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ELECTRICAL MICROSTIMULATION OF THE MONKEY DORSOLATERAL PREFRONTAL CORTEX IMPAIRS ANTISACCADE PERFORMANCE

Stephen Peter Wegener
Western University

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Stephen Peter Wegener

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CERTIFICATE OF EXAMINATION

Supervisor	Examiners
Dr. Stefan Everling	Dr. Daniel Ansari
Supervisory Committee	Dr. Steve Lomber
Dr. Brian Corneil	Dr. Tutis Vilis
Dr. Jon Hore	
Dr. Lique Coolen	

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Stephen Peter Wegener

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Abstract:

The dorsolateral prefrontal cortex (DLPFC) has been implicated in response suppression. This function is frequently investigated with the antisaccade task, which requires suppression of the automatic tendency to look toward a flashed peripheral stimulus (prosaccade) and generation of a voluntary saccade to the mirror location. To test the functional relationship between DLPFC activity and antisaccade performance, we applied electrical microstimulation to the DLPFC of two monkeys while they performed randomly interleaved pro- and anti-saccade trials. Microstimulation increased the number of direction errors and slowed saccadic reaction times (SRTs) on antisaccade trials when the visual stimulus is presented on the side contralateral to the stimulated hemisphere. Also, we observed shorter SRTs for contralateral prosaccades and longer SRTs for ipsilateral prosaccades on microstimulation trials. These findings do not support a role for the DLPFC in response suppression, but suggest a more general role in attentional selection of the contralateral field.

Keywords: dorsolateral prefrontal cortex, saccade, antisaccade, attention, suppression, inhibition, monkey, electrical microstimulation

The brain is the last and grandest biological frontier, the most complex thing we have yet discovered in our universe. It contains hundreds of billions of cells interlinked through trillions of connections. The brain boggles the mind.

James D. Watson

For Marie – wife, best friend, and one true love

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List of Abbreviations:

BG – basal ganglia
BSG – brainstem saccade generator
ChR2 – *Chlamydomonas reinhardtii* Channelrhodopsin-2
CN – caudate nucleus
DBS – deep brain stimulation
DLPFC – dorsolateral prefrontal cortex
EBN – excitatory burst neuron
ER – error rate
FEF – frontal eye field
fMRI – functional magnetic resonance imaging
FP – fixation point
GPe – external segment of the globus pallidus
IBN – inhibitory burst neuron
i.m. – intramuscular injection
i.v. – intravenous injection
LIP – lateral intraparietal area
LLBN – long lead burst neuron
MN – motoneuron
MR – magnetic resonance
MRI – magnetic resonance image
NpHR – *Natronomonas pharaonis* halorhodopsin
OPN – omnipause neuron
PPRF – paramedian pontine reticular formation
s.c. – subcutaneous injection
SC – superior colliculus
SCFN – superior colliculus fixation neurons
SEF – supplementary eye field
SMA – supplementary motor area
SNpr – substantia nigra pars reticulata
SRT – saccadic reaction time
STN – subthalamic nucleus
V4 – visual area 4
VS – peripheral visual stimulus

List of Symbols:

° – degree(s)
ms – millisecond(s)
s – second(s)
Hz – Hertz (cycles/second)
μA – microampere(s)
kg – kilogram(s)
mg – milligram(s)
μm – micrometer(s)

Chapter 1 - Introduction and Literature Review

All normally functioning animals, humans included, have the ability to respond reflexively when appropriate stimuli are presented. For instance, if surprised by either friend or foe, most will respond with an automatic motor behavior before they can form a counter voluntary response. These automatic responses depend on relatively straightforward relationships between stimulus and response. However, the ability to perform volitional responses, rather than strictly relying on hardwired stimulus-response programming, is an essential aspect of daily human activity.

For the performance of a voluntary action we have to anticipate possible futures, and coordinate thought and action in order to produce the appropriate response, which may or may not require suppression of a competing more automatic response. The inability to suppress unwanted or inappropriate responses, such as a stimulus bound action, is the hallmark of humans who, by virtue of immaturity or disease, have poorly functioning frontal lobes (Fuster, 1989). The role of the frontal lobe in higher executive function has been suggested for over 150 years. David Ferrier (1878) cited the case of Phineas Gage, originally described by Harlow in 1848 (Harlow, 1999), as a primary example. Gage was a railroad worker who suffered severe frontal lobe damage by way of an iron bar passing through his head. After the accident, Gage appeared to be unable to suppress inappropriate behavior such as indulging in uncharacteristic profanity, and being capricious and fitful (Harlow, 1868).

Although Harlow was unable to identify any motor deficits as a result of Gage's frontal lobe damage, more recent lesion studies suggest the opposite (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991; Walker et al., 1998; Gaymard et al., 2003; Ploner et al., 2005). This clear contradiction demonstrates the need to identify a sensory-motor system whose output can be easily quantified for experimental investigation. The incorporation of such a quantifiably-sensitive sensory-motor system could be the key to unlock many of the central problems that exist in our present understanding of the brain.

The oculomotor system holds great promise as a research tool in neuroscience. Within this system, an experimenter can find all the big issues (sensory processing, motor coordination, learning, attention, response suppression) in a form that is uniquely suitable for quantifiable testing. Although, the output of the oculomotor system can be in the form of five different types of eye movements (Dodge, 1902), saccadic eye movements have become the most popular measure for neuronal investigation. Saccades are easily accessible to clinical observation or measurement in the laboratory, and their dynamic properties are well defined. Additionally, the neurobiological substrate underlying saccades is considerably understood.

1.1 - Saccadic Eye Movements

The eyes have a simple, yet well defined repertoire of movements (Dodge, 1902) that can be easily quantified. We make hundreds of thousands of eye

movements every day, but why do we need to move our eyes? The primate retina has a specialized region in its center, called the fovea, which provides the highest visual acuity and serves the central 1° of the visual field (Perry and Cowey, 1985). The fovea has the greatest representation in most cortical and subcortical visual areas, which emphasizes the importance of foveal vision in most aspects of visual processing and visually guided behavior (Dow et al., 1981; Van Essen et al., 1984). To maximize our foveal vision, or highest acuity vision, we must rapidly move our eyes to align the fovea onto objects of interest and then hold the fovea on these objects, or maintain fixation, long enough to acquire the appropriate amount of visual information to guide future behaviors. The rapid, conjugate eye movements used to move the fovea to the image an object of interest are called saccades. The alternating generation of saccades and fixation is critical for complex acts such as reading (Hering, 1879; Erdmann and Dodge, 1898; Vernon, 1931) and visual search (Noton and Stark, 1971).

Much information has been gained, regarding the cortical and subcortical structures involved in the generation of saccades and the maintenance of fixation, with the use of the prosaccade task. The prosaccade task is an automatic task which requires the subject to look from a central fixation point (FP) to a peripheral visual target. There have been numerous variations of this task. Some variations include the overlap prosaccade task (Figure 1A) and the gap prosaccade task (Saslow, 1967; Figure 1B).

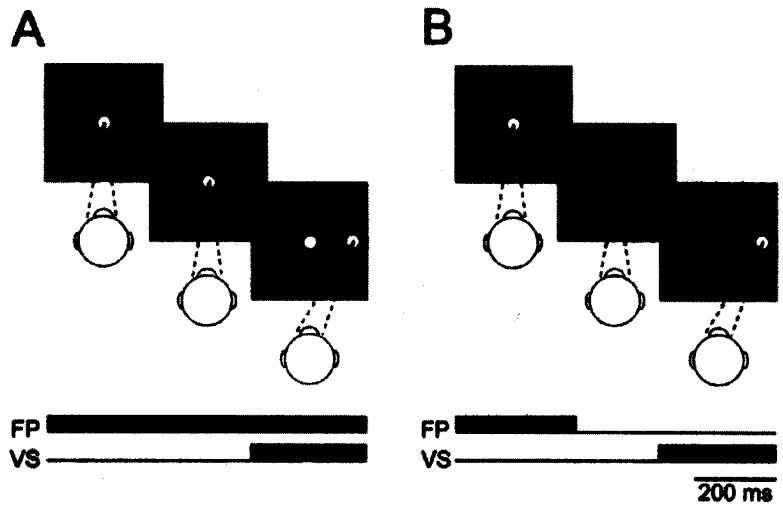


Figure 1. Variations of the prosaccades task. ***A,*** Overlap prosaccade task: central fixation point (FP) remains illuminated throughout the duration of the trial. ***B,*** Gap prosaccade task: a temporal gap is inserted between central FP offset and peripheral visual stimulus (VS) onset, during which time the subject must maintain central fixation. In both tasks, the signal to move the eyes is the onset of a VS which also serves as the target. Dashed line indicates the alignment of the fovea.

The introduction of a temporal gap between FP offset and peripheral target onset (Figure 1B) reduces saccadic reaction times (SRTs) in the prosaccade task. This reduction has been termed the 'gap effect', and SRTs reach a minimum with a gap of 200 ms (Saslow, 1967; Fischer and Boch, 1983; Weber et al., 1993; Pare and Munoz, 1996). In general, it has been suggested that the disappearance of the FP can both reduce the activity of neurons involved in fixation and act as a temporal warning signal allowing the subject to prepare for the upcoming target appearance (Ross and Ross, 1980; Reuter-Lorenz et al.,

1991; Dorris and Munoz, 1995; Pare and Munoz, 1996). In addition, the gap prosaccade task can also facilitate the production of 'express' saccades, the latencies of which approach the minimal time required for sensory-motor transformation (Weber et al., 1993; Pare and Munoz, 1996). These express saccades form a distinct mode in the distribution of SRTs that is different from that of longer-latency, regular, saccades. That is, the gap paradigm often results in a bimodal SRT distribution, with a first mode (~100ms) of express saccades and a second mode (~150ms) of regular saccades (Fischer and Boch, 1983; Fischer and Ramsperger, 1984; Fischer et al., 1993). Therefore, even simply employing variations of the prosaccade task can result in behavioral observations which can suggest underlying neuronal mechanisms.

1.2 - The Primate Saccade Generating System

Many neural structures are involved in the performance of saccadic eye movements (Figure 2). The brainstem saccade generator (BSG) is composed of the neural elements responsible for providing saccade-triggering signals to the motoneurons (MNs) which innervate the extraocular muscles (Figure 2). For horizontal saccade generation, the BSG is located in the paramedian pontine reticular formation (PPRF; Moschovakis and Highstein, 1994). Eye movement signals that reach the PPRF synapse on omnipause neurons (omnidirectional pause neurons; OPNs), long-lead burst neurons (LLBNs), excitatory burst neurons (EBNs), and inhibitory burst neurons (IBNs) of the BSG (reviewed in

Scudder et al., 2002). OPNs project to all burst-neuron regions, where they provide monosynaptic, tonic inhibition (Fuchs et al., 1985). Conversely, it has been suggested that LLBNs can directly excite agonist MNs (Scudder et al., 2002) and also function as an obligatory relay from BSG input structures to EBNs (Raybourn and Keller, 1977; Hepp and Henn, 1983; Scudder et al., 1988). In turn, EBNs monosynaptically excite agonist MNs (Sasaki and Shimazu, 1981), while activation of IBNs results in antagonist MN inhibition (Hikosaka et al., 1978).

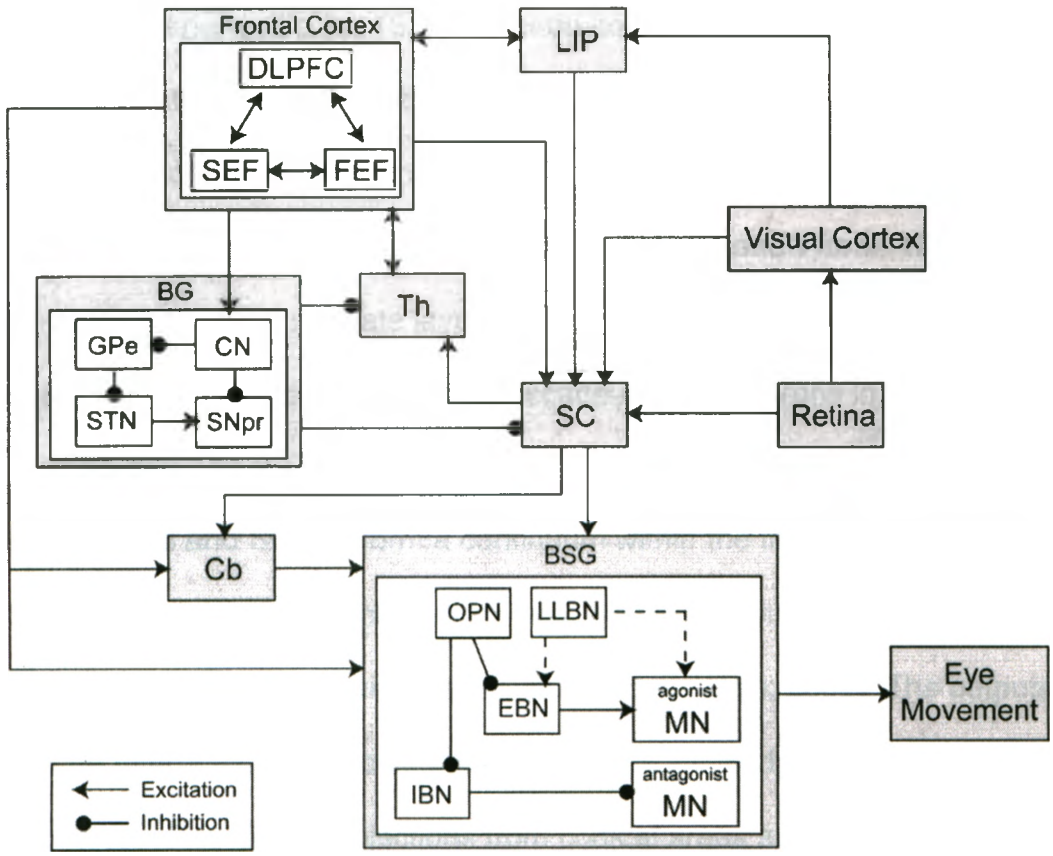


Figure 2. Brain areas and neural pathways involved in saccade control. This schematic is a simplified depiction of the saccade generating system in the non-human primate. Solid lines show identified neuronal projections, while dashed lines represent hypothesized neuronal projections. Abbreviations: BG – basal ganglia; brainstem saccade generator (BSG); Cb - cerebellum; CN - caudate nucleus; DLPFC - dorsolateral prefrontal cortex; EBN - excitatory burst neuron; FEF - frontal eye field; GPe – globus pallidus (external segment); IBN - inhibitory burst neuron; LIP - lateral intraparietal area; LLBN - long-lead burst neuron; OPN - omnipause neuron; MN - motoneuron; SC - superior colliculus; SEF - supplementary eye field; SNpr - substantia nigra pars reticulate; STN – subthalamic nucleus; Th - Thalamus.

The superior colliculus (SC) has been considered to be the primary source of saccade-related commands to the BSG (Scudder et al., 2002). The SC is located in the dorsal mesencephalon and is critical for the initiation of saccadic eye movements (Wurtz and Goldberg, 1972; Hikosaka and Wurtz, 1983). Neurons within the intermediate layers of the SC are organized into a retinotopically coded motor map, with saccade-related neurons in the caudal pole and fixation neurons (SCFNs) in the rostral pole (Robinson, 1972). Saccade-related neurons and SCFNs form a continuum within the intermediate layers of the SC, and their local interconnections are used as the substrate for motor programs to compete (for review see Munoz and Fecteau, 2002). The outputs from these interactions project to the BSG (Figure 2) (Rodgers et al., 2006). The SC in turn receives direct projections from cortical areas such as the lateral intraparietal area (area LIP; Asanuma et al., 1985; Lynch et al., 1985; Andersen et al., 1990), the supplementary eye field (SEF; Shook et al., 1990), the frontal eye field (FEF; Kunzle et al., 1976; Kunzle and Akert, 1977; Segraves and Goldberg, 1987), the dorsolateral prefrontal cortex (DLPFC; Goldman and Nauta, 1976; Leichnetz et al., 1981; Johnston and Everling, 2006b), and the basal ganglia (Jayaraman et al., 1977; Beckstead et al., 1981).

Neurons in the substantia nigra pars reticulata (SNpr), of the basal ganglia, project to the intermediate layers of the SC (Jayaraman et al., 1977). SNpr neurons provide tonic inhibition to SC neurons. When SNpr neuron activity pauses, inhibition of SC saccade-neurons will cease, and SC saccade-related activity will result (Figure 2). Overall, it has been suggested that the tonic

inhibition of the SNpr is very important in preventing unnecessary saccades (for review see Hikosaka et al., 2000). Neurons in the SNpr are directly inhibited by the caudate nucleus (CN), which receives inputs from the FEF (Stanton et al., 1988; Parthasarathy et al., 1992) the SEF (Shook et al., 1991), the DLPFC (Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991), and area LIP (Selemon and Goldman-Rakic, 1985). In summary, activation of CN neurons in the direct pathway will inhibit SNpr neurons resulting in disinhibition of SC neurons (Figure 2). Conversely, an indirect pathway also exists between the CN and SNpr. In this pathway, activation of a different type of CN neurons (Gimenez-Amaya and Graybiel, 1990; reviewed in Smith et al., 1998) will inhibit SC neurons via projections through the globus pallidus (GPe) and the subthalamic nucleus (STN) (for review see Hikosaka et al., 2000) (Figure 2).

The FEF plays an important role in the generation of saccadic eye movements as demonstrated by the fact that saccades can be evoked by electrically stimulating the FEF with currents < 50μA (Bruce and Goldberg, 1985). The primate FEF is located within the anterior bank of the arcuate sulcus, extending anteriorly onto the surface of the prearcuate gyrus (Bruce et al., 1985), and posteriorly encroaching into the caudal bank (Segraves and Goldberg, 1987; Gottlieb et al., 1993; Gottlieb et al., 1994). The FEF projects directly to both the SC (Segraves and Goldberg, 1987) and the BSG (Segraves, 1992). Neurons in the FEF have been found to respond to visual stimuli and fixation, and also discharge before, during, and after saccade execution (Bizzi and Schiller, 1970; Mohler et al., 1973; Goldberg and Bushnell, 1981; Suzuki and Azuma, 1983;

Bruce and Goldberg, 1985). However, FEF neurons projecting directly to the SC or brainstem were found to relay primarily saccadic- and fixation-related discharges, and they rarely had only visual responses (Segraves and Goldberg, 1987; Segraves, 1992).

Similar to the FEF, electrical stimulation of the SEF can also evoke saccadic eye movements (Schlag and Schlag-Rey, 1987). Anatomically, the SEF is located in the rostral part of the supplementary motor area (SMA) in the mesial portion of area 6. The SEF directly innervates the FEF (Kunzle, 1978; Huerta et al., 1987; Arikuni et al., 1988; Schall et al., 1993) and SC (Fries, 1984; Shook et al., 1990), as well as various brainstem (Huerta et al., 1986; Shook et al., 1988; Keizer and Kuypers, 1989; Shook et al., 1990; Parthasarathy et al., 1992) and spinal cord (Hutchins et al., 1988; Keizer and Kuypers, 1989; Dum and Strick, 1991; He et al., 1993) nuclei involved in the execution of eye, head, and limb movements. Rostral SEF neurons discharge during the presentation of visual stimuli (Schall, 1991; Russo and Bruce, 1996), and a large proportion of cells respond during active fixation (Bon and Lucchetti, 1990, 1992; Schlag et al., 1992; Lee and Tehovnik, 1995; Bon and Lucchetti, 1997).

Projections from the SC, SEF, and FEF not only innervate the BSG, they also project to the nucleus reticularis tegmenti pontis and other pontine nuclei of the cerebellum. Neurons in these nuclei then project to the cerebellar vermis, where electrical stimulation can elicit saccades (Noda and Fujikado, 1987). Oculomotor signals from the vermis pass through the caudal fastigial nucleus to terminate on EBNs, IBNs, and OPNs of the BSG (reviewed in Robinson and

Fuchs, 2001). It has been suggested that the cerebellum is critical for both the accuracy (Zee, 1986; Robinson et al., 1993) and the consistency (Quaia et al., 1999) of saccades.

Another important saccade-related structure is area LIP, which has also been implicated in visual attention (Robinson et al., 1995; Colby et al., 1996; Gottlieb et al., 1998; Gottlieb and Goldberg, 1999; Powell and Goldberg, 2000). Area LIP can be found between the visual and saccadic systems (Blatt et al., 1990; Baizer et al., 1993; Suzuki and Amaral, 1994) in the posterior aspect of the lateral bank of the intraparietal sulcus (Ungerleider and Desimone, 1986; Andersen et al., 1990). Although area LIP has been thought to contribute to the generation of saccades (Gnadt and Andersen, 1988; Andersen et al., 1992), the relative weakness of non-visual saccade-related activity, compared to the more pronounced visual signal (Colby et al., 1996; Gottlieb and Goldberg, 1999), suggests that area LIP has a more general role in visuospatial behavior (Colby et al., 1996). Area LIP sends projections to the SC (Pare and Wurtz, 1997), the FEF (Schall and Thompson, 1999), and the SEF (Schall, 1997). Overall, it has been suggested that activity in area LIP reflects object salience (Gottlieb et al., 1998; Gottlieb and Goldberg, 1999), where salience is the relative property of one object standing out with respect to neighboring objects in the visual scene (Treisman, 1988; reviewed in Fecteau and Munoz, 2006).

The DLPFC is reciprocally interconnected with many of the saccade-related structures presented above (Figure 2) (for review see Miller and Cohen, 2001). For instance, the DLPFC projects directly to the FEF (Pandya and

Kuypers, 1969; Kunzle and Akert, 1977), the SC (Goldman and Nauta, 1976; Leichnetz et al., 1981; Johnston and Everling, 2006a, b), and is reciprocally connected to the SEF (Bates and Goldman-Rakic, 1993). The DLPFC also projects indirectly to the SC by way of the CN and SNpr (Selemon and Goldman-Rakic, 1985, 1988). Additionally, it is interconnected with the SMA, the pre-SMA, the rostral cingulate, premotor cortex, cerebellum, and visual, somatosensory, and auditory areas in the occipital, temporal, and parietal cortices (Fuster, 1991). Therefore, it is well positioned to coordinate a wide range of neural processes. In fact, Miller and Cohen (2001) have suggested that the DLPFC is important when top-down processing is needed; that is, when behavior must be guided by internal states or intentions, as opposed to when behavior is determined largely by the connection between nature of the stimulus and well-established neural pathways (bottom-up processing). Since the DLPFC acts to coordinate the activity of cortical and subcortical areas to which it is reciprocally connected, via top-down processing, it is a primary candidate for the investigation into response suppression and volitional control.

1.3 - The Antisaccade Task

Top-down control in both humans and primates has been extensively investigated with the use of the antisaccade task (reviewed in Munoz and Everling, 2004). The antisaccade task has also been used to study response suppression and attention (for review see Everling and Fischer, 1998; Munoz and

Everling, 2004). Correct performance of the antisaccade task requires that the subject suppress the automatic tendency to look toward a flashed peripheral stimulus (prosaccade), and instead use the stimulus information to program and execute a voluntary saccade to the uncued diametrically opposite location (Figure 3). Overall, the antisaccade task provides an ideal paradigm to investigate executive function as it tests the subject's ability to suppress an automatic behavior in favor of achieving an internal goal. A deficit in either the inhibition of the automatic response (prosaccade) or the generation of the internal goal (antisaccade) will result in a higher number of direction errors (prosaccades) or a reduced number of correct antisaccades, respectively.

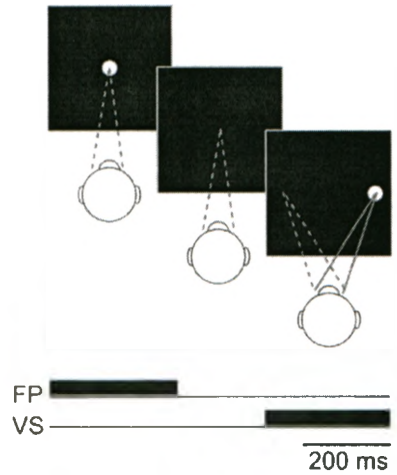


Figure 3. Schematic of the antisaccade task incorporating a temporal delay between central fixation point (FP) offset and peripheral visual stimulus (VS) onset. Correct performance requires the generation of a saccade to the mirror location of the VS. Dashed lines indicate the alignment of the fovea during correct antisaccade performance. Solid lines show foveal alignment during a direction error.

The antisaccade task was originally designed by Hallett (1978). In his first antisaccade study in normal subjects, Hallett reported some basic performance observations. The mean SRTs on antisaccade trials were prolonged compared to those on prosaccade trials, and, with practice, there was no significant improvement in antisaccade error rates (see also Hallett and Adams, 1980). In addition, antisaccade amplitude was variable within and between subjects, and peak saccade velocity was decreased on antisaccade trials compared with prosaccade trials (Smit et al., 1987; Van Gelder et al., 1997). However, it should be noted that Edelman and colleagues (2006) have recently shown that the reduction in antisaccade velocity and smaller antisaccade amplitudes results mainly from the lack of a visual stimulus at the saccade endpoint.

When a temporal gap of 200-250ms is inserted between FP offset and peripheral stimulus onset (Figure 3), the mean antisaccade error rate was maximal and the reaction time latency was minimal, when compared to longer or shorter gap periods (Fischer and Weber, 1997). It should be noted that the gap-effect difference in SRT for antisaccades was smaller than that for prosaccades (Forbes and Klein, 1996), and the direction errors performed on antisaccade trials are usually initiated earlier than correct responses (Munoz and Everling, 2004). Therefore, the gap-effect extends beyond the prosaccade task to also influence SRTs and the number of direction errors in the antisaccade task. This modulation in SRTs and error rates may be particularly useful to those experimenters investigating response suppression.

In summary, the antisaccade task provides an ideal paradigm to investigate the neural processes underlying response suppression. From over 30 years of research employing the antisaccade task, a vast amount of literature has emerged implicating a role for the DLPFC in antisaccade performance.

1.4 - The Dorsolateral Prefrontal Cortex and Response Suppression

Recently, Johnston and Everling (2006b) used antidromic stimulation to identify DLPFC neurons that project directly to the SC. These corticotectal neurons demonstrated an increased level of pre-stimulus activity (i.e., activity before peripheral stimulus onset), and higher contralateral stimulus-related responses, on antisaccade trials compared with prosaccade trials. Also, it was found that corticotectal pre-stimulus activity and SRTs were negatively correlated for antisaccade trials; however, there was no correlation found between corticotectal pre-stimulus activity and SRTs for prosaccade trials (Johnston and Everling, 2006b). Based on this evidence, Johnston and Everling (2006b) proposed a possible mechanism by which enhanced DLPFC saccade suppression signals could facilitate antisaccade task performance and reduce SRTs via direct input to the SC. The notion that the DLPFC participates in the inhibition of prosaccades has been supported by studies of human patients with lesions restricted to the prefrontotectal pathways. Specifically, patients with unilateral DLPFC lesions show higher error rates in the antisaccade task (Pierrot-Deseilligny et al., 1991; Walker et al., 1998; Gaymard et al., 2003; Ploner et al.,

2005), which is not observed in FEF and SEF lesion studies (Pierrot-Deseilligny et al., 1991; Rivaud et al., 1994; Gaymard et al., 1999; for an exception see Boxer et al., 2006). Some of these studies have found that unilateral DLPFC lesions only result in antisaccade errors when the visual stimulus is presented in the hemifield contralateral to the side of the lesion (Gaymard et al., 2003). Taken together, the saccade suppression model was proposed. In this model the DLPFC provides top-down signals to saccade-related brain areas to suppress contralateral prosaccades (Munoz and Everling, 2004; Ploner et al., 2005; Johnston and Everling, 2006b). In the same vein, more direction errors are observed during antisaccade performance with impaired functioning of the prefrontal cortex. Impairments of the prefrontal cortex include diseases such as schizophrenia, Alzheimer's disease, progressive supranuclear palsy, attention deficit hyperactivity disorder, Huntington's disease, and late stages of Parkinson's disease (for review see Everling and Fischer, 1998).

Previous DLPFC imaging experiments, which employed the antisaccade task, found higher blood-oxygenation-level-dependent (BOLD) signals on antisaccade compared with prosaccade trials (Curtis and D'Esposito, 2003; Desouza et al., 2003b; Desouza et al., 2003a; Ford et al., 2005). As with single neuron recordings, these results were interpreted in support of a role for the DLPFC in response suppression, despite the various other cognitive functions that have been ascribed to the DLPFC (Duncan and Owen, 2000; Duncan, 2001; Miller and Cohen, 2001).

In addition to response suppression, the primate DLPFC has been linked to a multitude of cognitive functions (Duncan and Owen, 2000) including working memory (Fuster and Alexander, 1971), short-term spatial memory (Fuster and Alexander, 1971), perceptual decisions (Kim and Shadlen, 1999), categorical decision making (Freedman et al., 2001), numerosity (Nieder et al., 2002; Nieder and Miller, 2003), memory retrieval (Tomita et al., 1999), and spatial attentional (Rainer et al., 1998; Everling et al., 2002; Desouza and Everling, 2004; Lebedev et al., 2004).

1.5 - The Dorsolateral Prefrontal Cortex and Spatial Attention

Spatial attention allows us to detect stimuli at relevant locations at the expense of stimuli at other locations (Posner et al., 1982). A role for the DLPFC in attentional selection has been suggested by many neuropsychological and functional imaging studies (Owen et al., 1996; Vandenberghe et al., 1997; Rowe and Passingham, 2001; Peers et al., 2005; Abe et al., 2007; Luks et al., 2007). Furthermore, using single neuron recordings in monkeys it was found that DLPFC neurons have increased responses for attended stimuli (Rainer et al., 1998; Everling et al., 2002, 2006), with a bias towards the contralateral field. In fact, Lebedev and colleagues (2004) demonstrated that activity related to attentional selection are more prevalent in DLPFC neurons than those related to working memory, long considered a hallmark of the DLPFC (Fuster, 1991; Levy and Goldman-Rakic, 2000; reviewed in Goldman-Rakic, 1995; Fuster, 2000). In

light of this evidence, the attentional selection model was proposed, which is different from the saccade suppression model presented previously. The attentional selection model proposes that the DLPFC selects objects or parts of visual scenes (Rainer et al., 1998), and via its anatomical connections, sends these signals to guide goal-directed behavior by using target-selection processes (Iba and Sawaguchi, 2003).

Anatomically, the DLPFC connects to other cortical structures implicated in attention. The main frontal area thought to be involved in directing attention has been the FEF (Corbetta et al., 1993; Corbetta et al., 1998), which receives reciprocal projections from the DLPFC (Pandya and Kuypers, 1969). In addition, the DLPFC also projects to the parietal cortex (Goldman-Rakic, 1988) and SEF (Bates and Goldman-Rakic, 1993), both of which play a role in attentional control (Kastner and Ungerleider, 2001).

In summary, models of DLPFC functioning have implicated its involvement in attentional selection and response suppression. It is important to note that both of these models were formed on the basis of a correlation between neural activity and behavior. Therefore, it remains to be determined if directly influencing DLPFC activity can support either of these models. Electrical microstimulation is one method used to directly activate neuronal elements (axons, cell bodies, etc) in a region of interest.

1.6 – Use of Electrical Stimulation

For more than 125 years, electrical stimulation has been used to explore the functions and uncover the psychological processes of the brain. David Ferrier (1875) pioneered the exploration of the motor function of the brain by employing electrical stimulation to cortical and subcortical areas in non-human primates. He discovered that eye movements could be evoked in the monkey from parts of the frontal, parietal, and temporal lobes, the SC, and the cerebellum. Since then, electrical microstimulation has been used to identify neuronal pathways, via antidromic stimulation and collision testing (Fuller and Schlag, 1976), and has disclosed topographic maps of various neuronal structures for the generation of ocular responses (SC (Robinson, 1972; Schiller, 1972); FEF (Robinson and Fuchs, 1969; Bruce et al., 1985); SEF (Tehovnik and Lee, 1993; Lee and Tehovnik, 1995)).

Overall, the effects of electrical microstimulation are usually interpreted as an artificial activation of neuronal elements at the tip of the microelectrode (reviewed in Ranck, 1975; Tehovnik, 1996; Tehovnik et al., 2006). In this manner, an experimenter can activate a region of interest with temporal precision while monitoring the corresponding effects.

1.7 - Research Questions and Hypothesis

The ability to perform volitional responses, rather than strictly relying on well-established automatic behaviors, is an essential aspect of daily human activity. At times volitional responses are in conflict with automatic responses. In these cases, it is important to inhibit the competing automatic response, termed response suppression, in order to produce the desired volitional response.

The neuronal mechanisms underlying response suppression are frequently studied with the antisaccade task. Correct performance of this task requires the inhibition of the automatic task in favor of a voluntary task (Everling and DeSouza 2005). Many studies employing the antisaccade task have suggested a role for the DLPFC in response suppression.

Evidence for a role of the DLPFC in the performance of the antisaccade task has come from single-neuron recordings in monkeys (Funahashi et al., 1993; Everling and Desouza, 2005; Johnston and Everling, 2006a,b), functional imaging studies in humans (Sweeney et al., 1996; Doricchi et al., 1997; McDowell et al., 2002; Curtis and D'Esposito, 2003; Desouza et al., 2003a; Ford et al., 2005; Brown et al., 2007), and lesion studies in human patients (Pierrot-Deseilligny et al., 1991; Walker et al., 1998; Gaymard et al., 2003; Ploner et al., 2005). Recent single-neuron studies have shown that corticotectal neurons demonstrate increased pre-stimulus activity (i.e., neuronal activity before peripheral stimulus onset), and higher contralateral stimulus-related responses, on antisaccade trials compared with prosaccade trials (Johnston and Everling,

2006b). Additionally, it was found that this corticotectal pre-stimulus activity was negatively correlated with SRTs for antisaccade trials (Johnston and Everling, 2006b). Based on this evidence, a response suppression model was proposed by which enhanced DLPFC saccade suppression signals facilitate antisaccade task performance and reduce SRTs via direct input to the SC (Johnston and Everling, 2006b). However, it remains to be determined if DLPFC activity can directly influence antisaccade performance, as the notion that the DLPFC is involved in suppression of automatic saccades was based on a correlation between corticotectal pre-stimulus activity and antisaccadic reaction time (Johnston and Everling 2006b).

Here, we tested the hypothesis that DLPFC activity inhibits prosaccades to visual targets located in the contralateral hemifield. In turn, this contralateral prosaccade inhibition will facilitate antisaccade performance when the visual stimulus is presented on the side contralateral to the stimulated hemisphere. To test the hypothesis, electrical microstimulation was applied to the DLPFC of two monkeys, at the time of peripheral stimulus presentation, while they performed randomly interleaved prosaccade and antisaccade trials.

Four predictions of the hypothesis were investigated (Figure 4). Based on the response suppression model, DLPFC microstimulation will prolong SRTs on contralateral prosaccade trials without influencing the number of direction errors (Figure 4A). In contrast, based on the results of single-neuron studies, which have suggested that the DLPFC has a preference for targets presented in the contralateral field, we predict that microstimulation will not affect SRTs or

performance on either ipsilateral prosaccade (Figure 4B) or contralateral antisaccade (Figure 4C) trials. Finally, DLPFC microstimulation will reduce SRTs and direction errors on antisaccade trials with contralateral stimulus presentations (Figure 4D). This final prediction assumes that the competing contralateral prosaccade is inhibited by DLPFC activity. This study is the first to investigate the effects of unilateral DLPFC electrical microstimulation on antisaccade and prosaccade performance.

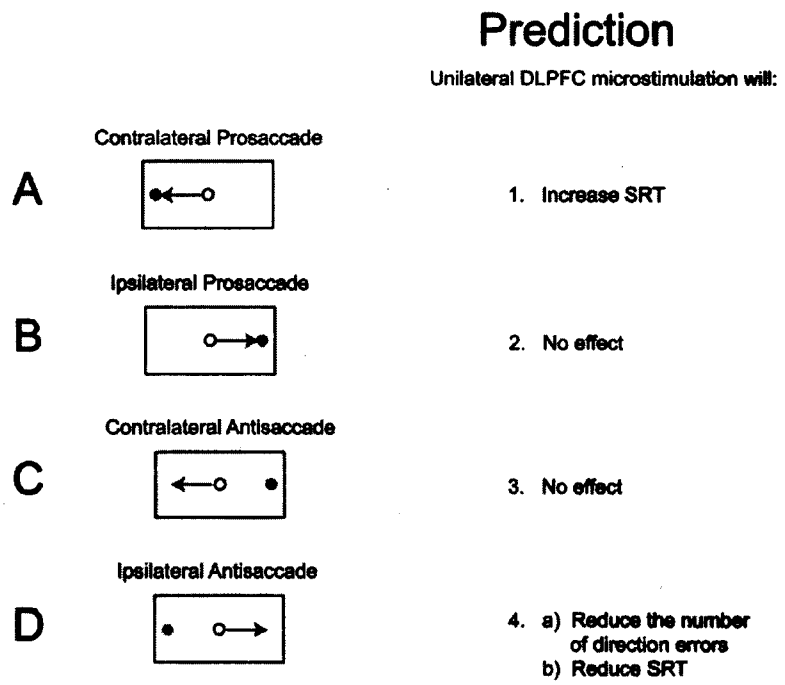


Figure 4. Based on the hypothesis that DLPFC activity inhibits prosaccades to visual targets located in the contralateral hemifield, the following four predictions can be made. Trial conditions: ***A,*** contralateral prosaccade trials. ***B,*** ipsilateral prosaccade trials. ***C,*** contralateral antisaccade trials. ***D,*** ipsilateral antisaccade trials. DLPFC microstimulation occurred in the right hemisphere of both monkeys.

Chapter 2 - Methods

Two male rhesus monkeys (*Macaca mulatta*) weighing 8 and 11 kg were subjects in the present experiment. All experimental methods described were performed in accordance with the guidelines of the Canadian Council on Animal Care policy on the care and use of experimental animals, and an ethics protocol approved by the Animal Users Subcommittee of the University of Western Ontario Council on Animal Care (Appendix 1). Animal health and well-being was monitored closely by the Veterinarians at the University of Western Ontario.

2.1 - Surgery

Both monkeys were prepared for chronic electrophysiological experiments by undergoing a surgical procedure to place an implant, containing both a recording chamber and a head post, on the skull.

Monkeys were sedated for surgery with ketamine hydrochloride (10 mg/kg i.m.). Atrophine (0.05 mg/kg s.c.) was given to reduce bradycardia and salivary secretions. Anesthesia was initiated with a bolus of propofol (2.0 mg/kg i.v.) and maintained with propofol (0.2 mg/kg/min i.v.) and midazolam (0.35 mg/kg/min i.v.). Heart rate, blood oxygen, respiratory rate, blood pressure, and body temperature were monitored closely for the duration of the surgery. For a 10-day period after surgery, animals received a daily dose of antibiotic (amoxicillin, administered orally) to prevent infection. Animals were also given the analgesic

buprenorphine hydrochloride (0.01 mg/kg i.m.) postoperatively to alleviate any potential discomfort.

The head implant was constructed from dental acrylic and anchored to the skull with titanium screws. A titanium head post was anchored into the head implant. The head post served to restrain the head during the behavioral paradigm. A recording chamber, suitable for the magnetic resonance (MR) scanner (Crist Instruments, Hagerstown, MD), was placed over a 19 mm diameter craniotomy located above the principal sulcus of the right hemisphere. Stereotaxic coordinates used for chamber placement (31 mm anterior, 18 mm posterior) were based on information from an anatomical atlas (Paxinos et al., 1999). The correct placement of the recording chamber was verified after surgery by a high-resolution T2-weighted magnetic resonance image (MRI) obtained in a 4 Tesla MR-scanner.

After training on the behavioral task, monkeys underwent a second surgery for preparation of eye movement recordings using the magnetic search coil technique (Fuchs and Robinson, 1966). A preformed eye coil (3 turns of stainless steel wire, Cooner Wire, Chatsworth, CA) was implanted into one eye behind the conjunctiva (Judge et al., 1980). The coil lead was passed subcutaneously to the head implant. The connector was then attached to the coil lead and firmly anchored with dental acrylic to the head implant.

Monkey weight and health status were carefully monitored throughout the duration of the experiment. Fluid supplements were given as needed.

2.2 - Behavioral Task

Monkeys performed an experimental task of randomly interleaved prosaccade and antisaccade trials (Everling et al., 1999). Prosaccade trials required the monkeys to look towards a flashed peripheral stimulus, and antisaccade trials required the monkeys to look away from the stimulus in a direction opposite the stimulus (Figure 5). Each trial began with the presentation of a white fixation point (FP) at the center of a black 21-inch CRT monitor at a viewing distance of 42 cm in front of the animals. Monkeys were required to fixate on this white center FP within a 3 x 3° window for a period of 500 ms. The central FP then changed color, either to red or green, to provide the task instruction. For Monkey W a red FP was an instruction for a prosaccade, and a green FP was an instruction for an antisaccade. The instructional cues were reversed for Monkey R to avoid possible confounds with cue coloring. Monkeys were required to continue fixation on the colored FP within a 3 ° x 3° window for a period of 500 ms, after which time the FP disappeared. A 200 ms gap period followed FP offset in which the monkey had to maintain central fixation. The 200-ms gap was included because it is known to decrease the fixation-related activity and increase the saccade-related activity in the superior colliculus (Dorris et al., 1997; Everling et al., 1999), which results in a larger proportion of erroneous prosaccade responses on antisaccade trials (Fischer and Weber, 1992; Forbes and Klein, 1996; Bell et al., 2000). After the gap period, a 0.15° visual stimulus was presented pseudorandomly with equal probability of being either 8° to the left or right of fixation. The visual stimulus was red for Monkey W and green for

Monkey R. Saccade endpoints were required to fall within a 6 ° x 6° window surrounding the saccade target location. The monkeys received a juice reward if their behavior met the following conditions: maintained central fixation for the fixation (1000 ms) and gap periods (200 ms); generated a saccade in the correct direction with the correct amplitude within 500 ms; and maintained eccentric fixation for at least 100 ms (Figure 5).

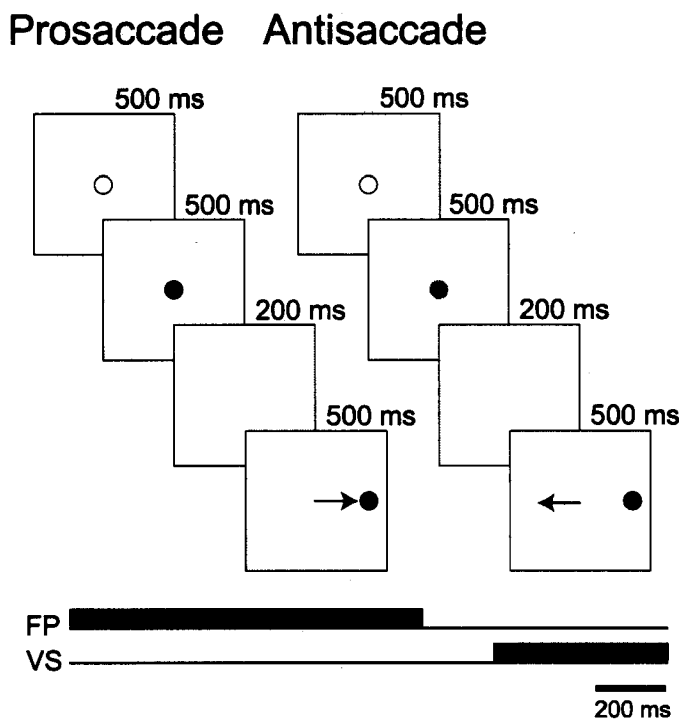


Figure 5. Schematic of the behavioral paradigm. Monkeys were required to generate either a saccade to a peripheral stimulus (prosaccade) or to its diametrically opposite location (antisaccade) depending on fixation point (FP) coloring, either red or green. The paradigm included a gap period, i.e., FP extinguished 200 ms prior to peripheral stimulus onset (VS).

Stimulus presentation, administration of the behavioral paradigm, control of the microstimulator, and reward delivery were controlled by a CORTEX data acquisition system. Horizontal and vertical eye movements were recorded at 1000 Hz by using a magnetic search coil technique (David Northmore Institute, Newark, DE). Eye positions and trial events were stored with the Plexon MAP system (Plexon Inc., Dallas, TX) and analyzed both on-line and off-line using custom-designed software running in MATLAB 7.3 (The Mathworks Inc., Natick, MA). In this report the directions of prosaccades and antisaccades are defined in relation to the hemisphere stimulated (Figure 6).

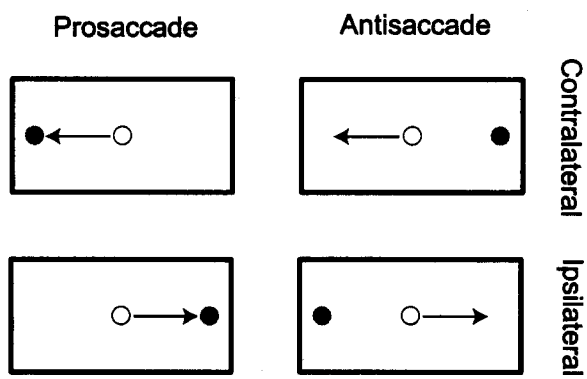


Figure 6. Defining prosaccades and antisaccades based on saccade direction in relation to the stimulated hemisphere. The right DLPFC was stimulated in both monkeys.

2.3 - Electrical Micostimulation

In each session, a single commercially available dura-puncturing tungsten microelectrode (UEWLGDSMNN1E, FHC Inc., Bowdoinham, ME) was driven into the dorsal bank of the principal sulcus using either a computer-controlled microdrive (NAN; Plexon Inc., Dallas TX) or manually-controlled hydraulic microdrive (Narashige, Type MO-95, Tokyo Japan). Coordinates for electrode penetration were based on reconstructed MR anatomical images. Stainless steel guide tubes placed near, but not through the dura, were used to guide the microelectrodes and were stabilized by a delrin grid held rigidly in the recording chamber (Crist Instruments, Hagerstown, MD). The grid system served as a guide to produce parallel penetrations with a resolution of 1 mm.

Multiunit extracellular activity was monitored using the Plexon multichannel acquisition processor (MAP) system (Plexon Inc., Dallas TX). Once single- or multi-unit activity was observed and stable recordings were obtained, the electrode was disconnected from the recording system and connected to a microstimulator with a photoelectric stimulus isolation unit (Grass S88 with PSIU6 photoelectric stimulus isolation unit, Astro-Med, RI) and the paradigm commenced.

Microstimulation was applied randomly on 50% of the trials and consisted of a 200 ms pulse train (0.3 ms biphasic pulses, 200 Hz, 50μA) that began coincident with the time of peripheral stimulus presentation (Figure 7). The microstimulation parameters were chosen based on a few initial experiments in

which modifications were made to duration (range: 50-200 ms), frequency (range: 100-300 Hz) and current (range: 50-200μA) in order to determine threshold parameters for obtaining consistent behavioral effects. Note that varying microstimulation parameters to optimize evoked responses is in accordance with the recommendations of Tehovnik (1996). The chosen parameters are similar to those used in past studies for microstimulation of the pre-supplementary motor area (300 ms train of 0.2 ms cathodal pulses, 200 Hz, 60-80 μA) (Isoda and Hikosaka, 2007). Microstimulation currents of up to 200 μA did not evoke saccades at the stimulation sites (200 ms, 300 Hz, 0.3 ms biphasic pulses).

A microstimulation train of 200 ms composed of 0.3 ms biphasic pulses at a rate of 200 Hz and a current of 50 μA would have an effective current spread of approximately 130 - 470 μm. This current spread estimate uses adjusted current-distance constants of Stoney and colleagues (1968), and assumes that the directly stimulated elements of cortex are similar to the pyramidal cells of motor cortex and that the current-distance constants of monkey pyramidal cells are similar to those of cat pyramidal cells. Charge-balanced biphasic pulses (cathodal pulse followed by anodal pulse) were chosen to reduce neuronal damage (Lily et al., 1955; Bartlett et al., 1977; Brummer and Turner, 1977), as previous studies have suggested that neuronal damage can result from pH changes and gas production around the electrode tip with applied stimulation (for review see Tehovnik 1996).

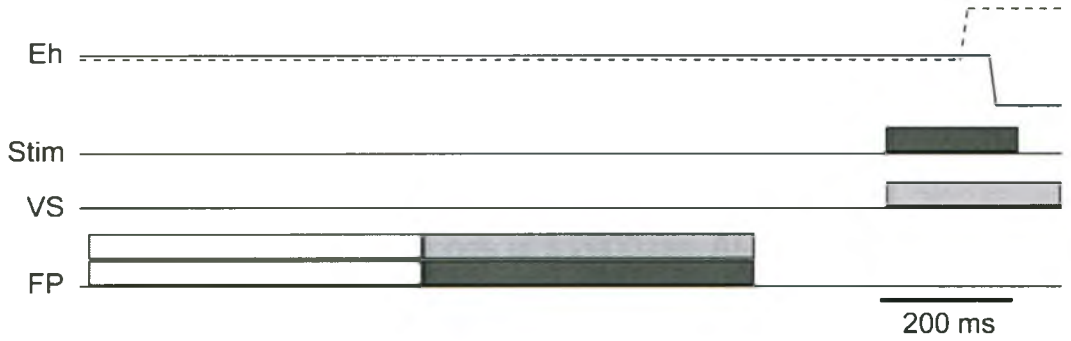


Figure 7. Experimental paradigm. Monkeys were required to generate either a prosaccade or antisaccade depending on fixation point (FP) coloring, either red or green. The paradigm included a gap period, i.e. FP extinguished 200 ms prior to peripheral visual stimulus (VS) onset. Eh – horizontal eye trace. Dashed line shows the Eh of a correctly performed prosaccade. Solid line shows the Eh of a correctly performed antisaccade. Stim – applied microstimulation (200 ms, 200 Hz, 50 μA).

The effects of microstimulation on saccadic reaction times (SRTs) of prosaccades and antisaccades were monitored on-line during the stimulation session using a customized program in MATLAB 7.3. If no effect on SRTs was observed after 22 trials per condition (t-tests, $p>0.05$ for all conditions), the electrode was moved by at least 500 μm and a second data file was collected. Monkeys performed between 22-65 trials per condition (176-520 trials).

2.4 - Training Protocol

Initially, the monkeys were trained to fixate a white FP at the center of a black 21-inch CRT monitor for periods of ≤ 2000 ms. At the start of fixation training, the central FP and accuracy window were kept relatively large and, overtime, were gradually decreased until our the monkeys could perform this task accurately (within a 3° x 3° window) at our desired target size (0.15°).

Monkeys were then required to perform a simple saccade task consisting of a 0.15° central stimulus, that changed from white to red, and a 0.15° red stimulus presented either 8° to the left or right of fixation in both the gap and overlap conditions. The monkeys were required to generate a foveating saccade within 500 ms of stimulus presentation to obtain a liquid reward. As with the fixation task, the on-line accuracy window was kept relatively large (10° x 10° window) at the start of training and was gradually decreased to our desired sized: 6° x 6° window around the visual stimulus, and 3° x 3° window around the central FP. Once the monkeys performed this task correctly on >85% of trials, antisaccade training commenced.

Antisaccade training was based on a color-matching task. Here, each monkey was required to make a foveating saccade to a visual stimulus that matched the color of the central FP. In detail, the monkeys first fixated upon a central FP that changed from white to either red or green, then two visual stimuli, one green and one red, were presented randomly in opposite hemifields, 8° from center. The monkey was rewarded for making a saccade to the target that

matched the color of the central FP. Initially, the monkeys performed a sequence of interleaved trial blocks with each block consisting of either red-FP trials or green-FP trials. Once a high level of performance was achieved in each trial block, the trial types, red-FP trials and green-FP trials, were randomly interleaved. After a sufficient level of performance was achieved (>85%), the circumference and luminance of either the red or green visual stimulus was gradually decreased. As mentioned previously, the color of the central FP instructs the monkey to perform either a prosaccade or an antisaccade. Thus, for Monkey W the relative size and luminance of the green peripheral visual stimulus was reduced, while for Monkey R the relative size and luminance of the red peripheral visual stimulus was reduced. Once the target luminance decreased to its physical limits, bound by the dot pitch of the CRT monitor, the visual target was removed. The removed target replaced the barely visible targets at a rate that maintained a sufficient level of task performance (>70%). Eventually, each monkey was able to perform a task of randomly interleaved prosaccade and antisaccades instructed by the color of the central FP. This represented the final form of the prosaccade and antisaccade task used in this study.

2.5 - Data Analysis

In an offline analysis, saccade onsets were automatically identified by a custom-written computer program using MATLAB 7.3. Saccade onset was defined as the time when horizontal eye velocity first exceeded 30°/s following stimulus presentation, while saccade offset was identified as the time, after saccade onset, when horizontal eye velocity fell below 30°/sec. Trials were visually inspected to ensure accurate marking of saccade onset and offset. Trials with SRTs less than 80 ms or greater than 500 ms were excluded as anticipations or no-response trials, respectively. Trials with incorrect or broken fixation were also excluded.

All values are reported as means ± standard error of the mean. Mean error rate (ER) was calculated for each task condition by taking the number of direction errors divided by the total number of trials performed (correctly performed trials and direction error trials) multiplied by 100.

For each stimulation site, a Wilcoxon rank sum test was used to compare SRTs on stimulated and control trials for each condition. A site was defined as significant if the p value reached < 0.05 for any condition at that site. Across the population of microstimulation sites, statistical comparisons between stimulation and control conditions for mean SRTs and mean ERs were conducted using Wilcoxon sign rank tests evaluated at $p < 0.05$.

In addition to SRTs and ERs, we also computed saccade durations, peak saccade velocities, and horizontal gains for the significant microstimulation sites.

We calculated horizontal gain by dividing the saccadic amplitude in the stimulation conditions by the saccadic amplitude in the control conditions. The gain means were statistically compared to a normal distribution with a mean of 1.00 using a t-test.

Chapter 3 - Results

We stimulated a total of 56 DLPFC sites in two monkeys (34 in Monkey W; 22 in Monkey R; Figure 8). If DLPFC microstimulation resulted in a statistically significant change in SRT for either of the four trial conditions ($p<0.05$, Wilcoxon rank sum test), the microstimulation location was defined as a significant site. From the 56 DLPFC sites electrically stimulated, 57.1% were defined as significant sites (32 total; 18 (53%) from Monkey W; 14 (64%) from Monkey R).

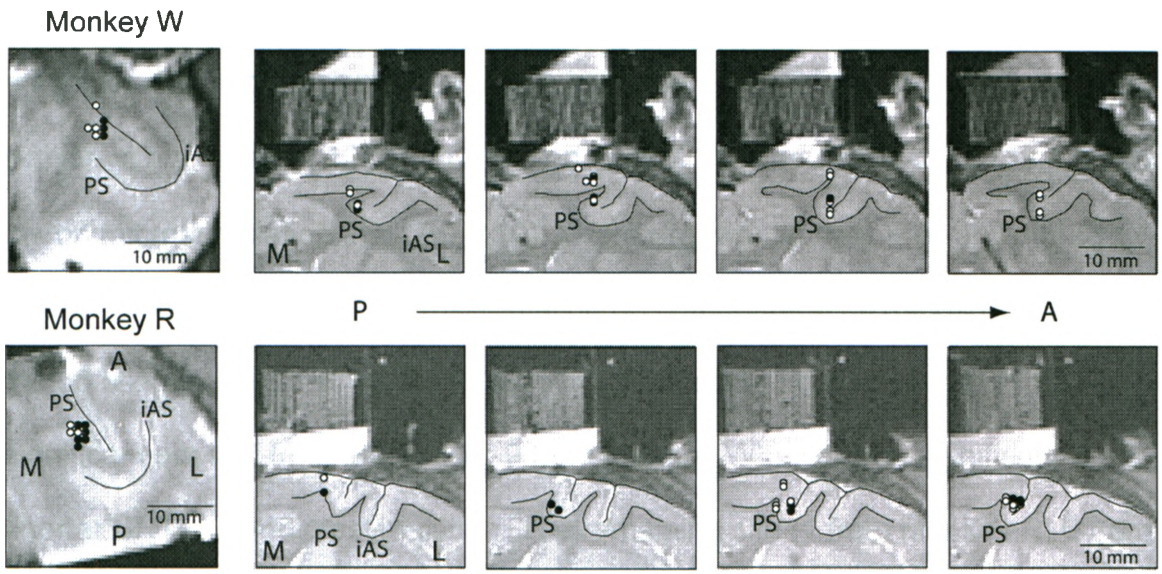


Figure 8. DLPFC microstimulation locations in Monkeys W (top) and R (bottom), reconstructed from MR anatomical images. Slices are separated by 1 mm. White circles represent DLPFC locations showing no significant change in ipsilateral antisaccadic reaction time with microstimulation ($p>0.05$, $n=38$). Black circles represent locations at which a significant change in SRT was shown on ipsilateral antisaccadic trials with microstimulation ($p<0.05$; $n=18$). PS - principal sulcus; iAS - inferior arcuate sulcus; A – Anterior; P – posterior; M – medial; L – lateral.

3.1 - Saccadic Reaction Times

Contrary to the hypothesis, the mean SRT for contralateral prosaccades on microstimulation trials (151.4 ± 1.0 ms) was significantly shorter than the mean SRT on control trials (155.9 ± 1.0 ms; $p<0.05$; Figure 9A top panel). Although the collective mean SRT on microstimulation trials was significantly shorter than the collective mean SRT on control trials, we must acknowledge that these affects were only found to be significant in one subject. The mean SRT for monkey W decreased from 168.3 ± 1.0 ms on control trials to 160.0 ± 1.0 ms on microstimulation trials ($p<0.001$). While in monkey R, SRTs were statistically similar with a mean of 137.2 ± 1.8 ms on control trials and a mean of 139.4 ± 1.8 ms on microstimulation trials ($p>0.10$). Therefore, we cannot make any strong claims about the effect of microstimulation on contralateral prosaccade trials. Of the 56 stimulation sites, we found significant effects at 10 sites. Nine of these significant sites (0 from Monkey R; 9 from Monkey W) displayed significantly shorter SRTs with microstimulation. The remaining site (1 from Monkey R; 0 from Monkey W) exhibited significantly longer SRTs with microstimulation.

The hypothesis predicted that no effect should be observed on ipsilateral prosaccade trials, however the mean SRT for ipsilateral prosaccade trials was significantly longer on microstimulation trials than on control trials (164.3 ± 3.9 ms versus 158.9 ± 3.5 ms, respectively) ($p<0.005$; Figure 9A bottom panel). This effect was consistent across all eight significant sites (4 from Monkey R; 4 from Monkey W). When mean SRTs were determined from only the significant sites,

monkey W demonstrated an increase from 136.0 ± 2.9 ms on control trials to 161.3 ± 4.2 ms on microstimulation trials ($p<0.001$). Similarly, monkey R showed an increase in mean SRT from 179.0 ± 3.5 ms on control trials to 204.3 ± 3.6 ms on microstimulation trials ($p<0.001$).

When we investigated SRTs for contralateral antisaccades (i.e. visual stimulus on the ipsilateral side) we found that the mean SRT during stimulation trials (176.9 ± 4.1 ms) did not significantly differ from that during control trials (177.1 ± 3.7 ms; $p>0.90$; Figure 9B top panel). This is in accordance with the hypothesis predictions. In monkey W, mean SRT on microstimulation trials (154.3 ± 1.6 ms) was statistically similar to the mean SRT on control trials (157.0 ± 1.7 ms) ($p>0.20$). Similarly for monkey R, no significant difference was found between the mean SRT on microstimulation trials (211.9 ± 3.2 ms) and that on control trials (208.1 ± 3.0 ms) ($p>0.10$). We found seven significant sites, in which three sites displayed significantly longer SRTs with microstimulation (2 from Monkey R; 1 from Monkey W), while the remaining four demonstrated the opposite (0 from Monkey R; 4 from Monkey W).

The hypothesis predicted that DLPFC activity should decrease SRTs on ipsilateral antisaccade trials, however for ipsilateral antisaccade trials (i.e. stimulus on the contralateral side) DLPFC microstimulation resulted in a significant increase in SRT (microstimulation = 188.9 ± 5.4 ms; control = 176.8 ± 4.3 ms; $p<0.001$; Figure 9B bottom panel). Significant SRT differences between microstimulation and control trials were found for 18 sites (10 from Monkey R; 8 from Monkey W). For the eight significant sites in monkey W, the mean SRT

increased from 157.1 ± 1.8 ms on control trials to 177.4 ± 2.2 ms on microstimulation trials ($p<0.001$). Similarly for the ten significant sites in monkey R, the mean SRT increased from 210.6 ± 2.3 ms to 237.9 ± 2.6 ms on microstimulation trials ($p<0.001$).

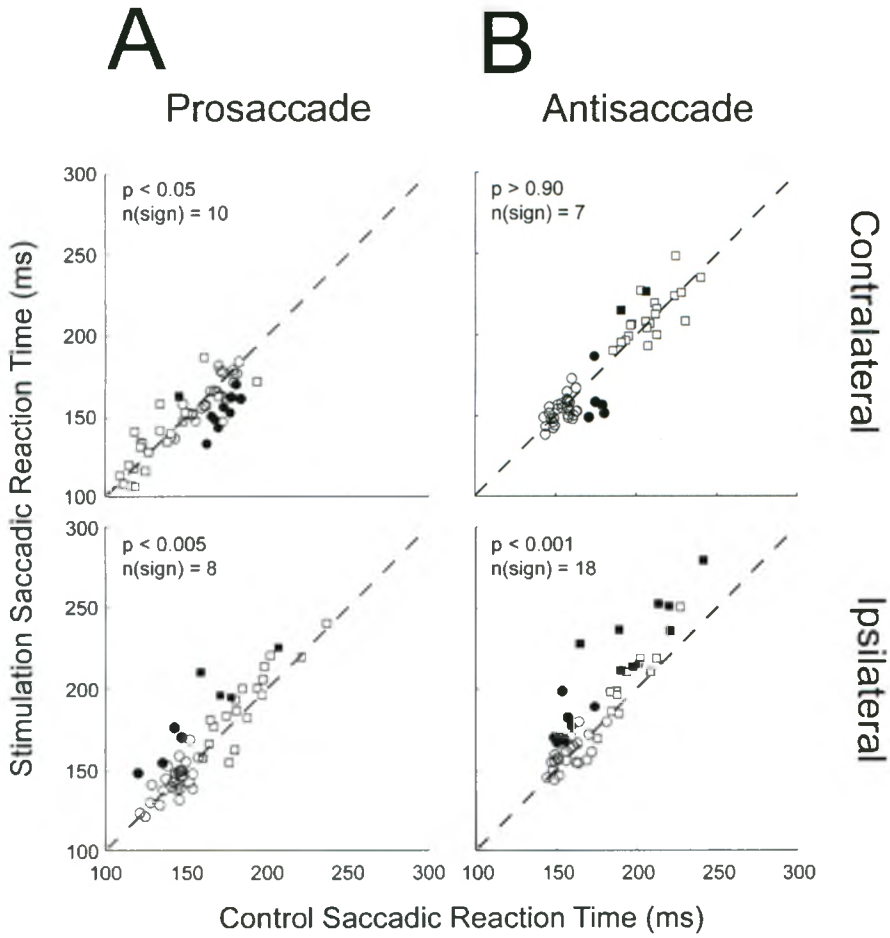


Figure 9. Effect of microstimulation on saccade reaction times (SRTs). The mean SRT for each DLPFC stimulation site in the control condition is plotted against the mean SRT in the stimulation condition. Dashed line represents the unity line (slope=1). Therefore, any point located above the dashed line represents a site in the DLPFC where the mean SRT on control trials was less than the mean SRT on microstimulation trials. Circles represent data from Monkey W (n=34); squares represent data from Monkey R (n=22). Filled symbols indicate significant sites. n(sig) – number of significant stimulation sites; p – p value, Wilcoxon sign rank test (n=56). Ipsilateral and contralateral refers to the direction of the saccade. ***A,*** Prosaccades. ***B,*** Antisaccades.

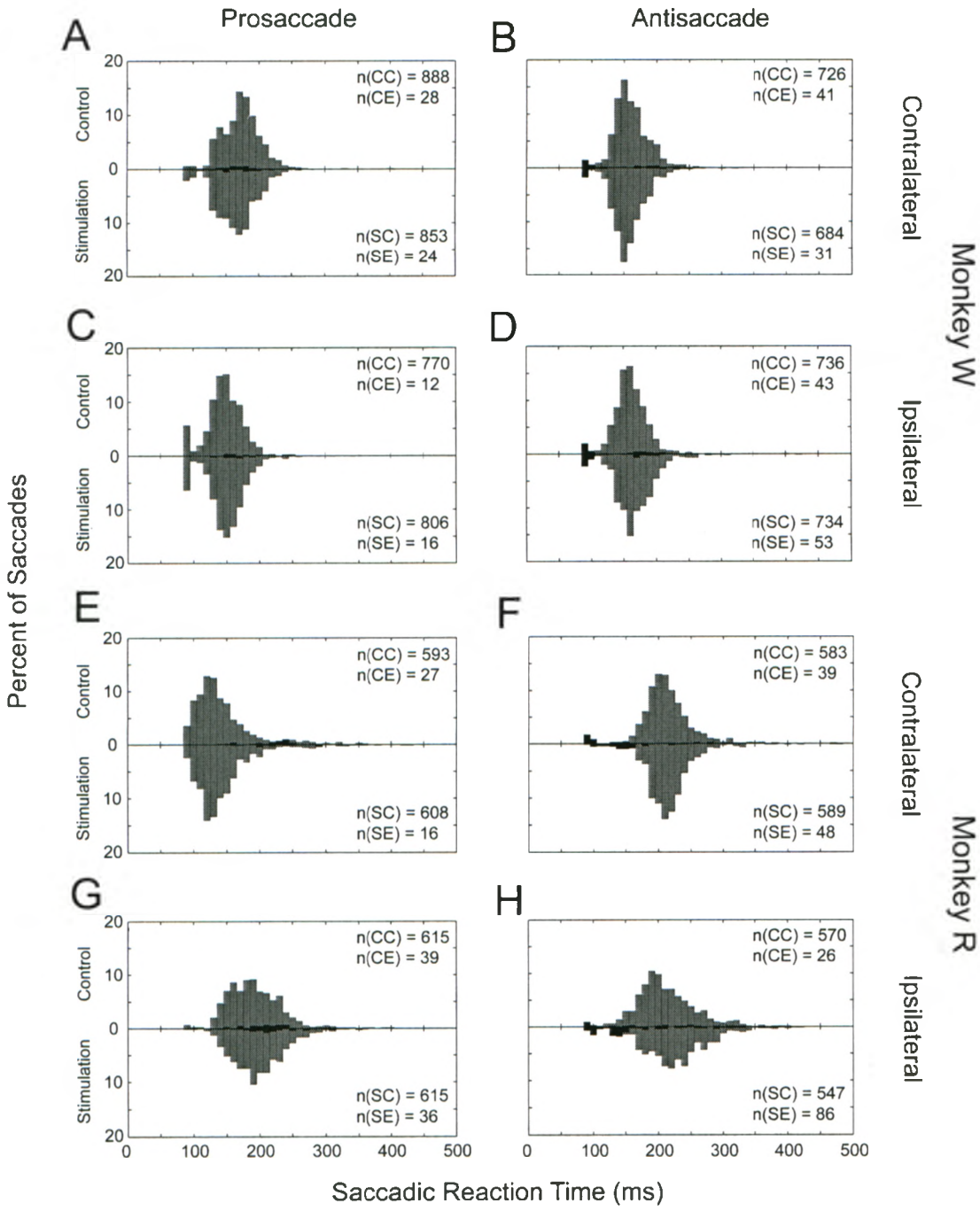
3.2 - Distribution of Saccadic Reaction Times

In summary, and contrary to the hypothesis predictions, DLPFC microstimulation significantly decreased SRTs on contralateral prosaccade trials and increased SRTs on ipsilateral prosaccade and antisaccade trials (Figure 9). In other words, contralateral prosaccades became faster while ipsilateral prosaccades and antisaccades became slower with microstimulation. Although mean SRTs can be used to describe an overall trend, caution should be taken as a mean can be skewed by the presence of an outlier. In this case, an outlier is a SRT that is numerically distant from the rest of the data collected during an experimental session. Therefore, we must investigate the possibility that DLPFC activity, evoked through electrical microstimulation, affected mean SRTs by increasing the number of outliers. To address this concern the distribution of SRTs was plotted (Figure 10). If DLPFC microstimulation increased the number of outliers, then a separate mode in the SRT distribution should exist on microstimulation trials compared with control trials.

Most of the correct SRT distributions show a very similar shape in both stimulation and control conditions (Figure 10 B, C, D, E, F, G), which suggests that microstimulation did not increase the occurrence of outliers. Similarly, the SRT distributions for control and stimulation conditions are similar for ipsilateral antisaccades in Monkey R (Figure 10H). However, in this case microstimulation appears to have shifted the SRT distribution to longer response latencies (Figure 10H). In contrast, DLPFC microstimulation skewed the bimodal contralateral

prosaccade SRT distribution in Monkey W to displaying more reaction times in the 'express' saccade latency (Figure 10A). The SRT distributions for direction errors on prosaccade trials appears to fluctuate with the distributions for correct responses (Figure 10 A, C, G), an exception is the SRT distribution for direction errors on contralateral prosaccade trials for Monkey R (Figure 10E). Here, most errors occurred at latencies longer than the majority of correct SRTs (Figure 10E), which could result from the monkey forgetting the task instruction. The SRT distribution for direction errors in the antisaccade task is short-latency skewed, i.e. the majority of direction errors occurred at latencies shorter than correct responses (Figure 10 B, D, F, H). From viewing the direction error distribution for ipsilateral antisaccades (Figure 10 D, H) it seems that microstimulation increased the number of these faster-latency direction errors when compared to the distribution in the control condition.

Figure 10. Distribution of reaction times for Monkey W (top four panels) and Monkey R (bottom four panels) under control (above the abscissa) and stimulation (below the abscissa) conditions. Correct responses are shown in gray while direction error responses are shown in black. Reaction time distributions incorporate data from all stimulation sites (34 in Monkey W; 22 in Monkey R). Left panels display reaction time distributions during the prosaccade task. Right panels show reaction time distributions during the antisaccade task. n(CC) – number of correct responses in the control condition; n(CE) – number of direction error responses in the control condition; n(SC) – number of correct responses with DLPFC microstimulation; n(SE) – number of direction error responses with DLPFC microstimulation.


Prosaccade
Antisaccade
A
B
C
D
E
F
G
H
n(CC) = 888
n(CE) = 28
n(SC) = 853
n(SE) = 24
n(CC) = 726
n(CE) = 41
n(SC) = 684
n(SE) = 31
n(CC) = 770
n(CE) = 12
n(SC) = 806
n(SE) = 16
n(CC) = 736
n(CE) = 43
n(SC) = 734
n(SE) = 53
n(CC) = 593
n(CE) = 27
n(SC) = 608
n(SE) = 16
n(CC) = 583
n(CE) = 39
n(SC) = 589
n(SE) = 48
n(CC) = 615
n(CE) = 39
n(SC) = 615
n(SE) = 36
n(CC) = 570
n(CE) = 26
n(SC) = 547
n(SE) = 86
Control
Stimulation
20
10
0
10
20
0
100
200
300
400
500
Percent of Saccades
Saccadic Reaction Time (ms)
Contralateral
Ipsilateral
Contralateral
Ipsilateral
Monkey W
Monkey R

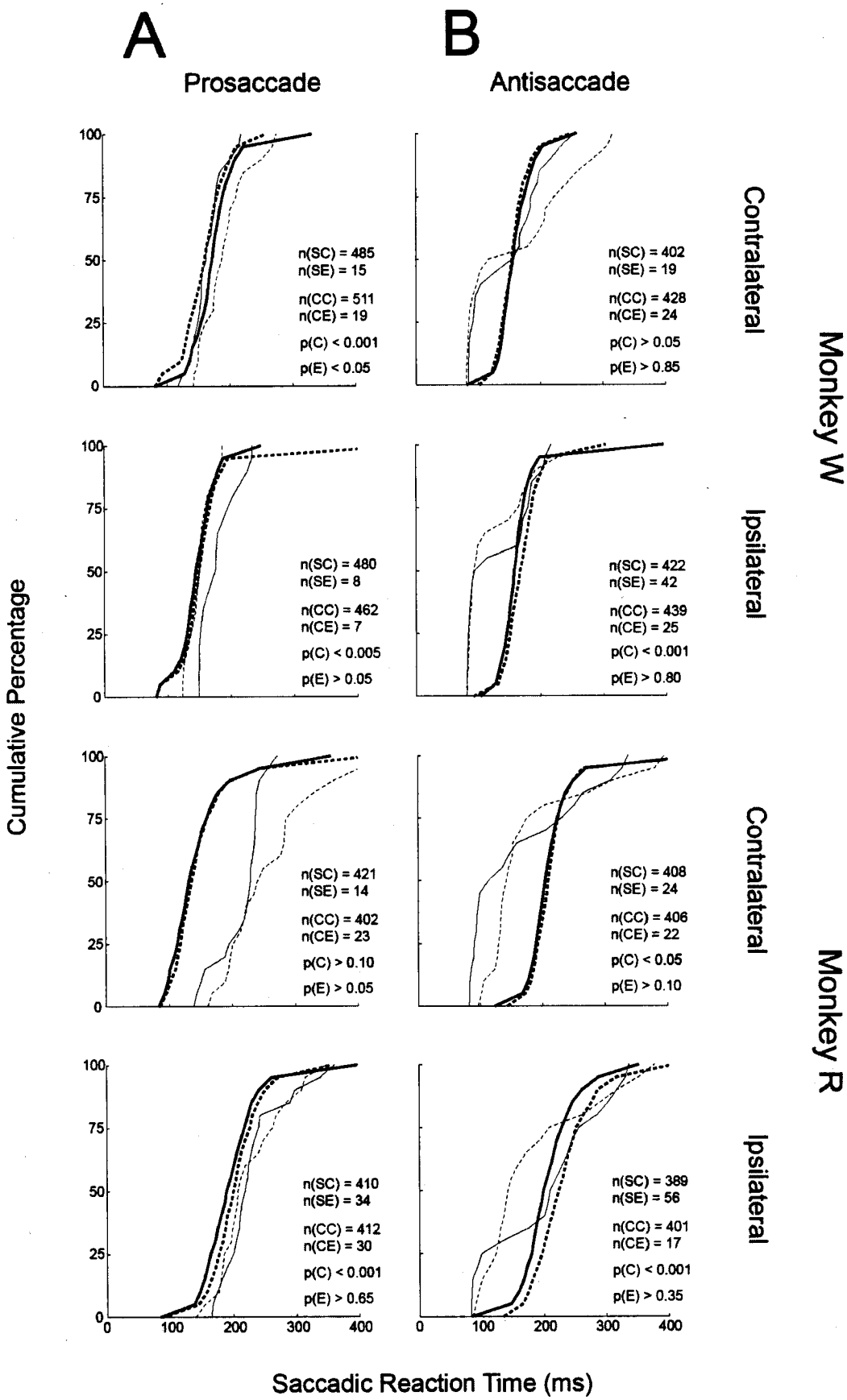
3.3 - The Effect of Microstimulation

As proposed by Johnston and Everling (2006b), the DLPFC sends saccade suppression signals directly to the SC. As such, if the DLPFC is active for a longer period of time before the saccade motor program is generated, then the corresponding saccade suppression signals may build-up to a greater extent in the SC. If this is true, the difference in SRT between control and microstimulation trials will be greater for longer SRTs compared to shorter SRTs.

To address this concern, correct and direction error responses were plotted as a cumulative percentage (Figure 11). In this figure, it is important to note the difference between microstimulation (dashed lines) and control (solid lines) conditions as a function of SRT which increases along the x-axis. If DLPFC activity, evoked by microstimulation, has a greater effect on longer SRT trials, then the difference between the two lines (dashed and solid) should increase along the y-axis. This was not the case. Instead, for all correct responses across both monkeys, the control condition lines appear to closely parallel the stimulation condition lines (Figure 11, thick lines). Therefore, the effects of DLPFC microstimulation are independent of the SRTs on correctly performed trials. In contrast, there does appear to be variability between control and microstimulation condition lines for direction error responses (Figure 11, thin lines). For the majority, this variability is mostly likely due to a small sample size (n(CE); n(SE); Figure 11). However for monkey W, there also appears to be a strong discontinuity between cumulative percentage lines for direction error

responses. This discontinuity for monkey W exists for both antisaccade conditions and can be found around a SRT of 100 ms (thin lines, Figure 11B). This quick divergence from shorter SRTs to longer SRTs, at a cumulative percent around 50%, is probably the result of different error types. The shorter SRTs could be the result of prosaccade responses that were not sufficiently suppressed, while the longer SRTs could be the result of the monkey forgetting the task instruction and as such an inappropriate response was generated at a normal response latency.

Figure 11. Effect of microstimulation on prosaccade (***A***) and antisaccade (***B***) trials for both Monkey W (top four panels) and Monkey R (bottom four panels). Traces show cumulative SRT distributions for control trials (solid lines) and microstimulation trials (dashed lines). Thin lines indicate direction errors and thick lines indicate correct responses. Cumulative percentage plots incorporate data from the 32 DLPFC sites (18 in Monkey W, 14 in Monkey R) at which microstimulation resulted in a statistically significant change in SRT for either of the four trial conditions ($p<0.05$; Wilcoxon rank sum test). p(C) – p value generated from a Wilcoxon rank sum test between correct responses in the stimulated and control conditions; p(E) – p value generated from a Wilcoxon rank sum test between direction error responses in the stimulated and control conditions. n(CC) – number of correct responses in the control condition; n(CE) – number of direction error responses in the control condition; n(SC) – number of correct responses with DLPFC microstimulation; n(SE) – number of direction error responses with DLPFC microstimulation.


A
Prosaccade
B
Antisaccade
Monkey W
Monkey R
Contralateral
Ipsilateral
Contralateral
Ipsilateral
Cumulative Percentage
Saccadic Reaction Time (ms)
n(SC) = 485
n(SE) = 15
n(CC) = 511
n(CE) = 19
p(C) < 0.001
p(E) < 0.05
n(SC) = 402
n(SE) = 19
n(CC) = 428
n(CE) = 24
p(C) > 0.05
p(E) > 0.85
n(SC) = 480
n(SE) = 8
n(CC) = 462
n(CE) = 7
p(C) < 0.005
p(E) > 0.05
n(SC) = 422
n(SE) = 42
n(CC) = 439
n(CE) = 25
p(C) < 0.001
p(E) > 0.80
n(SC) = 421
n(SE) = 14
n(CC) = 402
n(CE) = 23
p(C) > 0.10
p(E) > 0.05
n(SC) = 408
n(SE) = 24
n(CC) = 406
n(CE) = 22
p(C) < 0.05
p(E) > 0.10
n(SC) = 410
n(SE) = 34
n(CC) = 412
n(CE) = 30
p(C) < 0.001
p(E) > 0.65
n(SC) = 389
n(SE) = 56
n(CC) = 401
n(CE) = 17
p(C) < 0.001
p(E) > 0.35
0
25
50
75
100
0
100
200
300
400

Although the effects of DLPFC microstimulation do not appear to depend on the reaction time of correct saccadic responses (Figure 11), it remains to be determined if the effects of microstimulation changed during an experimental session. As an experimental session progresses the subject's satiation will increase, and motivation will decrease. Even though an experimental session was terminated before the effects of satiation could be apparent through on-line monitoring (MATLAB 7.3), a motivation gradient may exist which could facilitate or hinder the effects of microstimulation.

To verify that the effects of microstimulation did not change as a session progressed, a comparison analysis was performed for each DLPFC microstimulation site (n=56). Here, the number of trials performed, direction error trials and correctly performed trials, were divided in half for each experimental session. Session division resulted in an equal number of observations in each time epoch. Mean SRTs were calculated and the mean SRT difference was plotted (1^{st} epoch – 2^{nd} epoch) (Figure 12). In this figure, any line directed to the top right quadrant corresponds to a site at which SRT increased during an experimental session for both microstimulation and control trials. Application of a Wilcoxon sign rank test failed to identify any significant difference between the changes in mean SRT under control and microstimulation conditions ($p>0.45$ in all conditions; n=56; Figure 12). In other words, the change in mean SRT during control trials was statistically similar to the change in mean SRT during microstimulation trials. We also found that significantly more stimulation sites had difference values falling within the top right quadrant of this plot for all conditions

using a χ^2 test ($p<0.01$; Figure 12); that is, as a session progressed the mean SRT increased for both microstimulation and control trials.

Therefore, although SRT generally increases as an experimental session progresses, this change in SRT is similar for both control and microstimulation conditions. From this analysis it is suggested that the effects of microstimulation were not dependent on the subject's motivational state.

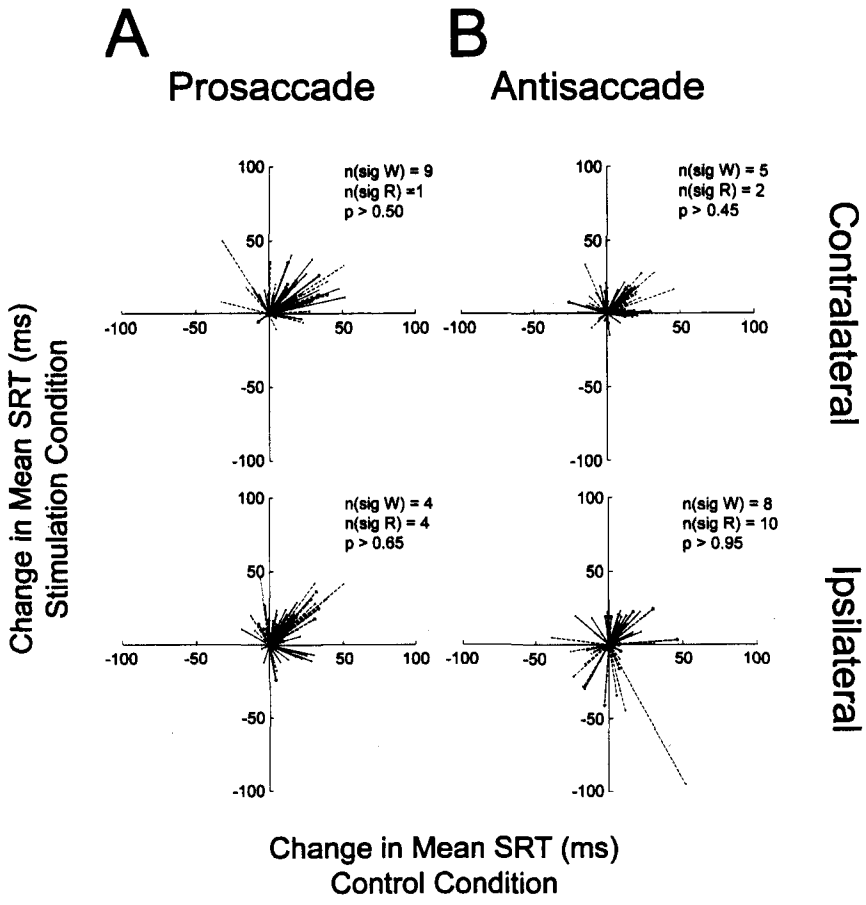


Figure 12. The change in mean SRT during an experimental session. Each experimental session (n=56) was divided into two equal halves based on the number of complete observations. Change was calculated by subtracting the mean SRT of the second epoch from the mean SRT of the first epoch. Solid lines represent data from Monkey W (n=34); dashed lines represent data from Monkey R (n=22); thick lines represent data from significant sites while thin lines represent data from non-significant sites; p – p value determined from a Wilcoxon rank sum test between the change in mean stimulation SRT and the change in mean control SRT; n(sig W) – number of significant stimulation sites from Monkey W; n(sig R) – number of significant stimulation sites from Monkey R. ***A***, Prosaccades. ***B***, Antisaccades.

In summary, the effects of microstimulation did not change with SRT (Figure 11) or during an experimental session (Figure 12). Similarly, microstimulation did not change the SRT distribution (Figure 10). These results alleviate concerns about changes in the effects of microstimulation with decreased motivation as the subject becomes satiated.

3.4 - Error Rates

Microstimulation did not change the number of direction errors on contralateral prosaccade (microstimulation: 2.5 ± 0.5%; control: 3.5 ± 0.6%; $p>0.20$; Figure 13A top panel) or ipsilateral prosaccade trials (microstimulation: 3.4 ± 0.0%; control: 3.1 ± 0.7%; $p>0.80$; Figure 13A bottom panel) as predicted by the hypothesis.

Also as predicted, we found no significant difference in error rates (ERs) between the microstimulation (4.8 ± 0.7%) and control conditions (6.1 ± 0.7 %) on contralateral antisaccade trials ($p>0.15$; Figure 13B top panel). For ipsilateral antisaccade trials, the hypothesis predicted that DLPFC microstimulation would reduce the number of direction errors, to the contrary we found that microstimulation trials had more direction errors than control trials (9.4 ± 1.3% and 5.9 ± 0.9%, respectively; $p<0.005$; Figure 13B bottom panel).

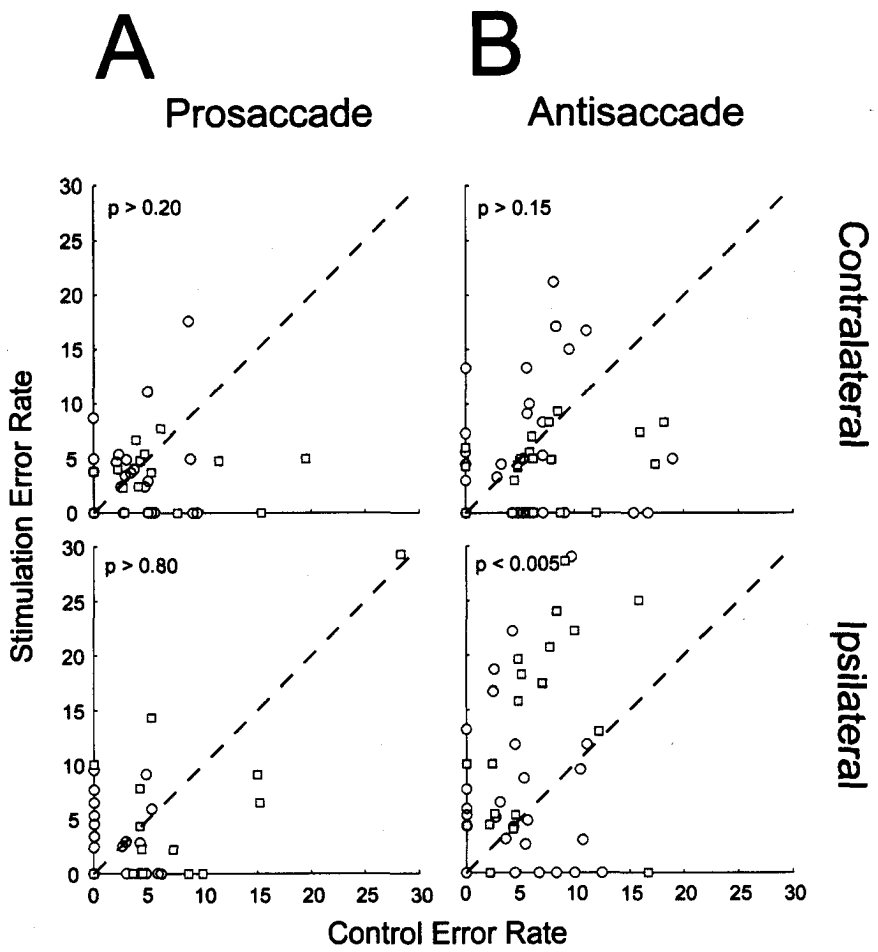


Figure 13. Effect of microstimulation on error rates (ERs). The mean ER for each DLPFC stimulation site in the control condition is plotted against the mean ER in the stimulation condition. Dashed line is the unity line (slope=1). Therefore, any point located above the dashed line represents a site in the DLPFC where the mean ER on control trials was less than the mean ER on microstimulation trials; that is, performance decreased with microstimulation. Circles represent data from Monkey W (n=34); squares represent data from Monkey R (n=22). ER statistical significance could not be determined for each DLPFC microstimulation site. p – p value, Wilcoxon sign rank test (n=56). Ipsilateral and contralateral refers to the direction of the saccade. ***A***, Prosaccades. ***B***, Antisaccades.

3.5 - Comparing Ipsilateral Antisaccade Reaction Times and Error Rates

Contrary to the hypothesis, DLPFC microstimulation increased both SRT and ER on ipsilateral antisaccade trials. In order to identify whether these changes in SRT and ER increased together, we plotted the percent change in SRT [((stimulation/control)*100)-100] against the percent change in error rate (stimulation minus control) (Figure 14). Here, any point located in the top right quadrant corresponds to a site in the DLPFC where microstimulation increased both SRTs and ER on ipsilateral antisaccade trials. For an example please refer to the filled square, circled with a dashed line, located in the top right of Figure 14. This point represents data from a single site in the DLPFC of monkey R at which microstimulation resulted in a statistically significant change in SRT. For this example, DLPFC microstimulation resulted in a 13.0% increase in ER and a 38.2% increase in SRT on ipsilateral antisaccade trials.

When comparing all DLPFC microstimulation sites (n=56), we found a positive correlation between the percent change in SRT and the percent change in ER ($r = 0.39$, $p<0.005$; Figure 14). We also found that significantly more stimulation sites had difference values falling within the top right quadrant of this plot using a χ^2 test ($p<0.001$). These results suggest that microstimulation of the DLPFC influences both SRT and ER during performance of the ipsilateral antisaccade task.

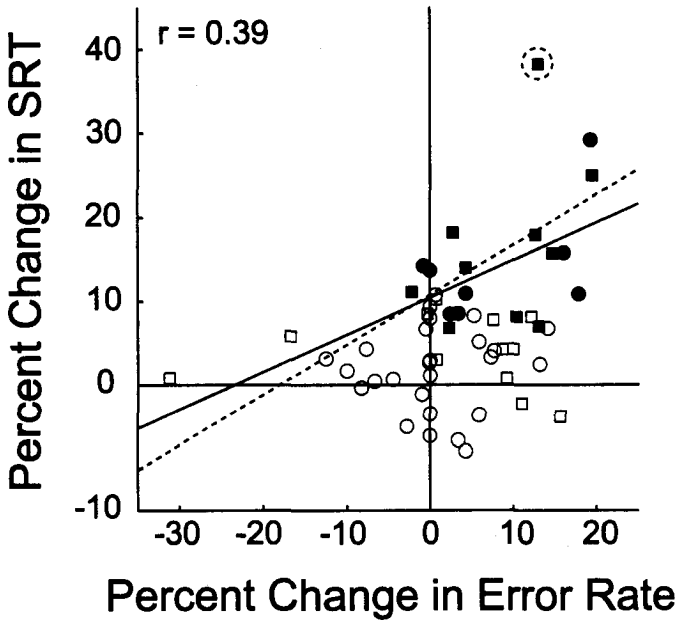


Figure 14. Changes in saccadic reaction time (SRT) and error rate (ER) for ipsilateral antisaccades. The percent change in SRT is plotted against the corresponding percent change in ER for each stimulation site (n=56). Circles represent data from Monkey W (n=34); squares represent data from Monkey R (n=22). Filled symbols indicate significant sites (n=18 total; n=8 for Monkey W; n=10 for Monkey R). Solid and dashed lines are best-fit lines through the significant site data of Monkey W and Monkey R, respectively. The dashed circle indicates the example described in the text.

3.6 - Additional Saccade Parameters

No significant difference was found in mean saccadic duration, mean peak saccadic velocity, and/or mean horizontal gain for either contralateral or ipsilateral prosaccades ($p>0.05$; Table 1).

For contralateral antisaccades, DLPFC microstimulation resulted in higher saccade peak velocities ($p<0.01$). For ipsilateral antisaccades, microstimulation reduced saccade durations ($p<0.01$), reduced peak velocities ($p<0.01$), and reduced the horizontal gains ($p<0.001$). Although statistically significant, these saccade metric differences are small and may reflect indirect effects of DLPFC microstimulation.

Table 1. A summary of saccade metrics (duration, peak velocity, and horizontal gain) for significant stimulation sites (n=32).

		Mean (n = 32)	Control Mean (n = 32)	Stimulation Mean (n = 32)	p Value (t-test)
Contralateral Prosaccades	Duration (ms)		38.4 ± 0.2	38.3 ± 0.2	0.30
	Peak Velocity (°/s)		347.4 ± 12.3	350.2 ± 12.3	0.15
	Horizontal Gain	1.00 ± 0.01			0.41
Ipsilateral Prosaccades	Duration (ms)		38.3 ± 0.3	38.1 ± 0.6	0.07
	Peak Velocity (°/s)		349.5 ± 6.2	349.5 ± 5.7	0.97
	Horizontal Gain	1.00 ± 0.00			0.52
Contralateral Antisaccades	Duration (ms)		48.5 ± 0.7	47.7 ± 0.6	0.07
	Peak Velocity (°/s)		302 ± 10.3	307.6 ± 10.6	*<0.01
	Horizontal Gain	1.01 ± 0.01			0.49
Ipsilateral Antisaccades	Duration (ms)		39.3 ± 0.5	38.4 ± 0.5	*<0.01
	Peak Velocity (°/s)		269.3 ± 8.5	263.7 ± 9.6	*<0.01
	Horizontal Gain	0.96 ± 0.01			*<0.001

* $p < 0.05$

Chapter 4 – Discussion

The dorsolateral prefrontal cortex (DLPFC) has been implicated in various cognitive functions (Duncan and Owen, 2000; Duncan, 2001; Miller and Cohen, 2001). However, the higher activity of DLPFC neurons (Johnston and Everling, 2006b) and higher blood flow or blood-oxygenation-level dependent (BOLD) signals for antisaccades, compared with prosaccades (Sweeney et al., 1996; Curtis and D'Esposito, 2003; Desouza et al., 2003a; Ford et al., 2005; Brown et al., 2007), have almost exclusively been interpreted in terms of a role for the DLPFC in response suppression.

Here, it has been shown that unilateral electrical microstimulation of the monkey DLPFC increases direction errors and slows SRTs for ipsilateral antisaccade trials. We also observed shorter SRTs for contralateral prosaccades and longer SRTs for ipsilateral prosaccades on microstimulation trials. These performance effects are vastly different from our original predictions (Figure 15). Therefore, these findings do not support a role for the DLPFC in response suppression during performance of the antisaccade task. Instead, they point towards a more general role for the DLPFC in attentional selection of the contralateral field. A role for the DLPFC in attentional selection has been supported by single neuron recordings in monkeys (Rainer et al., 1998; Hasegawa et al., 2000; Everling et al., 2002; Desouza and Everling, 2004; Lebedev et al., 2004; Everling et al., 2006) and functional imaging studies in

humans performing other tasks (Owen et al., 1996; Vandenberghe et al., 1997; Rowe and Passingham, 2001; Abe et al., 2007; Luks et al., 2007).

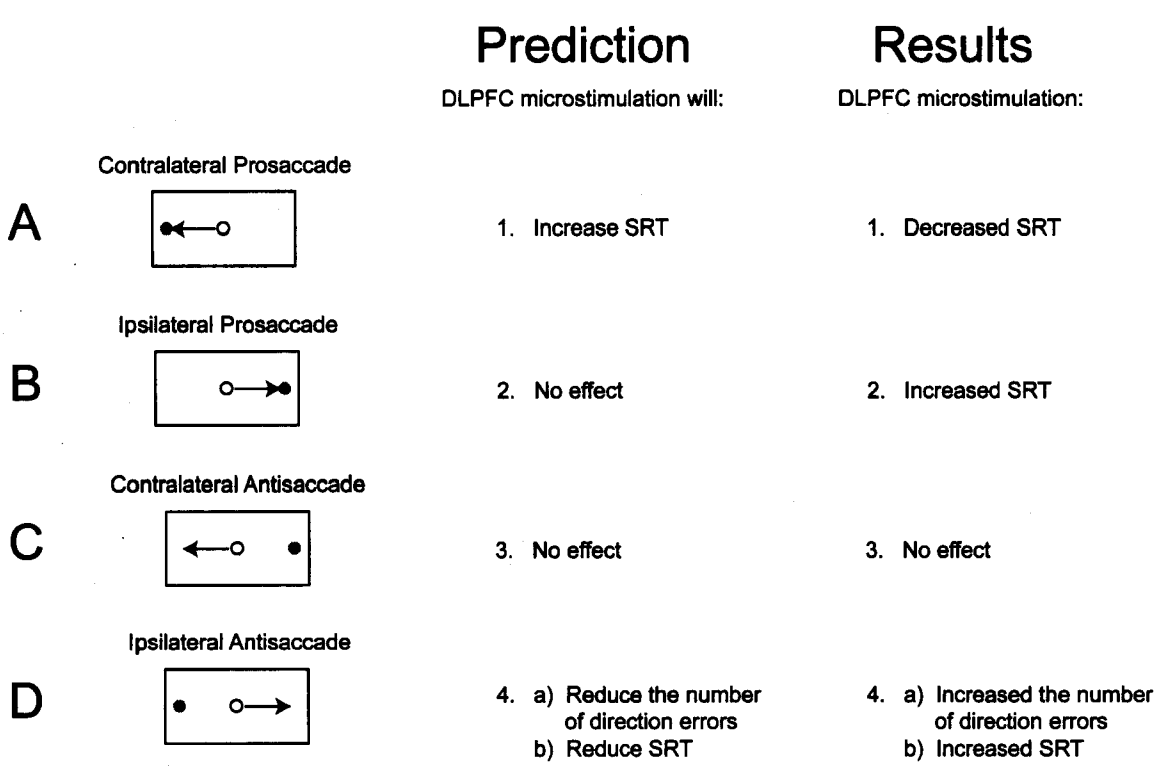


Figure 15. The experimental findings disagree with the predictions of the hypothesis. Trial conditions: ***A,*** contralateral prosaccade trials. ***B,*** ipsilateral prosaccade trials. ***C,*** contralateral antisaccade trials. ***D,*** ipsilateral antisaccade trials.

4.1 - DLPFC Microstimulation and the Response Suppression Model

The initial idea that the DLPFC participates in the suppression of the automatic prosaccade during the antisaccade task has come from lesion studies

in human subjects. Although Guitton (1985) hypothesized in his seminal investigation of antisaccade performance in patients with frontal lobe damage that lesions of the FEF are responsible for the increased error rates, subsequent studies have pointed towards a specific role for the DLPFC in response suppression during the antisaccade task (Pierrot-Deseilligny et al., 1991; Walker et al., 1998; Gaymard et al., 2003; Ploner et al., 2005). The majority of these lesion studies have reported a bilateral increase in error rates and little impairment of SRTs in patients with unilateral DLPFC lesions (except Gaymard et al., 2003). In addition to these DLPFC lesion studies, position emission tomography (Sweeney et al., 1996; Doricchi et al., 1997) and fMRI studies (McDowell et al., 2002; Curtis and D'Esposito, 2003; Desouza et al., 2003a; Ford et al., 2005; Brown et al., 2007) have also found higher DLPFC activations for antisaccade compared with prosaccade trials. Ford and colleagues (2005) observed a higher level of preparatory activation before correct, compared with incorrect, antisaccade responses. This finding supports the idea that a certain activation level in the DLPFC is necessary for saccade suppression. Taken together, it has been proposed that the DLPFC provides top-down signals to saccade-related brain areas to suppress contralateral prosaccades (Munoz and Everling, 2004; Ploner et al., 2005; Johnston and Everling, 2006b).

According to the saccade suppression model presented above, an increase in DLPFC activity should improve ipsilateral antisaccade task performance. However, the present study shows that a manipulation of DLPFC activity, via electrical microstimulation, does not improve ipsilateral antisaccade

performance, but in fact impairs performance on these trials and increases SRTs for ipsilateral pro- and anti-saccades, a finding inconsistent with a simple suppression model.

Previous studies have suggested that other prefrontal cortex regions may be involved in response suppression. A study by Condy and colleagues (2007), which used muscimol injections to temporally deactivate sites in the monkey prefrontal cortex, found increased error rates on ipsilateral antisaccade trials after injections into the ventral bank of the principal sulcus, but observed no effects for injections into the dorsal bank of the principal sulcus. The ventral bank of the principal sulcus is located in the same anatomical area as our applied microstimulation as defined by cytoarchitecture (Petrides and Pandya, 1999). However, the lack of effective sites in the dorsal bank of the principal sulcus suggests that an alternative subregion of the DLPFC is responsible for response suppression during the antisaccade task. Alternatively, Aron and colleagues (2004) have suggested that response inhibition is under control of the inferior frontal cortex (areas 45A and 45B in the monkey).

The effects of electrical microstimulation are usually interpreted as an artificial activation of neurons at the tip of the microelectrode (reviewed in Tehovnik et al., 2006). However, neurons located further from the electrode tip can also be indirectly activated by electrical stimulation (McIlwain, 1982; Strick, 2002; Tolias et al., 2005). In fact, it is practically a certainty that when current is delivered to one cortical area to induce a behavioral change, there will be changes in activity in other areas of the brain as pathways are activated that

underlie the alternative behavior caused by stimulation (Histed and Miller, 2006). For example, stimulation of the FEF produced changes in V4 responses (Moore and Armstrong, 2003). Thus, although microstimulation of the DLPFC did not facilitate antisaccade performance as predicted by the response suppression model, our observed effects could have been mediated through indirect current spread to other structures such as the FEF.

Generally, each FEF is considered responsible for directing contralateral eye movements (Bruce and Goldberg, 1985; Bruce et al., 1985). In the FEF, movement neurons that generate similar saccades enhance each other, whereas neurons that generate saccades in mutually exclusive directions inhibit each other (Schlag et al., 1998). Additionally, the FEF exerts a direct inhibitory control on its counterpart in the other hemisphere (Schlag et al., 1998), and excites saccade-related neuron homologues, while silencing non-homologous neurons, in the SC (Schlag-Rey et al., 1992). Thus, evoked ipsilateral FEF activation, through DLPFC microstimulation, could allow ipsilateral FEF saccade-related neurons to reach threshold earlier, resulting in faster generation of a contralateral prosaccade, while also suppressing the opposing saccade plan in the contralateral FEF, whereby ipsilateral prosaccades would take longer to generate. In addition, the latency of memory-guided antisaccades increases, without disrupting the subject's ability to perform the task, with the application of low-intensity microstimulation to the FEF (20-50 μA, applied simultaneously with the cue to initiate a saccade) (Burman and Bruce, 1997). However, low-intensity FEF microstimulation increased SRTs on both contralateral and ipsilateral

memory-guided antisaccade trials, with contralateral antisaccades being more strongly suppressed than ipsilateral antisaccades (Burman and Bruce, 1997). A finding inconsistent with our observed results. Therefore, regarding the response suppression model, it is unlikely that our observed effects are mediated through FEF activation via indirect current spread from the DLPFC.

4.2 - DLPFC Microstimulation: induced disruption of top-down processing

Even though, the majority of the literature suggests that the DLPFC is a potential source of automatic saccade suppression, modulating SC saccade-related neurons during antisaccades in a top-down fashion (Munoz and Everling, 2004), our experimental observations do not support activation of this pathway.

Although local neurons usually become active by direct depolization from the stimulation current (Stoney et al., 1968; Ranck, 1975), the alternative should also be considered as suggested by the effects of deep brain stimulation (DBS). It has been proposed that the overall effect of high frequency DBS is to inhibit the neural activity in the region stimulated. This suggestion has been based on the observation that the effects of high frequency DBS are similar to those produced by making a lesion in the same area (reviewed in Dostrovsky and Lozano, 2002). In this vein, it could be possible, although unlikely, that microstimulation in fact reduced DLPFC output signals to other brain areas like the FEF or SC. For example, if microstimulation increased the activity of local inhibitory interneurons, more than excitatory pyramidal neurons, then the resulting DLPFC output would

be decreased, thereby decreasing any putative suppression signal sent to saccade-related brain areas.

It has been suggested that DLPFC output to the SC excites either fixation neurons or inhibitory interneurons, which then suppress the activity of SC saccade-related neurons during the antisaccade task (Johnston and Everling, 2006b). Therefore, a microstimulated-disruption of DLPFC processing to the SC could explain the increased number of direction errors in the ipsilateral antisaccade task.

In comparison, the majority of DLPFC lesion literature reported a bilateral increase in error rates in patients with DLPFC lesions with little impairment of reaction times, while an increase in antisaccade reaction times has been reported after isolated unilateral FEF lesions (Rivaud et al., 1994; Gaymard et al., 1999). Also, patients with specific FEF lesions display significantly longer ipsilateral prosaccade latencies while performing either an overlap saccade task or a memory-guided saccade task (Rivaud et al., 1994; Gaymard et al., 1999; Ploner et al., 1999). Thus, a microstimulated-disruption of DLPFC processing to the FEF could explain both the increased SRTs on ipsilateral antisaccade trials, and the increased SRTs on ipsilateral prosaccade trials. Such a disruptive effect of electrical microstimulation has also been observed previously in the supplementary motor area (Histed and Miller, 2006), and dorsal premotor cortex (Churchland and Shenoy, 2007). Also, this microstimulation effect is reminiscent of the inhibitory effects of transcranial magnetic stimulation on DLPFC function

seen in human studies (Muri et al., 1996; Jahanshahi and Dirnberger, 1999; Mull and Seyal, 2001).

Is it possible that our observed performance effects are mediated by indirect projections through the basal ganglia to the SC? Previously, it has been suggested that the basal ganglia has a role in saccade suppression (for review see Hikosaka et al., 2000). A preliminary single-neuron study of the globus pallidus demonstrated higher neuronal activity during antisaccades compared to prosaccades, with most neurons also exhibiting task-dependent modulation even before target onset (Yoshida and Tanaka, 2007). Additionally, patients with Parkinson's disease, which results from degeneration of dopaminergic neurons in the substantia nigra pars compacta (Leenders and Oertel, 2001; Bergman and Deuschl, 2002), show increased direction errors in the antisaccade task, and also show more short-latency responses on prosaccade trials and slower reaction times on antisaccade trials, when compared to controls (Chan et al., 2005). Taken together, a microstimulated-disruption of DLPFC processing to the basal ganglia could explain most of our observed results, with the exception of our demonstrated increase in ipsilateral prosaccade SRTs. However, it is important to note that a small amount of evidence alternatively supports that neither the basal ganglia nor the thalamus plays a major role in automatic saccade suppression during the antisaccade task (Condy et al., 2004). In summary, although some of our results could be explained by a disruption of DLPFC response suppression signaling to the basal ganglia, a more likely explanation

may involve microstimulated DLPFC activation and the role of the basal ganglia in spatial attention (discussed in section 4.3).

The SEF has also been implicated in response suppression (Sumner et al., 2007). SEF neuronal discharges are consistently greater before antisaccades than before prosaccades with the same trajectories, and this increased activity on antisaccade trials was already present before the target specified movement direction (Schlag-Rey et al., 1997). Additionally, the activity of these neurons is lower on direction error trials during the antisaccade task (Schlag-Rey et al., 1997). It has also been found that prolonged SEF stimulation holds the eyes in place at that position, inhibiting further execution of movements (Penfield and Welch, 1951). Although the DLPFC makes reciprocal connections with the SEF (Bates and Goldman-Rakic, 1993), these projections probably would not mediate our observed effect on SRTs or performance of antisaccades, especially since our stimulation was aligned to visual target onset. This is supported by the fact that there is no observed increase in antisaccade error rate with unilateral lesions isolated to the SEF (Gaymard et al., 1990; Pierrot-Deseilligny et al., 1991). Finally, the majority of our significant results involved ipsilaterally directed saccades, while the SEF is known have a bilateral representation of saccades and hand movements (Tehovnik et al., 2000; Fujii et al., 2002; Sumner et al., 2007).

As an alternative to the suggestion that microstimulation reduced DLPFC output signals, the application of microstimulation may have disrupted the temporal flow of information processing in the prefrontal cortex, which has been

shown to be important in execution of a behavioral task (Constantinidis et al., 2002). In this case, DLPFC activity would consist of an inane, or nonsense, signal sent directly to saccade-related brain areas paralleling the effects of a microstimulation-induced disruption of top-down processing as discussed above. A temporal disruptive effect has also been seen in human studies employing transcranial magnetic stimulation on the DLPFC (Muri et al., 1996; Jahanshahi and Dirnberger, 1999; Mull and Seyal, 2001).

Although it is unlikely that electrical microstimulation of the DLPFC resulted in lesion-like effects, the possibility has been addressed. From this discussion it should be apparent that neither of the microstimulation-induced disruption models, presented above, fully encompass all of our significant results. Thus, an alternative explanation should be considered.

4.3 - DLPFC Microstimulation: a change in attentional allocation

A more direct explanation of our results is that microstimulation evoked an attentional or preparatory bias towards the contralateral visual field. Spatial attention allows us to selectively perceive stimuli at relevant locations at the expense of stimuli at other locations (Moore and Fallah, 2001). For example, Moran and Desimone (1985) showed that if two stimuli are presented in the receptive field of a visual neuron in V4, one for which the neuron is selective and one for which it is not, the response of the neuron to the optimal stimulus is reduced when the monkey attends to the other stimulus.

A role for the DLPFC in attentional selection has been suggested by many neuropsychological and functional imaging studies (Owen et al., 1996; Vandenberghe et al., 1997; Rowe and Passingham, 2001; Peers et al., 2005; Abe et al., 2007; Luks et al., 2007). Furthermore, single neuron recordings in monkeys found that DLPFC neurons have increased responses for attended stimuli (Rainer et al., 1998; Everling et al., 2002, 2006), with a bias towards the contralateral field. When attention is cued contralaterally, <100 ms before target onset, subjects are faster to saccade towards a target in the cued location and slower to saccade toward a target in the ipsilateral location (Posner and Cohen, 1984). Taking this information together, it is likely that DLPFC microstimulation enhanced the preference for contralaterally presented targets. This induced attentional shift to the contralateral hemifield would facilitate the more automatic contralateral prosaccade, resulting in faster SRTs, and would impede, or slow SRTs, for both ipsilateral prosaccades and the more voluntary ipsilateral antisaccades. This is what was found (Figure 15). It has been mentioned previously that the DLPFC acts to coordinate the activity of cortical and subcortical areas to which it is reciprocally connected, via top-down processing (reviewed in Miller and Cohen, 2001). In this manner the observed attentional shift, via DLPFC electrical microstimulation, may be mediated through other neuronal structures to which the DLPFC is connected.

For example, our observed attentional shift could be mediated through the basal ganglia as the caudate nucleus receives input from the DLPFC (Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991). Although, it was

previously suggested that our results could be partially explained through a microstimulation-induced disruption of response suppression processing in the basal ganglia, a more inclusive explanation involves the basal ganglia's role in attentional allocation. Previous studies have suggested that the monkey basal ganglia contributes to both oculomotor and attention orienting to the contralateral hemifield (Hikosaka et al., 1989; Apicella et al., 1991; Kori et al., 1995; Miyashita et al., 1995). Thus, electrically induced DLPFC activity could stimulate the caudate nucleus resulting in attentional selection of the contralateral visual field.

While neurons in the DLPFC appear to reflect attentional selection, the main frontal area implicated in directing attention has been the FEF (Corbetta et al., 1993; Corbetta et al., 1998). Transcranial magnetic stimulation (Grosbras and Paus, 2003; Muggleton et al., 2003; Ro et al., 2003) and neuroimaging studies (Hopfinger et al., 2000; Corbetta and Shulman, 2002; Kincade et al., 2005; Serences et al., 2005) in humans have shown that activity in the FEF reflects both voluntary and stimulus-driven deployments of attention during spatial cueing and visual search tasks, even when no eye movements are made (Serences and Yantis, 2006). Similarly, single-neurons studies revealed that FEF neuronal activity was modulated while paying attention to a stimulus in the peripheral visual field, even if the stimulus was not a target of eye movement (Kodaka et al., 1997). Therefore, our observed effects on SRTs and ERs may be mediated by projections from the DLPFC to the FEF (Pandya and Kuypers, 1969), or alternatively, by projections from the DLPFC to posterior cortical areas (Goldman-Rakic, 1988).

Area LIP, in the macaque parietal cortex (which can be identified with the parietal eye field in the human), is reciprocally connected to the DLPFC (Schwartz and Goldman-Rakic, 1984; Cavada and Goldman-Rakic, 1989; Hikosaka et al., 2000). Area LIP is involved in visual attention (Robinson et al., 1995; Colby et al., 1996; Gottlieb et al., 1998; Gottlieb and Goldberg, 1999; Powell and Goldberg, 2000), representing both voluntary and stimulus-driven contributions to attention priority (reviewed in Serences and Yantis, 2006). Monkey single-neuron studies have revealed that activity in area LIP continuously describes the locus of attention; however, this can only be determined by looking at the activity of the ensemble of neurons in area LIP representing all of the visual field (Bisley and Goldberg, 2003).

Another alternative could be that projections from the DLPFC to the ipsilateral SC (Goldman and Nauta, 1976; Leichnetz et al., 1981; Johnston and Everling, 2006b) could bias preparatory activity for contralateral saccades. For instance, Muller and colleagues (2005) found that application of microstimulation to visuomotor neurons in the SC induced a covert shift of attention and behavioral facilitation in a specific region of the visual field corresponding to the location of the stimulation site in the SC. This interpretation may appear to contradict the results from Johnston and Everling (2006b), who found enhanced activity on antisaccade compared with prosaccade trials. However, in the absence of data on the discharge pattern of these neurons for direction errors, we cannot rule out the possibility that DLPFC neurons provide an excitatory drive to saccade neurons in the SC.

4.4 – Technical Considerations

The present study adds to over 125 years of electrical stimulation studies, attesting to the importance of this technique in developing our present understanding of the brain. However, the application of electrical stimulation has two major short-comings: poor selectivity and poor spatial resolution.

Electrical microstimulation indiscriminately depolarizes excitatory neurons, all classes of inhibitory neurons, and fibers that pass through the stimulated area. Thus, electrical microstimulation may activate neural elements not implicated in the investigated behavior or disease. In other words, it is generally impossible to target specific classes of neurons in a heterogeneously populated tissue. This short-coming could explain the inconsistencies observed between microstimulation studies. For example, one study suggests that SEF electrical microstimulation evokes saccades that bring the eyes to a specific position of craniotopic space (Tehovnik and Lee, 1993), while another study suggests that SEF microstimulation evokes constant-vector saccades (Russo and Bruce, 1993).

Another issue concerning electrical stimulation is the lack of accurate estimates of effective current spread, which encompasses transynaptic spread. Such estimates of transynaptic spread have suggested a roughly two- to four-fold greater current-spread estimate using functional magnetic resonance imaging (fMRI) compared to those determined by single-cell recordings and behavioral methods (Tolias et al., 2005; Tehovnik et al., 2006). Although, current spread into

non-targeted regions is a major concern, it can often be reduced or eliminated by adjusting the electrical pulse parameters. Unfortunately, a reduced current spread is often accomplished at the cost of a decreased behavioral effect.

Presently, new stimulation techniques have been introduced which can overcome the poor specificity and spatial control of electrical microstimulation. Optogenetics is an emerging field which combines optics and genetics to probe neuronal circuits. Here, microbial light-sensitive proteins, *Chlamydomonas reinhardtii* Channelrhodopsin-2 (ChR2) and *Natronomonas pharaonis* halorhodopsin (NpHR), are virally introduced into specific neuronal populations allowing for on/off control of these neuronal circuits (Aravanis et al., 2007; Zhang et al., 2007b). ChR2 allows sodium ions to enter the cell following exposure to ~470 nm blue light, whereas the NpHR is a chloride pump that activates upon illumination with ~580 nm yellow light (Zhang et al., 2007a). Thus, transfected neurons can be activated or silenced through the application of particular wavelengths of light delivered into the brain via a fibreoptic-based system (Aravanis et al., 2007) or by using high intensity light-emitting diodes (LEDs). Although opitical neuromodulation remains in the early stages of research, its future application will allow investigators to activate, or inhibit, specific types of neurons that have been implicated in disorders and behavior.

Chapter 5 – Summary and Conclusion

The primate DLPFC has been linked to a multitude of cognitive functions (Duncan and Owen, 2000), including response suppression (Pierrot-Deseilligny et al., 1991; Gaymard et al., 2003; Ploner et al., 2005; Johnston and Everling, 2006b). This study is the first to employ electrical microstimulation to the DLPFC and investigate its effects on response suppression during the antisaccade task.

We hypothesized that DLPFC activity would inhibit contralateral prosaccades, thus facilitating ipsilateral antisaccades. The hypothesis was tested by electrically microstimulating the DLPFC of two monkeys, aligned to peripheral target onset (200 ms, 200 Hz, 50 μA), while they performed a task of randomly interleaved prosaccade and antisaccade trials. Based on the hypothesis and task conditions, four predictions were made. We predicted that DLPFC microstimulation would prolong SRTs on contralateral prosaccade trials (Figure 15A), have no SRT effect on either ipsilateral prosaccade or contralateral antisaccade trials (Figure 15 B,C), and would reduce SRTs and the number of direction errors on ipsilateral antisaccade trials (Figure 15D).

Contrary to our predictions, it was found that unilateral DLPFC microstimulation increased the number of direction errors and slowed SRTs on ipsilateral antisaccade trials. We also observed shorter SRTs for contralateral prosaccades and longer SRTs for ipsilateral prosaccades on microstimulation trials. These findings do not support a role for the DLPFC in response suppression during the antisaccade task. Instead, our observations suggest that

DLPFC microstimulation evoked an attentional or preparatory bias towards the contralateral visual field in a possible top-down control fashion.

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Western

12.18.07
*This is the 3rd Renewal of this protocol
*A Full Protocol submission will be required in 2008

Dear Dr. Everling

Your Animal Use Protocol form entitled:

Neural Basis of Visual Attention and Response Suppression in Primates

has been approved by the Animal Use Subcommittee.
This approval is valid from 01.01.08 to 12.31.08
The protocol number for this project remains as 2004-099-12

1. This number must be indicated when ordering animals for this project.
2. Animals for other projects may not be ordered under this number.
3. If no number appears please contact this office when grant approval is received.
   If the application for funding is not successful and you wish to proceed with the project, request that an internal scientific peer review be performed by the Animal Use Subcommittee office.
4. Purchases of animals other than through this system must be cleared through the ACVS office. Health certificates will be required.

ANIMALS APPROVED FOR 1 YEAR **Highest Pain Level:** D

Species	Other Detail	Housing/Use Locations	Animal # Total for 1 Year
Rhesus	3-15 kg, male	CBM / CBM	10

REQUIREMENTS/COMMENTS
Please ensure that individual(s) performing procedures on live animals, as described in this protocol, are familiar with the contents of this document.

c.c. Approved Protocol - S Everling, T Admans, W Lagerwerf
Approval Letter - T Admans, W Lagerwerf