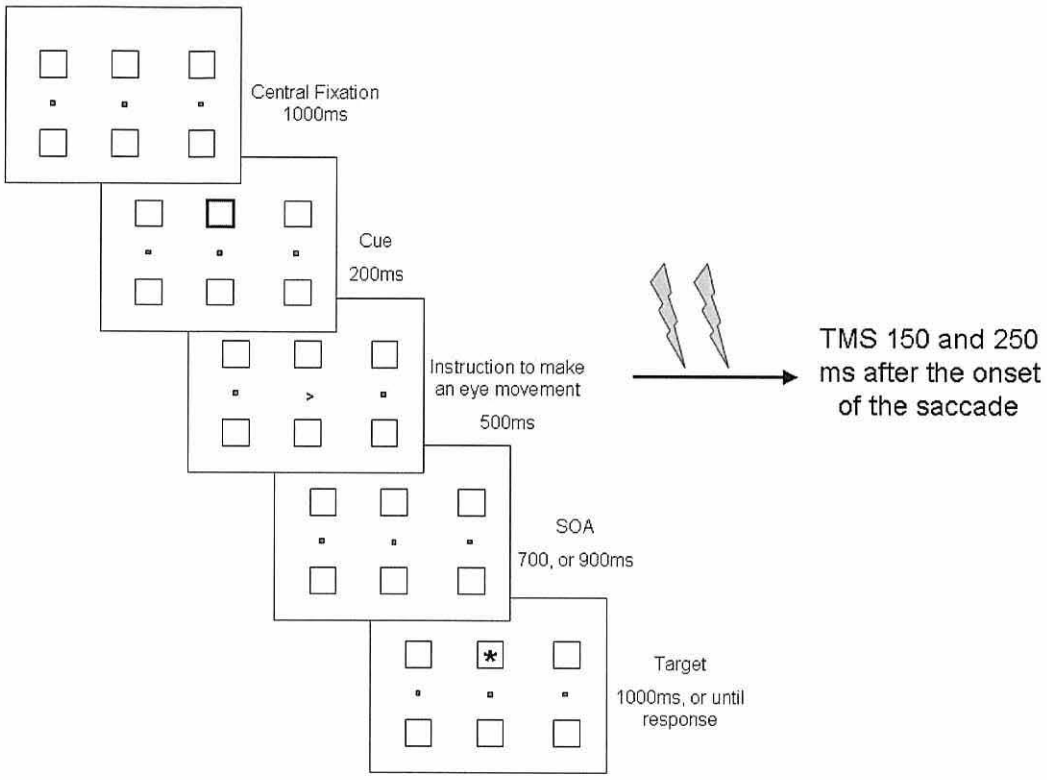

Figure 4.1 *Trial Structure and stimulation sequence for a cued target with a saccade to the right between the cue and target presentation*

Results

The subjects were divided into two different groups: one group received TMS over the Right Parietal Cortex and Vertex, whereas the other group received Left Parietal and Vertex stimulation. First, the effects of Right Parietal relative to vertex TMS are reported. Next, the effects of Left Parietal TMS are reported. Lastly, both groups are compared.

TMS location

An anatomical MRI scan of 6 subjects (4 from the right parietal group) was made to determine the anatomical location in more detail (see Figure 4.2). The parietal TMS stimulation was over the anterior PPC, including the anterior part of the IPS, rostral superior parietal lobule. This is in accordance with region of maximum overlap in the Sapir et al study.

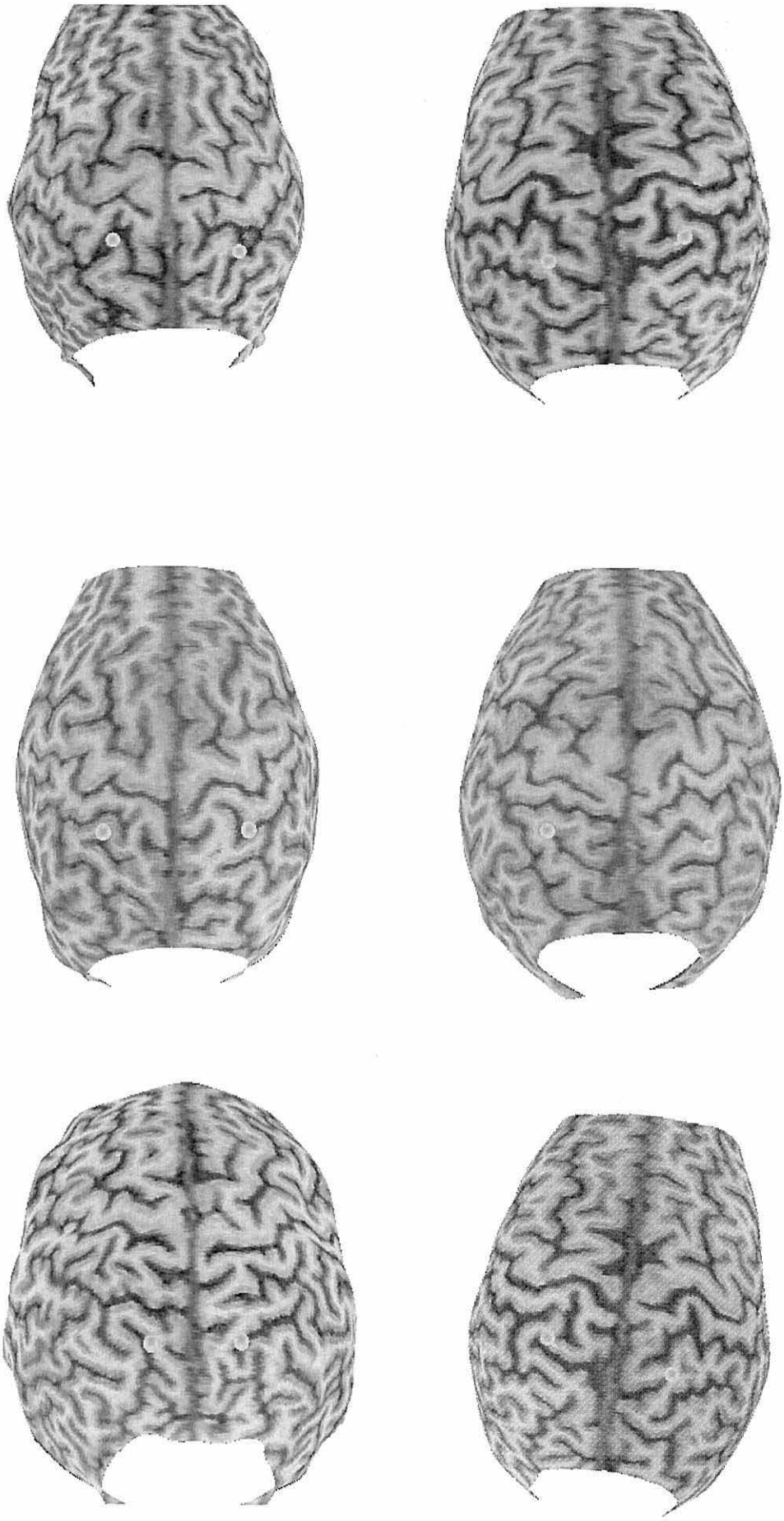

Figure 4.2 *Anatomical location of the TMS Stimulation*

THE EFFECT OF RIGHT PARIETAL TMS

Errors

There were two different types of errors subjects could make: an eye movement error, or a manual key press error. A failure to keep fixation at the centre, a blink, an eye movement which was not in the right direction or was too slow (>500 ms), or a failure to keep fixation at the peripheral fixation point after a successful eye movement were all classified as eye movement errors. We used such a strict criterion since TMS stimulation was given relative to the saccade onset. Subject made an average of 6.5% eye movement errors, which did not differ between TMS condition, Saccade Direction, or the interaction between these two ($F<1$). All trials with a saccade error were aborted. Subjects made a very small number of manual key press errors (1.5%), and were therefore not further analyzed. Catch trials were omitted from the analyses.

Saccadic Reaction Times

The overall mean saccadic reaction time was 306 ms. This means that, on average, the two TMS pulses were given 456 ms, and 556 ms after the onset of the arrow, i.e. 150 and 250 ms after the saccade onset. Saccadic Reaction Times were analyzed with a repeated measures analysis of variance (ANOVA) with TMS condition (Right Parietal or Vertex) and Saccade Direction (Left or Right) as factors. There was no significant effect of TMS condition on the saccadic latencies, $F(1,13) < 1$. The interaction between TMS condition and Saccade Direction was also not significant, $F(1,13) < 1$. However, the leftward directed saccades were significantly faster (302 ms) than rightward directed saccades (309 ms), $F(1,13) = 7.48$, $p < 0.05$, $\square_p^2 = 0.37$. Although the difference is significant, it was only 7 ms.

Manual Reaction Times

Anticipation responses (faster than 90 ms) and slow responses (slower than 750ms) were excluded from the analysis. Note that if subjects did not execute the saccade correctly, the trial would have been aborted. A repeated measures ANOVA with TMS condition (Right Parietal or Vertex), Saccade Direction (Left or Right), Cue (valid or invalid), and SOA (700 or 900 ms) as within subject factors was performed. There were only two significant effects. Firstly, there was a significant effect of Cue, $F(1,13) = 7.24$, $p < .05$, $\square_p^2 = 0.36$, reflecting the fact that reaction times were slower for cued targets (296 ms) than for

uncued targets (291 ms), i.e. there was a significant IOR. Secondly, the interaction between cue and TMS location was also significant, $F(1,13) = 24.72$, $p < .01$, $\square_p^2 = 0.66$. No other effects were significant, including the interaction between TMS x Cue x Saccade Direction ($F<1$). See table 4.1 for all the values of the ANOVA.

Paired wise comparisons were performed to investigate the interaction between cue and TMS location. There was a significant effect of cue on reaction times during vertex stimulation, $t(13) = 5.64$, $p<0.001$, i.e. there was a significant IOR of 11 ms. However, when TMS stimulation was administered over the Right Parietal Cortex there was no significant difference in RT for Cued and Uncued targets ($t<1$). This suggests that Right Parietal TMS hinders the remapping of this inhibitory tag. There was no interaction between TMS x Cue x Saccade Direction indicating that the remapping impairment was independent of the direction of the eye movement. The reaction times for the two-way interaction are summarized in Figure 4.3.

Table 4.1 Effects of Right Parietal TMS

Factor	*df*	*Mean Square*	*F*	*p.*		*Partial Eta Squared*
TMS	1, 13	2160.51	0.11	0.74		0.01
Saccade Direction	1, 13	1.52	0.00	0.95		0.00
SOA	1, 13	1551.50	2.93	0.11		0.18
Cue	1, 13	1428.87	7.24	0.02	*	0.36
TMS x Sac Direction	1, 13	32.15	0.07	0.80		0.01
TMS x SOA	1, 13	95.46	0.29	0.60		0.02
TMS x Cue	1, 13	1852.01	24.72	<0.01	**	0.66
Sac Direction x SOA	1, 13	247.45	0.92	0.36		0.07
Sac Direction x Cue	1, 13	62.72	0.17	0.69		0.01
SOA x Cue	1, 13	90.08	0.32	0.58		0.02
TMS x Cue x Sac Direction	1, 13	22.75	0.05	0.83		0.00
TMS x SOA x Sac Direction	1, 13	192.96	0.65	0.44		0.05
TMS x SOA x Cue	1, 13	241.87	1.04	0.33		0.07
Sac Direction x SOA x Cue	1, 13	16.54	0.08	0.79		0.01
TMS x SOA x Cue x Sac Direction	1, 13	808.34	2.39	0.15		0.16

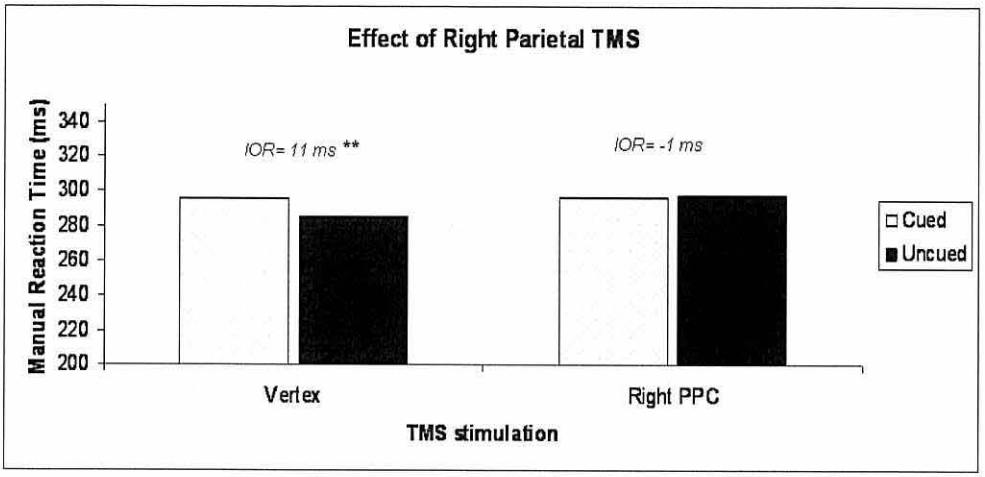

Figure 4.3. *The mean manual reaction times for cued (white bars) and uncued (black bars) targets. Reaction times for Vertex stimulation are on the left, and RTs for right parietal stimulation are on the right.*

Effect of Left Parietal TMS

Errors

Subject made an average of 6.7% eye movement errors, which did not differ between TMS condition, Saccade Direction, or the interaction between these two ($F<1$). Subjects made a very small number of manual key press errors (1.9%), and were therefore not further analyzed.

Saccadic Reaction Times

The overall mean saccadic reaction time was 335 ms. This means that, on average, the two TMS pulses were given 485 ms, and 585 ms after the onset of the arrow, i.e. 150 and 250 ms after the saccade onset. Saccadic Reaction Times were analyzed with a repeated measures ANOVA with TMS (Right Parietal or Vertex) and Saccade Direction (Left or Right) as factors. There were no significant effects ($F<1$).

Manual Reaction Times

A repeated measures ANOVA with TMS (Left Parietal or Vertex), Saccade Direction (Left or Right), Cue (valid or invalid), and SOA (700 or 900 ms) as within subject factors was performed to study the effects of Left Parietal TMS. The effect of cue was significant, $F(1,13) = 19.45$, $p < 0.01$, $\square_p^2 = 0.6$, with slower reaction times for cued targets (305 ms) than for uncued targets (290 ms), indicating that there was a significant IOR of 15 ms. There was also a significant interaction between Cue and SOA, $F(1,13) = 7.01$, $p < 0.05$, $\square_p^2 = 0.35$. To explore the nature of this interaction, a t-test comparing the size of IOR of the two different SOA's was conducted. This comparison revealed that the size on the IOR was significantly larger for the short SOA (700ms; 21 ms) than for the long SOA (900ms; 9 ms), $t(13) = 2.65$, $p = 0.20$. Lastly, there was a significant interaction between Saccade Direction x TMS, $F(1,13) = 5.61$, $p < 0.05$, $\square_p^2 = 0.30$. In order to study this interaction, four pair wised comparisons were conducted. Reaction Times were significantly faster after a saccade to the left (280 ms) than after a saccade to the right (289 ms) when Left Parietal TMS was administered, $t(13) = 5.96$, $p < 0.01$. There were no other significant effects. Most important, the interaction between TMS x Cue was not significant ($F<1$), suggesting that TMS to the left parietal and TMS to the Vertex have similar effects. Figure 4.4 depicts the RT for this interaction. It can be seen that there still is a significant IOR after Left Parietal TMS, i.e. Left Parietal TMS does not influence the remapping of the inhibitory tag. See table 4.2 for all the values of the ANOVA.

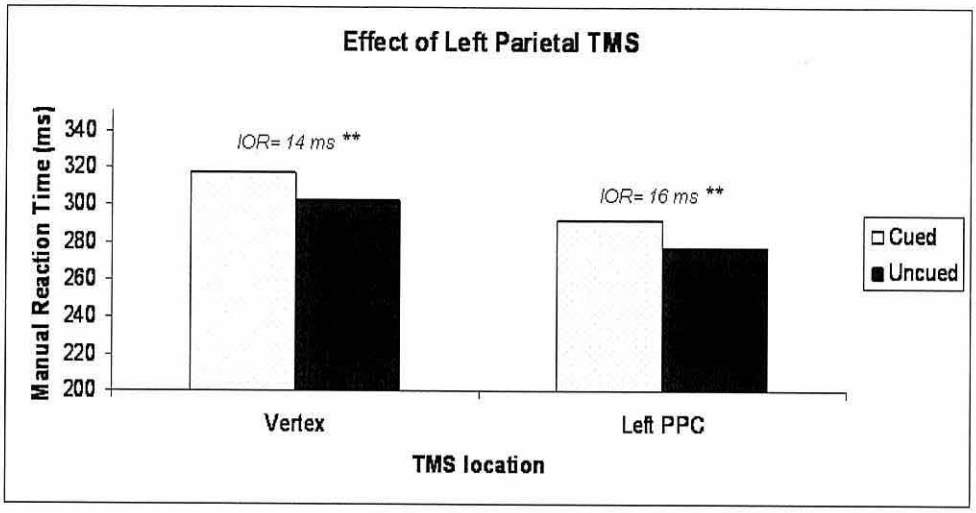

Figure 4.4. *The mean manual reaction times for cued (white bars) and uncued (black bars) targets. Reaction times for Vertex stimulation are on the left, and RTs for left parietal stimulation are on the right.*

Table 4.2 Effects of Left Parietal TMS

Factor	*df*	*Mean Square*	*F*	*p.*		*Partial Eta Squared*
TMS	1, 13	36448.17	0.96	0.35		0.07
Saccade Direction	1, 13	208.05	0.52	0.48		0.04
SOA	1, 13	720.14	0.99	0.34		0.07
Cue	1, 13	12613.78	19.45	<0.01	**	0.60
TMS x Sac Direction	1, 13	3050.25	5.61	0.03	*	0.30
TMS x SOA	1, 13	171.66	0.31	0.59		0.02
TMS x Cue	1, 13	15.14	0.02	0.89		0.00
Sac Direction x SOA	1, 13	73.27	0.12	0.73		0.01
Sac Direction x Cue	1, 13	427.91	1.04	0.33		0.07
SOA x Cue	1, 13	1741.32	7.01	0.02	*	0.35
TMS x Cue x Sac Direction	1, 13	260.59	0.70	0.42		0.05
TMS x SOA x Sac Direction	1, 13	183.60	0.43	0.52		0.03
TMS x SOA x Cue	1, 13	305.42	0.88	0.36		0.06
Sac Direction x SOA x Cue	1, 13	12.82	0.02	0.88		0.00
TMS x SOA x Cue x Sac Direction	1, 13	549.42	1.62	0.23		0.11

Comparing the effect of Right and Left PPC TMS

Two different ANOVA's were performed to study the difference between Right and Left PPC TMS with Group as a between subjects factor. One ANOVA compared the effect of Vertex TMS for both groups, whereas the other ANOVA compared the effect of Parietal TMS for both groups. The reason for comparing the vertex stimulation between the groups was to determine whether there is a baseline difference between the groups. The mixed effect repeated measures ANOVA with Group (Right or Left group) as between subjects factor, and Saccade Direction (Left or Right), Cue (valid or invalid), and SOA (700 or 900 ms) as within subject factors revealed only a significant effect of CUE, $F(1,26) = 20.91$, $p < 0.01$, $\square_p^2 = 0.45$, which was caused by slower responses for cued (307 ms) than for uncued targets (294). There were no other significant effects, including no main effect of group, or interactions with the group factor. This means that the groups did not differ from each other in the vertex condition.

The same ANOVA was performed for parietal TMS. There was a significant effect of Cue, $F(1,26) = 8.10$, $p < 0.01$, $\square_p^2 = 0.24$. More interestingly, there was a significant interaction between Cue x Group, $F(1,26) = 9.70$, $p < 0.01$, $\square_p^2 = 0.27$. The nature of this interaction was studied by comparing the size of IOR for both groups. As expected, the size of the IOR was significantly bigger in the left Parietal TMS group (16 ms) than in the Right Parietal TMS group (-1 ms), $t(26) = 3.11$, $p < 0.01$. The effect of Saccade Direction was also significant, $F(1,26) = 5.05$, $p < 0.05$, $\square_p^2 = 0.16$. As was the interaction between Saccade Direction and Group, $F(1,26) = 6.52$, $p < 0.05$, $\square_p^2 = 0.20$. Follow up t-test found that there was no effect of Saccade Direction for the Right Parietal Group (RT was 297 ms independent of saccade direction). However, in the Left Parietal Group reaction times were faster after a saccade to the Left (280 ms) than after a saccade to the Right (289 ms), $t(13) = 5.96$, $p < 0.01$. No other effects were significant.

To confirm the bi-lateral remapping deficit after Right Parietal TMS we tested directly whether there was a significant IOR during Right or Left parietal TMS after either a left or rightward saccade. As can be seen in Figure 4.5, which shows the 95 % confidence interval for the mean size IOR, there was no longer a significant IOR after a right or leftward saccade ($t < 1$) during Right PPC TMS, whereas after TMS stimulation over Left PPC there was a significant effect in both the right ($p<0.5$) and left field ($p<0.5$). In other words, there was no significant IOR after right parietal TMS, independent of the saccade direction, i.e. the deficit was bi-lateral.

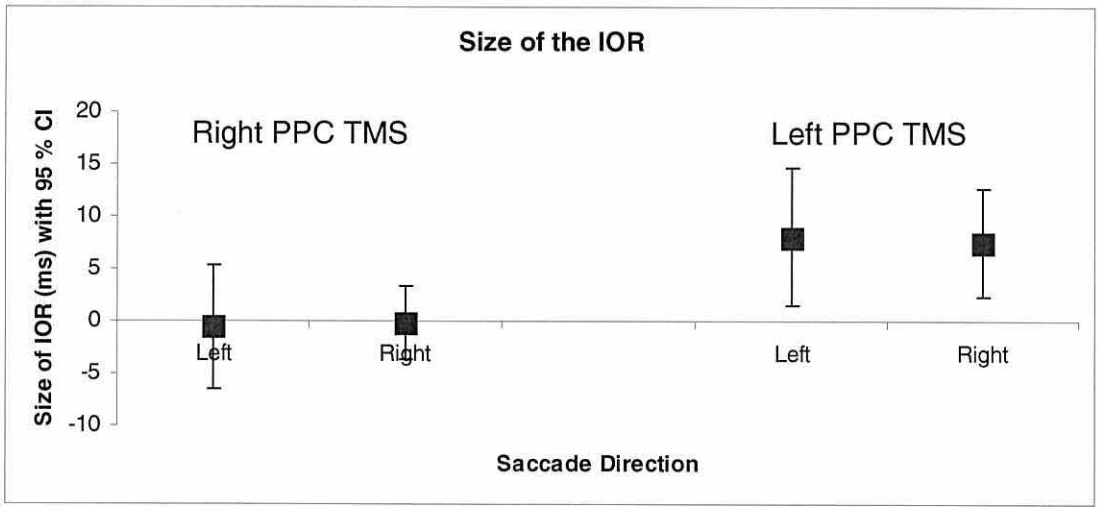

Figure 4.5 *The 95% confidence interval of the size of the IOR in each visual field as a function of right or left TMS.*

Control Experiment

The current result suggests that right parietal TMS impairs remapping of the inhibitory tag regardless of the direction of eye movements. However, the conditions in this study do not allow us to rule out the possibility that right parietal TMS abolishes IOR in general and not only the remapping of the inhibitory tag. Sapir et al. (2004) also presented targets at retinal cued locations, for which no remapping was required. Like the healthy controls, the patients' reaction times were slower for the cued retinal location. This finding demonstrated that patients had a normal IOR, but that this IOR was lost when they were required to remap the inhibitory tag. Since there were no such a targets presented in the current experiment, i.e. subjects were always required to remap the inhibitory tag we performed a control experiment, in a few participants, in which no remapping was required.

The procedure was identical, except that subjects were not required to make an eye movement. Instead of an arrow, an equal sign of the same size was presented, and subjects were instructed to maintain central fixation. The TMS pulses were given relative to mean saccadic reaction times of the previous session. We recruited 6 subjects who had participated in the study. They participated in one Vertex, and one Right Parietal TMS session. Reaction times were subject to a (2 (TMS) x 2 (Cue) x 2 (SOA)) repeated measures ANOVA. The main effect of cue was significant, $F(1,5) = 16.43$, $p = 0.01$, $\square_p^2 = 0.77$, reflecting the slow RTs to valid than invalid trials; i.e. IOR. There were no other significant effects. This indicates that Right Parietal TMS does not influence IOR when there is no need to update the saliency map.

Discussion

The results of these experiments confirm those reported in neurological patients (Sapir et al, 2004) implicating the rostral IPCx in updating saliency maps after eye movements. They also suggest a hemispheric asymmetry in representing salience maps. TMS stimulation over the right, but not the left, AIPCx did not prevent inhibitory tagging during a fixation task, but prevented remapping of the inhibitory tag after either left or right saccades. Interestingly, as was the case in the case of the patients studied by Sapir et al. (2004), the absence of environmental IOR was a result of a slower detection RT at invalidly cued locations. There was no difference between Right Parietal cued, Right Parietal uncued, and Vertex cued targets. One possible explanation for this effect is that the cued location has a reduced saliency, and that TMS impaired the updating of the whole saliency map, resulting in lower saliency and longer reaction times for all possible target locations. Another possibility is that IOR occurs because the other target location becomes more salient, and that this benefit has been disrupted.

The TMS pulses were given 150 and 250 ms after the onset of the eye movement. This time interval was chosen based on previous research indicating that this is the critical time of spatial updating in an ERP study (Bellebaum, Hoffmann, & Daum, 2005), single unit recordings (Duhamel, Colby, & Goldberg, 1992; Gottlieb, Kusunoki, & Goldberg, 1998), and in previous studies using the double step saccade paradigm (Morris, Chambers, & Mattingley, 2007; van Donkelaar & Muri, 2002). Although, no other time points were tested, it is interesting to note that there was no effect of SOA (700 or 900 ms) in right parietal TMS group. This indicates that once the representation of the inhibitory tag is affected by TMS it cannot be regained.

Like the patient study of Sapir et al. (2004), but unlike previous patient (Duhamel, Goldberg, Fitzgibbon, Sirigu, & Grafman, 1992; Heide, Blankenburg, Zimmermann, & Kompf, 1995; Heide & Kompf, 1998) and TMS (Morris, Chambers, & Mattingley, 2007; van Donkelaar & Muri, 2002) studies employing the double step saccade paradigm, disruption of remapping occurred when saccades were directed toward the ipsilateral, as well as contralateral fields. In double step saccade studies, the deficit has been observed only when saccades were directed contralateral to the disrupted cortex. The current results suggest that parietal cortex is not only responsible for generating an extra-retinal signal for updating a salience map of the visual

field, but that the right parietal cortex is critical for maintaining a durable representation of that map across saccades. These results converge with another recent TMS study reporting that stimulation over the right, but not left hemisphere, at a more dorsal site over the IPS than the one used here (i.e. at the P3 electrode site), disrupted trans-saccadic working memory (Prime, Vesia, & Crawford, 2008).

One possibility is that different regions of the IPS may be responsible for generating the extra-retinal signal, and for maintaining a remapped representation. A recent TMS study, using an adaptation of the double step saccade paradigm, reported inaccurate second saccades after stimulation of a posterior area of the right IPCx, but not after TMS of a more rostral site that approximated the region stimulated in the current investigation (Morris, Chambers, & Mattingley, 2007). We might speculate that the more posterior part of IPCx is necessary for generating an extra-retinal signal, such that its inactivation only affects performance after contralateral saccades, while more anterior parts of the right IPCx maintain durable representation of the remapped salience map after a saccade in either direction. However, it is notable that the effect specific to the posterior IPCx site in the Morris, Chambers, and Mattingley (2007) experiment was an increase in variability in the second saccade endpoint, suggestive perhaps of a degraded representation of the location of the second target. There was no evidence that TMS of this site resulted in saccades to the retinal location of the second target, as might be expected if TMS prevented the generation of a critical extra-retinal signal. Further TMS experiments, over the more posterior site examined by Morris, Chambers, and Marringley (2007), using the kind of paradigm used here or the transaccadic memory paradigm employed by Prime, Vesia, and Crawford (2008) may seek further evidence for a dissociation of function along the IPCx that may contribute to updating and maintaining salience maps across saccades.

All previous TMS studies using the double step saccade paradigm have, to our knowledge, only stimulated the right parietal lobe (Morris, Chambers, & Mattingley, 2007; van Donkelaar & Muri, 2002), and further research is needed to clarify whether there may be hemispheric asymmetries in saccade remapping in this paradigm.

The patient research using the double step saccade paradigm, reported by Heide's lab (Heide, Blankenburg, Zimmermann, & Kompf, 1995), does suggest

that the left parietal lobe participates in saccade remapping. In a double step saccade task in which the first and second targets occurred in opposite visual fields, patients with left parietal lesions did show a deficit, although patients with right parietal lesions were more impaired. fMRI studies have not revealed hemispheric updating asymmetries (Medendorp, Goltz, Vilis, & Crawford, 2003; Merriam, Genovese, & Colby, 2003): representations of stimuli presented to the right hemisphere are remapped to the left hemisphere after left saccades, and representations of stimuli presented to the left hemisphere are remapped to the right hemisphere after right saccades.

While there is, then, evidence for a role of both hemispheres in saccade remapping, there is also evidence that their contributions may differ. Heide, Blankenburg, Zimmermann, and Kompf (1995) also tested parietal lesioned patients on a within hemifield double step saccade task, in which both targets were presented in the same visual field. In this task, in which no between hemispheric spatial updating was necessary, an asymmetric effect of right and left parietal lesions was observed. In addition to impaired performance on the between hemifield task, patients with a right parietal lesions also had an impairment in the within hemifield condition in the left visual field. An ERP study by Bellebaum, Hoffman, and Daum (2005) also provided evidence for different contributions of left and right hemisphere in saccade remapping. Bellebaum, Hoffman, and Daum (2005) reported a larger slow positive wave when remapping was required, starting between 150 and 200 ms after first saccade onset. Source analysis showed that whereas the source was restricted to the right PPC in trials with leftward first saccades, left and right PPC were both involved in rightward trials. However, the cue and target were always presented above or below central fixation, and since only horizontal saccades were studied, the field of the target became predictable. The right Parietal cortex might have a dominant role in representing the remapped location of objects at fixation that are initially represented in both hemispheres, and/ or predictable remapping. Future research will study salience remapping after vertical saccades (which require engagement of both hemisphere for their generation), and in which the location of the inhibitory tag has to be remapped within the same visual field.

In conclusion these observations converge with those made in neurological patients with chronic lesions of the dorsal IPS implicating this region as a neural substrate for maintaining the spatial constancy necessary

for a coherent continuity of visual experience. The also suggest a special role for the right parietal lobe, at least under the conditions of the current experiments. The observation that remapping was disrupted when saccades were executed toward the field ipsilateral as well as contralateral to cortical disruption suggest that parietal cortex is not involved simply in generating the corollary discharge that provides the extra-retinal signal needed for remapping the visual scene. Rather the results implicate parietal cortex as a neural substrate that uses the extraretinal signal to maintain a continuous salience map across saccades. This account is consistent with the observations of Khan et al. (2005) who showed that patients with optic ataxia due to unilateral IPS lesions made reaching errors to the updated location of a target, i.e. when an eye movement was made before reaching. They suggested that parietal lesions may not disrupt generation of the corollary discharge that updates the visual environment, but the transformation of the updated representation into an action plan.

Chapter 5: A TMS investigation in the remapping and maintenance of visual saliency maps after vertical eye movements[4]

In the previous chapter I studied the effect of parietal TMS on the remapping of visual saliency maps by exploiting the fact that observers are slower in detecting targets at a previously cued location, known as inhibition of return—(IOR (Posner, Rafal, Choate, & Vaughn, 1985), and that the location of this inhibitory tag is updated after a saccade (Danziger, Fendrich, & Rafal, 1997; Maylor & Hockey, 1985; Posner, Rafal, Choate, & Vaughn, 1985; Tipper, Grison, & Kessler, 2003). We employed dual pulse TMS to transiently disrupt the function of parietal cortex, and to compare the effects of right and left parietal TMS in order to test for a hemispheric asymmetry. The parietal stimulation site, over the rostral IPCx, corresponded to the area of lesion overlap in the patients studied by Sapir et al. (2004). The timing of the TMS pulses, 150 ms and 250 ms after saccade onset was based on the observations of Van Donkelaar and Muri (2002). We found that stimulation over the right but not the left parietal cortex resulted in a loss of the inhibitory tag. Interestingly, this was independent of the direction of the eye movement. This finding suggests that the right parietal cortex is not only involved in the remapping, but also in the maintenance of the remapped representation.

However, the cue and target were always presented above or below central fixation. Centrally presented stimuli are likely to be represented in both hemispheres (Pouget & Driver, 2000). In addition, since only horizontal saccades were studied, the field of the target was predictable. In the current study, we studied the remapping of saliency maps for laterally presented cues and targets after vertical saccades. The cue and targets were presented in either the left or right visual field. A vertical saccade, either upwards or downwards, was required between the cue and target presentation. In this way, the field of the cue and target was unpredictable, and were represented in one hemisphere. In order to be able to compare both studies, the timing of the TMS pulses, and TMS location were the same as in the previous chapter.

[4] A version of this chapter is being prepared for publication: Van Koningsbruggen, M.G. & Rafal, R.D. (in preparation). A TMS investigation in the remapping and maintenance of visual saliency maps after vertical eye movements

Methods

Participants

Fourteen subjects (10 Female) participated in this study. None of the subjects participated in the previous horizontal remapping study. Their mean age was 22 (SD = 3.12). Written informed consent was obtained from each participant. In addition, subjects filled in a safety screening questionnaire for TMS (Keel, Smith, & Wassermann, 2001). Ethics approval was obtained from the School of Psychology at the University of Wales, Bangor, United Kingdom. Participants received £10/hour for their participation.

Apparatus

A limbus tracker (ASL 210, Bedford, MA) was used to monitor vertical eye position at a rate of 1000 Hz. The eye movement recording device was calibrated by a three point calibration every fifteen trials. A chin and cheek rest were used to reduce head movements. The analogue output of the eye tracker was processed online to determine the onset of saccades. When the velocity of saccades reached 50°/s, a TTL pulse was sent to the stimulus PC, which recorded the saccadic latency and direction. Next, the stimulus PC send out two TTL pulses to the TMS stimulator to trigger two TMS pulses 150 and 250 ms after the onset of the eye movement. Presentation software (Neurobehavioural systems) was used for stimulus presentation and triggering of the TMS machine. Stimuli were presented on an Ilyama vision master pro 512 monitor (200 Hz). A response device connected to the gameport was used to record manual reaction times.

TMS stimulation

A magstim super rapid with a 70mm figure eight coil was used for the TMS stimulation. First, the hand area of the motor cortex was localized in the left hemisphere. Next, the motor threshold was determined, by finding the minimum amount of TMS stimulation that was required to elicit a visible hand twitch in the right hand. Stimulation was set to 120% of the MT. Each participant participated in three sessions, separated by at least one week. TMS was given either over the right, or left parietal cortex, or the vertex. The location of the parietal TMS was chosen relative to the vertex; 3 cm lateral (either to the or right) and 4 cm posterior. A similar criterion for parietal cortex stimulation has been used in previous investigations (Chang & Ro, 2007;

Kapoula, Yang, Coubard, Daunys, & Orssaud, 2004, 2005; van Donkelaar & Muri, 2002)

Procedure

The experiment was conducted in a dimly lit room. The distance between the monitor and the subjects was 57 cm. The stimulus display consisted of three small white fixation points (0.1 x 0.1 degree) on a black background, one presented in the centre, and the other two presented 10 above or below the centre. A white unfilled box (3 x 3 degree) was presented 5 degree to the right and left of each fixation point. The six boxes and the two peripheral fixation points were presented throughout the experiment.

Each trial began with the onset of a central fixation point. If subjects did not look at the fixation point after 250 ms, the trial was aborted and an error sound was presented. After 1000 ms, a non-informative cue was presented in one of the central boxes. The cue was a thickening of the line for 200 ms. An upwards or downwards pointing arrow (1degree) was presented at central fixation 300 ms after cue offset. The arrow was presented for 200 ms. Subjects were instructed to move their eyes as fast as possible in the direction of the arrow towards either the higher or lower peripheral fixation point. If subjects made a saccade in the wrong direction, or did not make a saccade within 500 ms, the trial was aborted and an error sound was presented. Following the eye movement, Subjects were required to keep fixation at the indicated peripheral fixation point. After either 700, or 900 ms, a target was presented either above or below the central fixation point. The target was presented for 1000 ms, or until subject responded by pressing a button with their right index finger. See Figure 5.1 for a graphical illustration of the trial structure. Following a training session of 20 trials, a total of 176 trials were presented, with 10% catch trials. Catch trials were exactly the same as the other trials (i.e. including TMS stimulation), except that no target was presented.

All subjects participated in three sessions: left or right parietal TMS, and one with TMS stimulation over the vertex. Each session took around 60 minutes, and the order of sessions was counterbalanced across subjects. The inter trial interval was set to 4000 ms, to make sure that the time between two successive TMS trains was never shorter than 5000 ms (Wassermann, 1998).

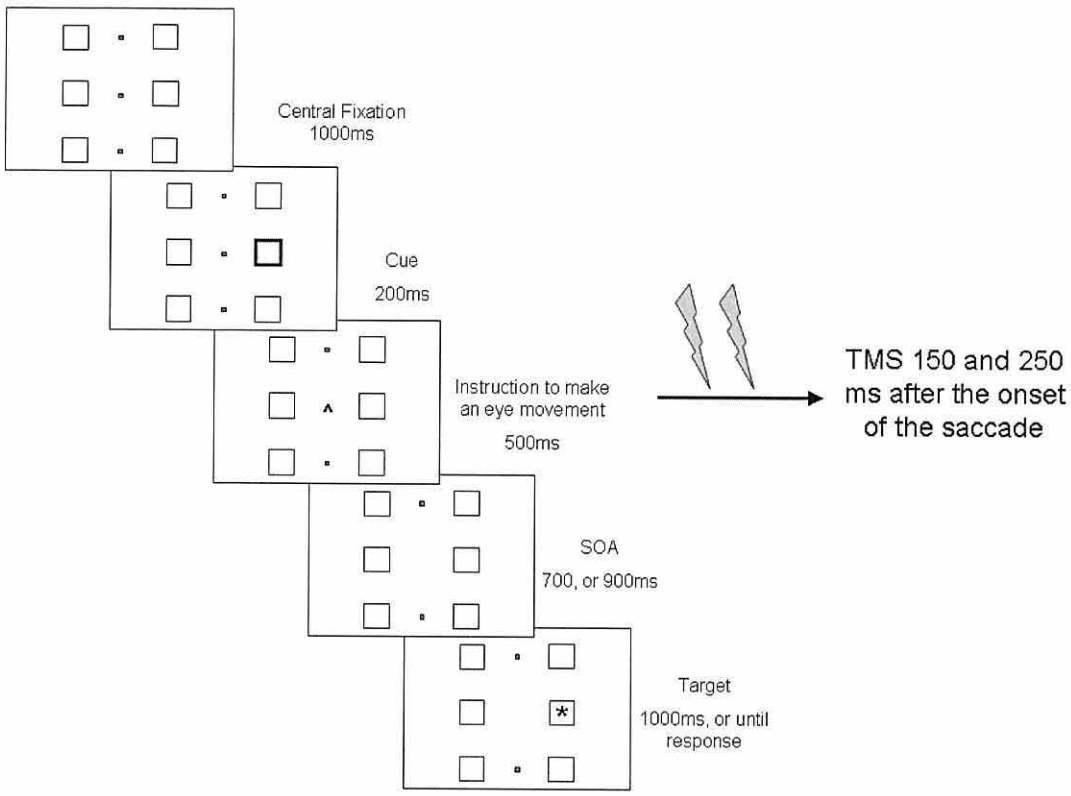

Figure 5.1 *Trial lay-out and timing of the TMS stimulation*

Results

Saccadic Reaction Times

Saccadic Reaction Times were analyzed with a repeated measures analysis of variance (ANOVA) with TMS (Vertex, or Right/Left Parietal) and Saccade Direction (Up or Down) as factors. There was no significant effect of TMS condition on the saccadic latencies, $F(2,26) < 1$. The main effect of saccade direction was significant, $F(1,13) = 14.33$, $p < 0.01$, $n = 0.52$. Saccades directed upwards were faster (297 ms) than downward saccades (316 ms). The interaction between TMS and Saccade Direction was not significant, $F(2,26) = 1.14$, $p=0.34$, $n = 0.08$.

Errors

There were two different types of errors subjects could make: an eye movement error, or a manual key press error. A failure to keep fixation at the centre, a blink, an eye movement which was not in the right direction or was to slow (>500 ms), or a failure to keep fixation at the peripheral fixation point after a successful eye movement were all classified as eye movement errors. We used such a strict criterion since TMS stimulation was given relative to the saccade onset. Subject made an average of 4.5% eye movement errors, which did not differ between TMS conditions, $F(2,26) = 2.93$, $p = 0.07$, $n = 0.18$, Saccade Direction, $F(1,13) = 2.634$, $p = 0.13$, $n = 0.17$, or the interaction between these two ($F<1$). All trials with a saccade error were aborted. Subjects made a very small number of manual key press errors (0.9%), and were therefore not further analyzed. Catch trials were not further analyzed.

Manual Reaction Times

Only trials in which no predictive responses were made (faster than 90 ms) or were too slow (slower than 800ms) were analyzed. In addition, outliers (+/- 3 sd) were removed (2.1 %). Reaction Times were subjected to 3 (TMS site) * 2 (Target field) * 2 (Cue field) * 2 (Eye Movement Direction * 2 (SOA) repeated measures MANOVA. Multivariate test statistics were used since the assumption of sphericity was violated. (Field, 2005). There was a significant main effect of Target location on reaction times, $F(1,13) = 26.16$, $p < 0.01$, $\square_p^2 = 0.67$. Reaction Times for right targets were shorter (243 ms) than for left targets (252 ms). There was a significant interaction between Target location and Cue location, $F(1,13) = 19.75$, $p < 0.01$, $\square_p^2 = 0.60$. More interestingly, the

interaction between TMS * Target * Cue * SOA was significant. $F(2,12) = 6.13$, $p < 0.05$, $\square_p^2 = 0.51$. To break down this interaction, three separate ANOVAs for each TMS condition were performed. There were no other significant effects (see table 5.1).

Table 5.1 *Values of the 3 (TMS) * 2 (Target) * 2 (Cue) * 2 (Eye Movement Direction * 2 (SOA) repeated measures MANOVA with manual reaction times as the dependent variable.*

Factor	***df***	***F***	***Sig.***		***Partial Eta Squared***
TMS	2,12	0.76	0.49		0.11
Target	1,13	26.16	0.00	**	0.67
Cue	1,13	3.03	0.11		0.19
SacDirection	1,13	0.10	0.75		0.01
SOA	1,13	3.92	0.07		0.23
TMS * Target	2,12	3.75	0.05		0.38
TMS * Cue	2,12	0.53	0.60		0.08
Target * Cue	1,13	19.75	0.00	**	0.60
TMS * Target * Cue	2,12	1.21	0.33		0.17
TMS * SacDirection	2,12	0.24	0.79		0.04
Target * SacDirection	1,13	4.85	0.05		0.27
TMS * Target * SacDirection	2,12	0.90	0.43		0.13
Cue * SacDirection	1,13	0.00	0.95		0.00
TMS * Cue * SacDirection	2,12	0.01	0.93		0.01
Target * Cue * SacDirection	1,13	0.01	0.94		0.00
TMS * Target * Cue * SacDirection	2,12	1.84	0.20		0.24
TMS * SOA	2,12	0.33	0.73		0.05
Target * SOA	1,13	0.36	0.56		0.03
TMS * Target * SOA	2,12	0.61	0.56		0.09
Cue * SOA	1,13	0.01	0.92		0.00
TMS * Cue * SOA	2,12	0.03	0.97		0.00
Target * Cue * SOA	1,13	0.12	0.73		0.01
TMS * Target * Cue * SOA	2,12	6.13	0.01	**	0.51
SacDirection * SOA	1,13	1.79	0.20		0.12
TMS * SacDirection * SOA	2,12	0.07	0.93		0.01
Target * SacDirection * SOA	1,13	0.17	0.69		0.01
TMS * Target * SacDirection * SOA	2,12	0.01	0.99		0.00
Cue * SacDirection * SOA	1,13	1.12	0.31		0.08
TMS * Cue * SacDirection * SOA	2,12	1.89	0.19		0.24
Target * Cue * SacDirection * SOA	1,13	2.53	0.14		0.16
TMS * Target * Cue * SacDirection * SOA	2,12	3.51	0.06		0.37

Effects of Right Parietal TMS

The effect of Right Parietal TMS on manual rt was investigated with a 2 (Target field) * 2 (Cue field) * 2 (Eye Movement Direction * 2 (SOA) repeated measures ANOVA. The main effect of Target location was significant, $F(1,13) = 21.19$, $p < 0.01$, $\square_p^2=0.62$, which was caused by the fact that subjects were faster to respond to targets in the right (246 ms) than in the left visual field (260 ms). There were no other significant effects, including no significant interaction between Cue location and Target location (all $F<1$). That means that there was no significant IOR after Right Parietal TMS (see Figure 5.2).

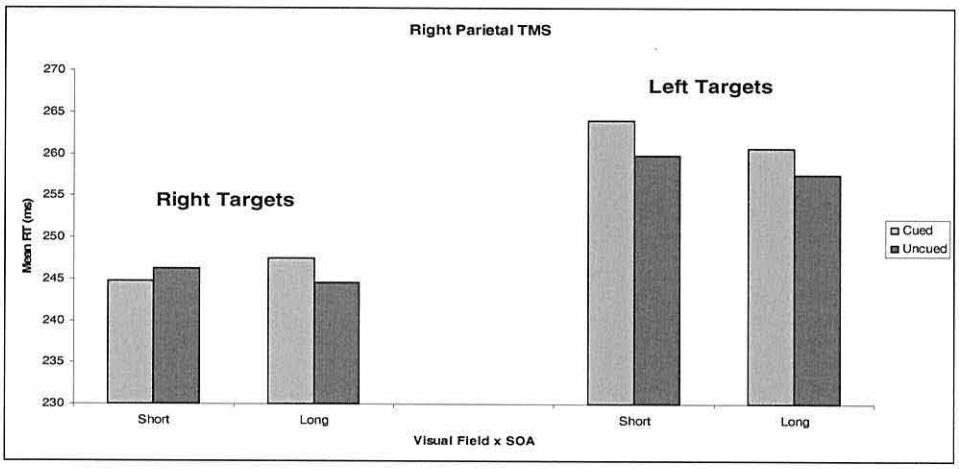

Figure 5.2 *Manual RTs during Right Parietal TMS*

Effects of Left Parietal TMS

The same ANOVA was conducted for Left Parietal TMS. The main effect of Target location was significant, F (1,13) = 21.19, $p < 0.01$, $\square_p^2$=0.62, since responses were faster for right (236 ms) than left targets (244 ms). There was a significant interaction between Target location and Cue location, F (1,13) = 6.04, $p < 0.05$, $\square_p^2 = 0.32$. The interaction between SOA and Target and Cue location was also significant, F (1,13) = 8.66, $p < 0.05$, $\square_p^2 = 0.40$ (see Figure 5.3). To investigate this interaction tested whether there was a significant IOR in each visual field for each SOA (corrected for Bonferroni). There was a significant IOR for targets in the left visual field, but only for the short SOA (IOR = 23 ms, $p < 0.01$).

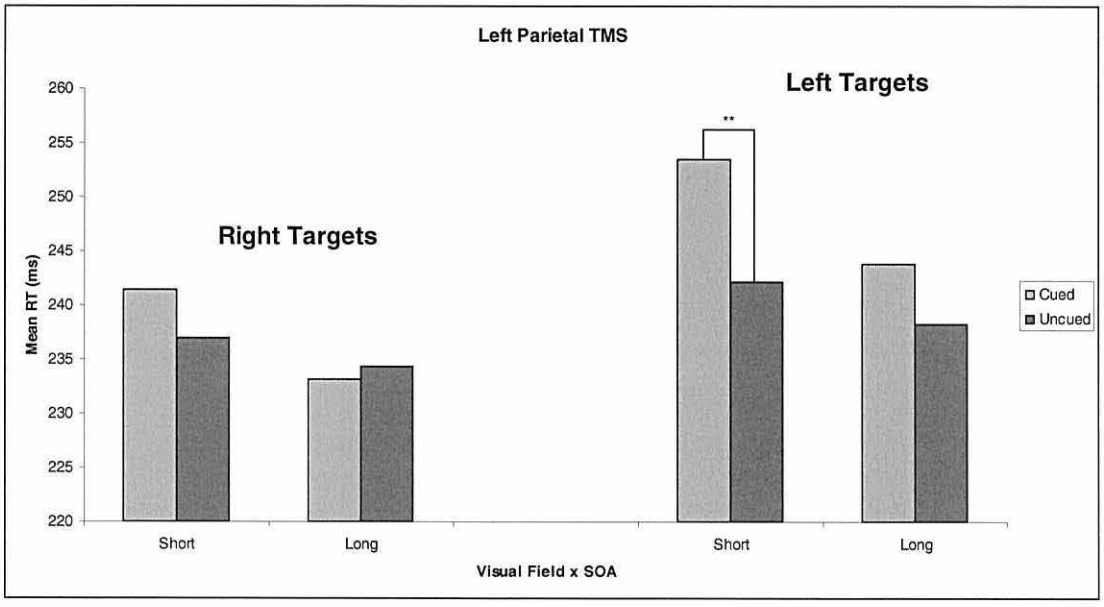

Figure 5.3 *Manual RTs during Left Parietal TMS*

Effects of Vertex TMS

The main effect of Target location was significant, $F(1,13) = 5.37$, $p < 0.05$, $\square_p^2 = 0.29$, since responses were faster for right (248 ms) than left targets (253 ms). There was a significant interaction between Target location and Cue location, $F(1,13) = 11.02$, $p < 0.01$, $\square_p^2 = 0.46$. To investigate this interaction tested whether there was a significant IOR in each visual field (corrected for Bonferroni). There was a significant IOR for targets in both the left (IOR = 10 ms) and right visual field (IOR = 7 ms). No other effects were significant (see Figure 4).

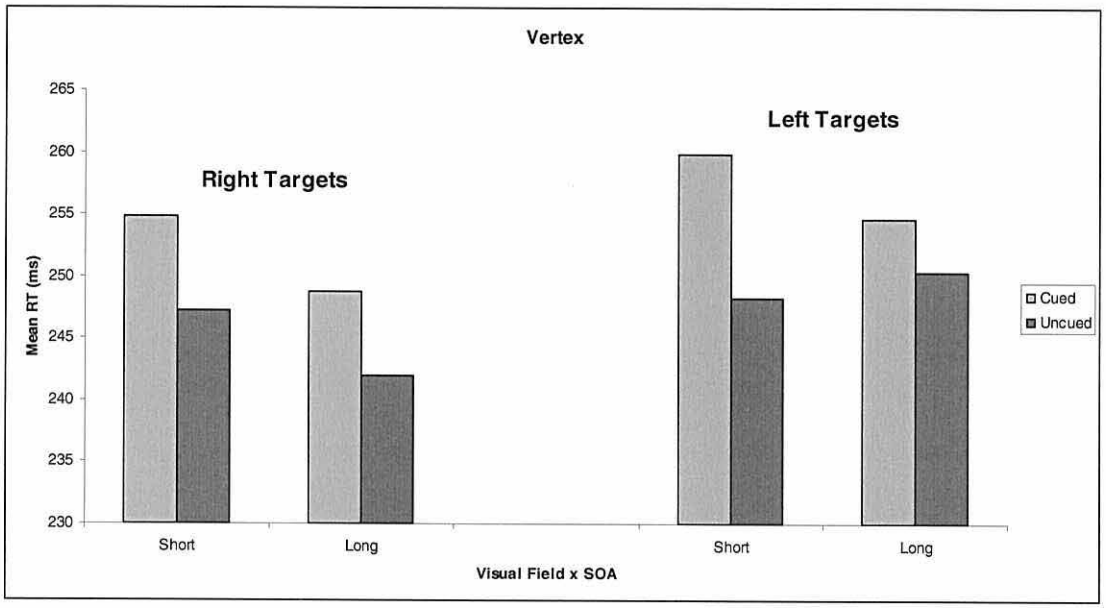

Figure 5.4 *Manual RTs during Vertex TMS*

Discussion

The results of the present experiment confirmed that the right parietal cortex is involved in the remapping of visual saliency maps. Interestingly, TMS stimulation over the right Parietal cortex disrupted the remapping of the inhibitory tag independent of the visual field in which the tag was generated. However, in contrast to the previous study, the TMS over the left parietal cortex also impaired remapping, but only when the tag was generated in the right visual field. When the tag was generated in the left visual field and TMS was applied over the left parietal cortex, there was only a significant IOR for the short SOA. IOR during the long SOA was no longer significant. This is likely to the caused by the fact that the strength of the inhibitory tag decays over time. It is unlikely that TMS causes this effect, since one would expect an immediate effect of TMS (i.e. on the short SOA). The same pattern of results was observed during Vertex TMS. Although not significant, the size of the IOR was smaller for the long SOA compared to the short SOA, especially in the left visual field. This further supports the idea that the strength of the inhibitory tag decays over time.

The difference in results between this study and the previous study could have occurred because of two task differences. First of all subjects were required to make vertical saccades. Vertical saccades are considered to be generated by both hemispheres (Bender, 1980). This could result in an efference copy being sent to both hemispheres, and leading to remapping of the visual field in both hemispheres. However, that does not explain why left parietal TMS only abolishes inhibitory tags in the right visual field. Another difference is that the location of the cue and target was more lateralized in the current study, instead of presented centrally in the previous study. The right PPC might be especially involved in the remapping of centrally presented inhibitory tags.

I hypothesize that the finding that the TMS over the left parietal cortex disrupts remapping contralesionally, whereas TMS over the right parietal cortex has a bilateral effect can be explained by the fact that two TMS pulses were given, and that each pulse might have disrupted a different process. TMS stimulation was given 150 and 250 ms after the onset of the saccade. It is possible that the first pulse would have disrupted the remapping process, whereas the second pulse would have disrupted the representation of the inhibitory tag. In

this case, contralesional inhibitory tags could not be remapped due to TMS stimulation. The first TMS pulse would disrupt right inhibitory tags during left parietal TMS, whereas it would disrupt left inhibitory tags for right parietal TMS. However, ipsilesional targets could be remapped, but we assume that the right parietal cortex is critical for maintaining a durable representation of that map across saccades, and the second TMS pulse would disrupt this representation. Future studies could test this hypothesis with dual pulse TMS with a shorter inter pulse interval (40ms) (Kalla, Muggleton, Juan, Cowey, & Walsh, 2008; Muggleton, Juan, Cowey, & Walsh, 2003), given at different times after the saccade onset.

There was a significant difference between upwards and downward eye movements. Saccades directed upwards were 19 ms faster than downwards directed saccades. However, the TMS was given relative to the onset of the saccades, since we were interested in studying the updating of the inhibitory tag, and the critical interval seems to be after the eye movement. In addition, subjects were faster to respond to targets on the right than on the left. This effect was present in all the TMS conditions, i.e. it was not influenced by the location of the TMS. It therefore reflects a general tendency of subjects being faster for right targets. This could be the result of the fact that subjects responded with their right index finger.

During Left parietal TMS there was only a significant IOR for targets in the left visual field for the short SOA, but not the long SOA. To determine whether this was a delayed effect of TMS, or whether it was a result of the normal time course of IOR, a paired t-test was performed comparing the size of IOR for left targets for the long SOA for vertex and left parietal TMS. There was no significant difference ($p = 0.77$), indicating that it unlikely caused by TMS.

Future experiments could focus on the transfer of saliency maps between hemispheres. So far, the targets and cues were presented centrally which is represented in both hemispheres (Pouget & Driver, 2000), or lateralized but the with the need to be updated within the same visual field. Berman, Heiserm Saunders, and Colby (2005) studied the updating of motor vectors between hemispheres. They trained three monkeys on a double step saccade. Next, the corpus collosum and anterior commissure, which is the direct path between the two cortical hemispheres, of two of three monkeys were surgically dissected. The performance of the split-brain monkeys was not impaired for within hemifield double step saccades. However, they were impaired on double step

saccades that required updating across hemifields. Heiser, Berman, Saunders, and Colby (2005) recorded from LIP neurons in the same monkeys. They found that neuronal signals were delayed and decreased in amplitude when across hemifield updating was required. These findings indicate that the direct cortico-cortical link is the main route for updating between hemispheres. It would be interested to study a between hemifield condition with the current task, to determine whether similar mechanisms occur in humans for visual saliency.

Posner and Cohen (1984)hypothesized that IOR would make visual searches more efficient by favouring attention towards new locations. For this to be useful in the real world, IOR should not only occur for static objects, but also for earlier attended moving objects. Tipper (1991) showed when a previously cued object moves, the inhibition moves with the object. More interestingly, Tipper et al. (1997) also studied split-brain patients on this paradigm. They discovered that those patients only have object based IOR when the object moves in the same hemisphere. However, when the objects moved between the hemispheres, the object based IOR was lost, suggestion that object based IOR requires information to be transferred between the hemispheres, but it does not specify which cortical site is involved. Vivas, Humphreys, and Fuentes (2008) studied five patient with a lesion to the parietal cortex. The lesion was more or less in the same area as the Sapir et al. (2004) study. They found object based IOR was lost when the cue box appeared in the ipsilesional field, and moved towards the contralesional field. It would be interesting to repeat the same experiment in a group of healthy participants with TMS over the location used in the current study. In this way, it will be possible to establish whether the same parietal area is not only involved in spatial updating, but whether it is also involved in updating the visual saliency map without an efference copy. In addition, one could study whether right and left parietal cortex have the same role.

Chapter 6: General Discussion

The experiments reported in this thesis aimed at investigating how voluntary control is exerted through the modulation of neural circuitry mediating reflexive behaviours. Eye movements were used as a model system to study how two primitive collicular reflexes, the fixation reflex and inhibition of return are integrated, for use in visual cognition. I observed that automaticity and control independently influence the FOE (Chapter 2), and that dopamine deficiency due to Parkinson's disease impairs voluntary control of the FOE (Chapter 3). In Chapter 4 and 5, I asked how the inhibitory tags, which are used by visual cognition to aid visual search, are remapped and represented by the parietal cortex. The findings suggest a different role for the right and left parietal cortex. The reported findings provide further support for the theoretical models which were discussed in the introduction, and therefore need to be considered in an evolutionary framework.

Contrary to the evolutionary frameworks as developed Easton (1972) and Rozin (1976), more recent theoretical models have proposed that automatic and reflexive behaviours are distinct from voluntarily control. However, there has been a renewed interest in a theoretical framework that considers reflexes to be the building blocks of more complex behaviour including visual cognition. Sumner and Husain (2008) have recently argued that automatic motor behaviour forms an 'intrinsic part' of all behaviour. In addition, they reviewed several recent studies, and provide further evidence that automatic behaviours are flexible, i.e. voluntary control can access them. For example, Ogment, Breitmeyer, Todd, and Mardon (2006) tested the effects of subliminal primes on subsequent responses. They argued that if a cue is presented very briefly so it becomes invisible, the effects of a cue would be automatic. In their experiment, an arrow was very briefly presented, and was immediately masked. After the mask another arrow was presented until the subjects responded with a key press in the direction of the arrow. They showed that reaction times were faster for compatible cues than for incompatible cues, which they argue provides evidence that non-conscious stimuli can automatically activate motor responses. Interestingly, different studies have found evidence that the effect of this non-conscious priming is dependent on the current task set, i.e. they are processed more elaborately when they are task related (van Gaal, Ridderinkhof, Fahrenfort, Scholte, & Lamme, 2008), or when attention is directed towards it (Sumner, Tsai, Yu, & Nachev, 2006).

This last chapter of the thesis includes a short discussion of the results, but it will mainly discuss future research directions.

Voluntary Control over the Fixation Offset Reflex

The reduction in saccade latency when the fixation point is removed (fixation offset effect – FOE) reflects the degree to which fixation neurons are under influence by a stimulus at fixation. Strategic manipulations of oculomotor readiness that bring these neurons under endogenous control reduce the magnitude of the FOE. I showed that, the FOE was smaller for antisaccades than for prosaccades, which is the result of strategic modulation. More interestingly, the effects of trace conditioning were similar for prosaccades and antisaccades. This is a clear demonstration that strategic and unconscious priming effects both independently modulate oculomotor reflexes.

In chapter 3, I investigated the ability of patients with Parkinson's disease to voluntarily control oculomotor reflexes. I observed that there was no significant difference in size of the FOE between the pro- and anti-saccade task for PD patients, which indicates that the basal ganglia mediates strategic control of oculomotor reflexes.

Implications for other oculomotor reflexes

In the introduction, I discussed Munoz and Fecteau's (2002) dynamic interactions model in order to explain how competition between activated saccade vectors is resolved in the intermediate layers of the superior colliculus. I reviewed arguments that there are two classes of neurons in the SC, and how collicular SN and FN mutually inhibit each other. However, the distinction between SN and FN is rather arbitrary. It could be argued that both types of neurons encode saccades, but differ only in the amplitude of the saccade they generate due to their different location on the motor map. Often several different stimuli induce an orienting response, but only one saccade can be generated. In other words, there is a constant competition between different saccade plans (Munoz & Fecteau, 2002).

Dorris, Olivier and Munoz (2007) examined whether suddenly appearing visual distracters interacted with the execution of saccades. In their experiment, monkeys were trained on saccades towards a target of which both the direction and timing were predictable. A visual distracter was presented while

the monkey was preparing a saccade, i.e. before the target onset. The location of the visual distracter was systematically varied. The activity of SC intermediate layer neurons was measured in two monkeys. The results showed that the effect of the distracter on the neuronal activity was dependent on the location relative to the target. Distracters presented at a remote location resulted in a suppression of the preparatory activity, whereas if the distracter was presented in the vicinity of the upcoming predictable target the neuronal consequences were different. Recall that the monkey was already preparing an eye movement to the target, and the activity level of the SN neurons in that location was therefore endogenously increased. The presentation of a distracter close to the target often led to an erroneous saccade to the distracter, as a result of excitation of nearby neurons. This finding is a further demonstration that there is a competitive integration throughout the whole SC motor map.

A related phenomena is referred to as the remote distracter effect (RDE) (Findlay, 1983; Levy-Schoen, 1969). The basic finding is that the latencies of saccades towards a target are longer when a distracter is presented in the opposite visual field, relative to when no distracter is presented. There is converging evidence that this is also a collicular reflex. For example, Rafal, Smith, Krantz, Cohen, and Brennan (1990) demonstrated that when a distracter is presented in the blind field of hemianopic patients, it still elicits a RD effect. In addition, Sumner, Adamjee, and Mollon (2002) demonstrated that s-cone stimuli, which are invisible to the retinotectal pathway, do not elicit a RDE.

Honda (2005) examined whether the FOE and RDE interact with each other. The author orthogonally manipulated both the presence (50%) of a distracter in the opposite field, and the fixation point condition (overlap vs. offset). Interestingly, there was only a reliable RDE for fixation point offset trials, indicating that both reflexes interact. It would be interesting to study whether RDE can be influenced by voluntary control. Another experiment could investigate whether similar effects of the foreperiod exist for RDE and FOE.

Cortical control of the FOE

In chapter 3, I observed that the basal ganglia are essential for the voluntary control of oculomotor reflexes. As discussed in chapter 3, there is ample evidence that the oculomotor cortex is involved in controlling oculomotor reflexes. In particular, the FEF, and dlPFC have been implicated. Future

research will employ TMS to study the involvement of those areas. We are planning a study in which repetitive TMS will be applied over either the FEF, or dlPF while the FOE is measured for both pro-saccades and anti-saccades.

Los's Trace Conditioning Model

Los's trace conditioning model offers a convincing single process explanation of the asymmetrical sequential effects. His model is based upon the trace conditioning literature, and assumes that similar processes give rise to the asymmetrical sequential effects. It has recently been demonstrated that the hippocampi are critically involved in trace conditioning . Clark and Squire (1998) showed that amnesic patients with bi-lateral hippocampi damage have normal classical conditioning. However, they no longer show trace-conditioning. I recently tested a patient with bilateral damage to the hippocampi, rendering her completely amnesic. She was tested on a manual foreperiod task. Interestingly, the patient we tested showed a normal FP period effect. In addition, like healthy controls, there was an asymmetrical sequential effect of the foreperiod of the previous trial. These results are inconsistent with Los's 'single process' trace conditioning account for preparatory effects across and aging foreperiod. In a recent study examining the effects of TMS on dorsolateral prefrontal cortex, Vallessi, Shallice, and Walsh (2007) observed that virtual lesions of the dorsolateral prefrontal cortex with TMS result in 'symmetrical' sequential priming effects: i.e. effects of the foreperiod of the preceding trial were observed at long foreperiods as well as short foreperiods. These results, and my preliminary observations in a patient with a bi-lateral hippocampal lesion, support a dual process model in which the lack of priming effects later in the foreperiod is the result of strategic expectancy effects.

Remapping of visual saliency maps

In Chapter 4 and 5, I investigated the effect of TMS over the anterior intra-parietal cortex employing a task that used inhibition of return as a marker for saccadic updating of visual salience maps. A hemispheric asymmetry in the remapping and encoding of inhibitory tags was observed: the right parietal cortex resulted in a loss of the inhibitory tags in both visual fields (Chapter 4 & 5), whereas TMS over the left parietal cortex had no effect (Chapter 4). By contrast, TMS over the left parietal cortex had an effect in Chapter 5, but only on contra-lateral inhibitory tags. In the discussion of chapter 5, I proposed the following explanation for this difference: each hemisphere is only involved in the remapping of the contralateral visual field, and that this remapping is likely to be completed before the second TMS pulse. In addition to the remapping, the right parietal cortex integrates this remapped inhibitory tag into a saliency map, i.e. it maintains a durable representation of the saliency map across saccades. The second TMS pulse disrupts this representation. Time resolved TMS can be employed to directly test this model. Specifically, it is predicted that earlier TMS pulses (<= 150 ms after saccade initiation) will result in a remapping deficit only when saccades are made to the field contralateral to stimulation.

Schluppeck, Glimcher, and Heeger (2005) investigated the organization of the IPS in an fMRI experiment. They showed that the IPS have different topographically organized regions of the contra-lateral field. In a recent study, Konen and Kastner (2008) identified a total of six different IPS regions, each with a topographically representation of the contralateral field. They established that each region preferentially responded to different types of eye movements (i.e. saccades, smooth pursuit), and or visual motion. Thus, the IPS seems to consist of different specialized sub regions. In chapter 4 and 5, I used skull landmarks to determine the TMS location. It is being planned to use fMRI guided TMS, to determine the effect of TMS on those different topographically organized areas.

However, in order to be able to better relate the TMS results to neurophysiological studies, spatial remapping across hemifields needs to be investigated. For example, similar to the paradigm used in Chapter 4, two boxes could be presented above and below a central fixation point. However, now the subjects would be instructed to fixate on a left or right peripheral fixation point. After the cue, they are required to make an eye movement across the vertical meridian to the peripheral fixation point in the opposite

hemisphere. In such a paradigm, the cue and target are in different hemifields, allowing the investigation of across hemifield updating.

Remapping of sensory consequences

One influential contemporary account of visual awareness proposes that awareness is not a state we are in, but something we do. It specifies that visual awareness arises from "exercising a mastery of sensorimotor contingencies": that is, learning to predict the sensory consequences of action (O'Regan & Noe, 2001). Studies from Colby's laboratory, reviewed in Chapter 4, have indeed shown that LIP neurons respond as if they are predicting what a monkey will see after a saccade. The O'Regan and Noe account is consistent with neuropsychological observations. As noted in Chapter 4, patients with unilateral parietal lesions to not make a saccade to the retinotopic location of the second target in a double step saccade task (as younger infants do) – they make no second saccade at all, as if the second target was not seen, or they do not know where the target was. Patients with Balint's syndrome due to bilateral parietal lesions do not report that objects across the visual scene jerk when they move their eyes (as happens when you passively move the eyeball). Rather, objects disappear. The patients have no awareness of space and can only be aware of one object at a time (simultaneous agnosia) (Rafal, 2001).

Bompas and O'Regan (2006a) reported direct evidence supporting the O'Regan and Noe (2001) account of visual awareness in an experiment that demonstrated saccadic colour adaptation. Subjects wore special spectacles that had yellow colour filters in right half of each glass, and a blue colour filter in the left half of the glass. In this way, they induced an 'artificial coupling' between saccades and colour perception, i.e. an eye movement to the left visual field would make the world appear blue. After an adaptation period of 40 minutes, white patches were presented in different locations of the visual field. The colour perception of the white patches was dependent on the direction of the eye movement. Eye movements to the left caused the white patches look more yellow, whereas they appeared to be bluer for rightward eye movements. In a subsequent study, they demonstrated that when subjects are tested after the adaptation phase, but are required to maintain gaze at a central location, no colour adaptation occurred (Bompas & O'Regan, 2006b). Further more, they also demonstrated that the location of the test patch in the visual field does not influence colour perception; only the saccade direction influences perception. The authors argue that sensorimotor transformations influence the perception of colours, and speculate that it might operate via the same cortical areas as prism adaptation. It would be interesting to test whether TMS over the same parietal areas as in Chapter 4 and 5

would abolish saccadic colour adaptation.

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Appendix – A *Data from individual participants Chapter 2*

Table A.1. Mean Pro-saccadic latencies (Experiment 1)

	Short				Long			
Foreperiod Previous Trial	**Short**		**Long**		**Short**		**Long**	
Subject ID	**Fixation Offset**	**Fixation Overlap**	**Fixation Offset**	**Fixation Overlap**	**Fixation Offset**	**Fixation Overlap**	**Fixation Offset**	**Fixation Overlap**
1	283	339	296.14	371.07	287.2	370.98	304.77	355.11
2	264.13	287.13	281.13	307.04	238.45	285.47	236.77	295.95
3	256.84	267.72	262.38	296.44	251.28	282.67	253.72	293.95
4	238.1	260.62	245.82	301.67	212.1	236.26	210.25	222.83
5	318.16	433.07	357.67	456.23	288.5	387.15	280.98	382.72
6	296.69	357.22	360.65	406.64	290.35	333.17	302.39	345.58
7	302.47	371.23	329.62	410.38	274.89	314.47	267.45	320.19
8	299.79	319.3	349.6	374.39	281.09	317.98	281.52	329.75
9	280.36	300.09	303.2	351.31	274.5	287.02	282.02	301.41
10	275.07	284.05	277.91	313.32	247.63	253.43	241.57	269.7
11	305.11	325.44	347.23	378.67	291.42	318.58	296.19	322.57
12	237.94	267.17	243.49	299.7	234.73	265.48	244.27	264
13	321.33	414.17	305.98	423.79	272.17	426.84	266.8	417.02
14	271.77	287.11	286.6	328.38	295.29	316.13	301.83	328.03
15	316.66	358.25	345.43	414.74	293.23	351.95	295.1	378.58

Table A.2. Mean Pro-saccadic error (Experiment 1)

Foreperiod Current Trial	Short				Long			
Foreperiod Previous Trial	Short		Long		Short		Long	
Subject ID	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap
1	4	6	8	2	13	6	13	10
2	0	2	2	2	0	0	4	2
3	2	0	2	2	0	0	8	6
4	6	4	15	6	4	15	15	17
5	2	4	2	6	2	8	8	4
6	2	2	4	0	6	2	0	6
7	2	4	2	2	0	4	4	2
8	2	0	2	0	0	2	0	0
9	2	0	2	6	6	6	4	4
10	2	6	2	6	2	0	0	2
11	2	0	6	8	6	0	0	2
12	2	0	2	0	2	2	8	8
13	4	2	2	10	10	0	2	13
14	6	4	6	2	8	13	10	8
15	4	15	2	8	8	10	13	4

Table A.3. Mean Anti-saccadic latencies (Experiment 2)

Foreperiod Current Trial	Short				Long			
Foreperiod Previous Trial	Short		Long		Short		Long	
Subject ID	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap
1	328.31	341.74	345.82	371.53	309	316.33	308.45	335.03
2	315.45	329.16	366.64	378.24	297.18	316.08	309.57	319.3
3	312.45	340.02	340.55	351.61	296.45	306.91	301.9	303.05
4	352.02	368.34	364.84	395.07	327.95	323.8	333.98	334.27
5	369.7	413.97	396.41	473.46	348.11	390	336.93	416.1
6	406.29	410.07	425.19	443.42	366.16	359.43	372.98	387.52
7	338.37	373.22	379.33	400.5	321.07	328.54	320.2	338.59
8	339.17	355.59	362.04	400.02	300.87	319.63	321.87	332.61
9	360.02	400.85	376.6	423.98	335.61	429.21	337.11	404.75
10	366.96	368.63	393.73	387.22	345.42	362.67	359.54	373.77
11	397.11	381.72	398.88	412.13	372.76	370.84	382.78	384.98
12	423.71	440.58	448.81	492.13	449.56	498.46	436.97	472.48
13	333.24	353.32	358.93	397.98	311.49	333.91	305.93	341.89
14	300.36	304.14	314.62	329.22	259.59	287.49	279.98	293.93
15	311.38	320.18	344.87	382.3	314.25	312.39	321.98	329.9
16	328.94	340.24	360.28	384.46	316.24	331.51	313.68	320.28
17	316.15	327.86	358.21	379.37	315.89	316.6	313.57	330.3
18	327.64	331.85	344.42	366.51	298.17	323.14	315.05	318.17
19	351.65	352.86	373.55	390.02	313.02	322.52	338.93	349.63
20	276.95	295.95	310.92	349.23	269.46	275.9	291.47	287.84
21	370.8	374.7	380.28	404.02	338.62	344.98	346.1	354.24

Table A.4. Mean Anti-saccadic errors (Experiment 2)

Foreperiod Current Trial	Short				Long			
Foreperiod Previous Trial	Short		Long		Short		Long	
Subject ID	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap	Fixation Offset	Fixation Overlap
1	0.18	0.04	0.06	0.02	0.13	0	0.04	0.04
2	0.02	0.02	0	0	0.08	0.02	0.04	0.08
3	0.06	0.04	0.06	0.04	0.1	0.04	0.13	0.02
4	0.04	0	0.02	0.02	0.06	0	0.08	0.04
5	0.13	0.13	0.1	0.06	0.06	0.04	0.08	0.06
6	0.02	0.02	0.04	0.02	0	0	0	0.06
7	0.02	0.02	0.02	0.04	0.1	0.1	0.04	0
8	0	0.02	0	0.02	0	0.02	0.02	0
9	0	0.04	0	0.04	0	0.02	0.02	0
10	0	0.04	0	0	0.02	0.06	0.02	0
11	0	0	0.02	0	0.02	0.02	0	0
12	0.08	0.08	0.1	0.04	0	0.06	0.17	0.06
13	0.02	0	0.02	0	0	0.02	0.02	0.02
14	0.02	0.02	0.02	0	0.02	0	0.04	0.02
15	0.02	0	0.02	0	0.04	0	0.02	0.06
16	0.04	0.04	0.09	0	0.06	0.02	0.02	0.1
17	0.04	0.04	0.06	0.02	0.02	0.02	0.06	0.13
18	0.02	0.06	0.02	0.02	0.09	0.02	0	0.04
19	0.02	0.02	0.06	0.02	0.02	0	0.02	0.02
20	0.08	0.02	0.09	0	0.13	0.04	0.02	0.17
21	0.02	0	0	0	0	0	0.06	0.02

Appendix – B *Data from individual participants Chapter 3*

Table B.1. Mean Pro-saccadic latencies, amplitudes, and error rates of healthy control subjects

Subject ID	Pro Offset RT	Pro Overlap RT	Pro Offset Amplitude	Pro Overlap Amplitude	Pro Offset Error	Pro Overlap Error
1	259	284	10.22	10.16	0	0
2	247.5	270	9.76	10.12	0.02	0
3	259	254	10.3	10.23	0	0
4	282	298	9.98	9.85	0	0
5	260	269	10.48	10.62	0	0
6	298.5	349	10.79	10.69	0	0
7	223.5	230.5	10.54	10.78	0	0
8	249	254.5	9.4	9.35	0	0.03
9	226	247	10.34	11.21	0	0
10	264.5	254	10.18	10.18	0	0
11	236	249	10.68	10.52	0	0
12	241	262.5	10.82	11.02	0.02	0
13	327	349.5	10.36	10.09	0	0
14	291	295.5	10.11	10.39	0.03	0.03
15	259.5	257	11.15	10.34	0	0.03
16	233	238	11.18	11.67	0.02	0
17	291.5	361.5	10.9	11	0	0
18	222.5	243.5	10.37	11	0	0
19	188	200	9.61	9.41	0	0.03
20	227	257	10.07	10.24	0	0

Table B.2. Mean Anti-saccadic latencies, amplitudes, and error rates of healthy control subjects

Subject ID	Anti Offset RT	Anti Overlap RT	Anti Offset Amplitude	Anti Overlap Amplitude	Anti Offset Error	Anti Overlap Error
1	285.5	304	12.13	10.96	0.06	0.05
2	274	292	9.3	9.31	0.05	0.05
3	316.5	326	10.38	10.42	0	0
4	364	381	10.09	9.62	0.04	0
5	277	277	10.51	10.45	0	0
6	367.5	385	11.16	10.6	0.11	0.06
7	240	239	10.96	11.07	0.12	0.08
8	270	279	9.91	8.52	0	0
9	257	275.5	10.07	10.17	0.02	0.02
10	305.5	289	10.06	9.79	0.13	0.09
11	290	301	11.63	11.89	0.02	0
12	254	269	11.46	11.06	0.02	0.04
13	384	394	9.62	10.21	0.11	0
14	326	301	11.06	10.37	0.11	0.05
15	253	290.5	9.94	10.14	0.17	0.08
16	278	267	11.66	12.12	0.02	0
17	393	413	10.66	10.57	0.09	0.02
18	225	217	10.57	10.36	0.03	0.02
19	196.5	200	10.53	10.63	0.07	0
20	307	329	10.54	10.38	0.18	0.02

Table B.3. Mean Pro-saccadic latencies, amplitudes, and error rates of PD Patients

Subject ID	Pro Offset RT	Pro Overlap RT	Pro Offset Amplitude	Pro Overlap Amplitude	Pro Offset Error	Pro Overlap Error
1	296	332	10.77	10.77	0	0
2	318	351	9.29	9.41	0.02	0
3	246	260	9.93	9.93	0	0
4	248.5	293	10.26	9.8	0	0.02
5	187	191	10.72	10.73	0	0
6	223	233	10.07	9.87	0	0.07
7	204.5	211	9.89	9.73	0	0
8	250	241.5	10.47	10.52	0	0
9	290.5	278	9.97	9.86	0	0.03
10	242	269	9.3	9.78	0	0
11	192.5	183.5	10.44	10.37	0	0
12	208	210.5	10.19	9.77	0	0
13	315.5	293.5	9.31	9.49	0.06	0.03
14	242	228	9.99	10.26	0	0
15	283	298.5	8.82	8.45	0.03	0.03
16	311.5	353	9.18	9.63	0.06	0.04
17	294	319	9.6	9.21	0	0
18	276	303	10.82	10.63	0	0.03
19	227	237	10.23	10.77	0	0

Table B.4. Mean Anti-saccadic latencies, amplitudes, and error rates of PD Patients

Subject ID	Anti Offset RT	Anti Overlap RT	Anti Offset Amplitude	Anti Overlap Amplitude	Anti Offset Error	Anti Overlap Error
1	445.5	577.5	10.85	10.3	0.29	0.06
2	334.5	377	9.48	9.69	0.03	0.08
3	310	320.5	9.07	8.61	0.04	0.04
4	358	378	9.86	9.81	0.11	0.1
5	260	261.5	11.07	11.31	0.15	0
6	260.5	287	10.42	10.28	0.03	0.02
7	260	264.5	10.14	9.63	0.08	0
8	256	259	10.55	10.46	0	0.02
9	264	264	9.81	10.27	0.12	0.03
10	276	301	9.21	10.61	0.24	0.09
11	225	227	10.63	10.92	0.04	0.04
12	236	266.5	9.29	8.38	0.03	0.03
13	332	320.5	9.47	9.13	0.19	0.05
14	361.5	403	10.71	10.73	0.08	0
15	344	361	9.69	9.2	0.29	0.3
16	420	499	9.46	8.81	0.29	0.14
17	290.5	308	9.99	9.76	0.08	0.11
18	312	297	10.8	9.91	0.09	0.08
19	249	262	11.02	11.31	0	0

Appendix – C *Data from individual participants Chapter 4*

Table C.1. Mean RT for individual subjects in Experiment 1 (Vertex & Right Parietal TMS).

	Vertex TMS								Right Parietal TMS							
	Left Visual Field				Right Visual Field				Left Visual Field				Right Visual Field			
Subject ID	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued
1	253.26	263.89	273.25	262.75	274.5	258.85	259.39	265.28	254.94	226.44	264.74	263.21	272.75	278.76	284.88	297.56
2	258.89	249.22	291.41	270.83	262	264.42	283.44	242.41	410.53	400.38	384.59	361.24	378.85	373	348.56	355.73
3	231.74	236.37	239.44	252.85	243.7	228.75	234.71	222.29	250.9	228.85	249.89	294.74	249.12	262.79	255.71	235.38
4	288.76	259.41	283.42	278.79	271.35	258.93	288.21	261.72	302.82	314.53	322.68	291.5	281.56	309.53	328	320.89
5	266.35	278.15	301.58	298.06	276.71	261.82	310.89	276.54	305.6	314.65	372.17	358.55	324.6	317.29	371.37	345.53
6	274	279	264.71	279.44	319.24	264.24	306.58	273.89	299.47	327.71	297.43	338.2	316.7	318.59	334.83	325.68
7	332.63	307.74	301.85	271.53	290.4	276.05	296.7	303	440.24	435.58	438	443.18	466.06	422.47	412.13	426.06
8	249.81	247.43	230.88	257.94	229.56	211.11	245.24	220.12	226.39	232.88	202.5	231.4	224.32	239.75	233.68	213.56
9	269.6	241.14	260.82	257.11	287.89	246.25	265.1	270.26	256.25	244.89	257.47	279.74	250.58	241.8	237.28	249.84
10	282.67	269.5	295.79	289.8	301.87	277.58	298.53	322.88	278.85	234.21	248.69	269.37	239.7	260.05	238.26	243.75
11	299.27	293.76	313.33	249.53	291.7	323.42	297.18	335.94	205.63	237.11	240.79	273	235.78	247.33	232.61	224
12	521.79	527.64	554.83	546.75	551.54	469	496.68	522.64	408.83	376.94	408.79	366.68	370	434.5	402.56	393.86
13	262.16	250.21	281.11	256.15	263.79	268.13	299.6	306.44	253.26	296.75	260.68	263.35	267.05	263.68	286.89	275.95
14	280.47	254.4	288.33	267.8	308.07	281.13	270.94	262.44	220.05	224.29	241.93	206.13	244.14	212.47	211.36	217.31

Table C.2. Mean RT for individual subjects in Experiment 2 (Vertex & Left Parietal TMS).

	Vertex TMS								Left Parietal TMS							
	Left Visual Field				Right Visual Field				Left Visual Field				Right Visual Field			
	Short SOA		Long SOA		Short SOA		Long SOA		Short SOA		Long SOA		Short SOA		Long SOA	
Subject ID	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued
1	247.55	238.61	244.17	256.9	238.83	235.61	262	248.33	298.53	284.28	301.84	300.42	300.15	282.75	322.81	326.56
2	215.33	204.63	225.88	218.56	249.65	225.42	196.87	212.22	237.06	207	225.19	250	238	241.39	237.78	231
3	249.75	244	245.94	236.88	245.28	243.06	263.05	253.63	292.74	268.84	283.94	260.59	291.22	265.11	274.61	292.47
4	279.3	280.26	246.94	263.2	288.3	264.71	275	261.42	361.4	364	312.88	332.79	376.47	316.8	377.72	357.78
5	225.74	223.21	218.78	216.5	248.53	236.45	228.15	232.68	282.56	246.58	259.61	237.44	282.89	248.05	264.52	243.63
6	351.3	286.28	285.3	301.12	296.84	263.68	280.18	248.89	360.11	306.13	325	301.53	324.47	362.83	355.28	314
7	226.83	261.4	319.67	295.13	259.29	299.69	282.22	291.22	419.2	332.47	369.42	323.73	380.79	346.07	377.07	337.63
8	480.16	454.27	407.35	342.08	428.07	405.94	386.06	408.68	394.86	320.38	349.67	368.06	423.29	351.75	353.5	352
9	286.17	303.53	363.29	311.57	362.63	304.57	316.25	327.94	268.14	245.44	310.76	247.47	302.58	288.37	282.6	263
10	271.35	247.33	262.82	249.24	265.21	247.56	249.68	253.38	213.65	212	216.78	230.4	216.15	213.78	216.47	225.75
11	302.11	240.79	269.67	256.47	251.13	265.94	254.17	246.24	220.35	213.53	202.18	233.82	220.56	235.16	217.84	235
12	558.17	460.87	488.77	491	409.28	462.58	417.72	459.89	267.11	260.45	246.33	248.58	279.67	260.65	262.67	259.83
13	308.92	275	377.67	275.06	339.71	270.31	327.47	256.88	222.13	213.06	236.56	218.88	269.25	218.68	247.47	222
14	523.85	539.8	542.1	507.73	590.46	517.82	522.38	521.78	282.67	272.55	297.4	305.86	290.33	281.93	315.5	309.93

Table C.3. Mean RT for individual subjects for control Experiment

	Vertex TMS				Parietal TMS			
	Short SOA		Long SOA		Short SOA		Long SOA	
Subject ID	Cued	Uncued	Cued	Uncued	Cued	Uncued	Cued	Uncued
1	330.97	329.63	331.74	337.54	319.34	290.67	310.13	298.53
2	300.59	278.61	269.69	265.06	255.33	262.57	256.73	254.08
3	238.7	226.13	248.49	236.21	255.8	233.36	244	230.9
4	313.39	307.56	323.87	307.12	281.13	309.81	291.53	278.09
5	283.05	270.24	266.72	255.84	328.97	315.08	316.1	311.05
6	288.43	293.02	289.95	251.84	283.95	265.21	268.44	246.95

Appendix – D *Data from individual participants Chapter 5*

Table D.1. Mean RT for individual subjects during Right Parietal TMS

Target Location	Right				Left			
Cue Location	Right		Left		Right		Left	
Direction Of Saccade	up	down	up	down	up	down	up	down
Subject ID								
1	265.63	286.43	279.67	284.53	301.44	321.67	307.14	288.81
2	248.56	237.43	245.63	238.22	258.88	246.33	248.44	243.65
3	359.94	385.58	369.23	378.81	366.28	365.78	420.04	409.26
4	236.72	219.28	210.17	215.5	227.38	233.67	229.7	250.44
5	236.09	238.85	237.88	226.61	230.02	235.5	249.11	262.51
6	223.08	240.99	237.13	226.6	235.09	232.75	244.53	235.95
7	269.69	259.5	255.96	255.07	266.74	306.75	266.33	253.59
8	240.17	215.58	229.55	231.1	242.28	237.8	229.06	234.34
9	186.82	168.44	182.15	166.63	218.06	211.67	213.43	184.58
10	267.85	229.34	229.7	221.28	234.7	257.67	267.58	228.96
11	191.94	191.72	186.72	184.3	195.53	188.86	203.03	196.56
12	211.83	218.22	219.72	219.13	212.95	214.11	242	234.41
13	303.69	303.34	298.95	346	329.76	401.5	311.29	395.29
14	223.19	230.69	252.2	243.13	244.33	225.5	241.42	254.01

Table D.2. Mean RT for individual subjects during Left Parietal TMS

Target Location	Right				Left			
Cue Location	Right		Left		Right		Left	
Direction Of Saccade	up	down	up	down	up	down	up	down
Subject ID								
1	206.37	233.93	218.67	211.28	225.95	233.75	243.31	242.12
2	265.85	265.35	291.24	269.92	262.78	273.9	277.44	282.29
3	222.75	252.7	243.44	236.13	233.51	231.56	239.86	287.65
4	216.75	207	206.04	210.6	228.97	222.25	238.69	241.45
5	258.29	286.46	250.58	283.39	276.76	250.56	253.01	295.85
6	264.42	247.45	250.65	247.94	258.68	239.11	287.36	265.67
7	271.27	245	248.67	246.36	244.36	231.44	239.4	248.22
8	303.88	289.19	314.69	284.99	312.72	313.11	316.78	317.73
9	194.36	194.83	194.9	176.25	177.02	202.9	198.42	191.63
10	204.97	207.44	200.26	197.85	218.39	229.67	228.01	228.05
11	207.25	195.44	198.85	193.64	197.76	208.63	200.88	208
12	222	251.86	238.14	245.18	226.04	241.25	237.5	255.4
13	261.06	257.62	269.77	262	263.95	289	252.97	255.4
14	203.25	207.85	197.25	209.39	219.7	212.6	206.94	221.83

Table D.3. Mean RT for individual subjects during Vertex TMS

Target Location	Right				Left			
Cue Location	Right		Left		Right		Left	
Direction Of Saccade	up	down	up	down	up	down	up	down
Subject ID								
1	260.69	253.74	259.8	251.25	254.25	267.57	255.04	262.57
2	264.5	244.76	231.39	243.33	229.85	253.33	252.47	260.17
3	247.01	240.3	254.39	254.21	233.5	281.9	280.56	258.39
4	243.55	233.05	244.06	225.76	252.01	246.44	256.15	240.19
5	260.81	269.45	248.5	269.83	248.85	257.9	253.94	238.17
6	260.58	261.6	268.78	245.06	253.94	239.22	263.1	269.31
7	301.31	280.59	277.29	254.97	273.79	273.83	288.06	282.3
8	247.67	229.61	251.42	239.94	251.15	235.1	255.44	239.55
9	227.32	251.08	208.79	217.41	225.39	238.5	224.12	240.12
10	282.97	271.19	250.39	253.75	249.77	262.56	265.38	278.46
11	226.04	217.04	218.81	213.4	214.04	239.22	227.57	232.63
12	257.38	247.75	245.94	242.02	253.13	248.33	262.88	264.92
13	264.11	266.38	261.94	258.22	239.63	264.25	260.58	299.44
14	221.57	219.08	225.61	232.32	234.76	257.89	241.4	249.28