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# Differential Effects of Macaque Dorsolateral Prefrontal Deactivations During Uncued and Cued Role Conditions

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science

# DIFFERENTIAL EFFECTS OF MACAQUE DORSOLATERAL PREFRONTAL DEACTIVATIONS DURING UNCUED AND CUED RULE CONDITIONS

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FUNCTIONAL SPECIALIZATION WITIN THE DLPFC

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Cognitive control enables us to guide our behaviour in an appropriate, context-dependent manner. This behavioral flexibility is probed by task-switching paradigms, which require working memory to maintain relevant rules and flexibility to switch between rules. The dorsolateral prefrontal cortex (DLPFC) has been implicated in rule maintenance by neuroimaging and electrophysiological studies. While these studies have identified a correlation between DLPFC activity and rule maintenance, deactivation studies allow us to establish a causal relationship. Here we have examined the effect of bilateral deactivation of areas 46 and 9/46d on rule maintenance, while a monkey (*Macacca mulatta*) performed blocks of pro- and anti-saccades.

Areas 46 and 9/46d were deactivated by pumping chilled methanol through bilaterally implanted cryoloops. Rule maintenance was tested while monkeys performed blocks of pro- and anti-saccades with and without instruction cues. Monkeys had to look toward the stimulus on pro-saccade trials and away from the stimulus to its mirror location on anti-saccade trials. After 15-25 correct responses, the task switched (e.g. from pro-saccades to anti-saccades) without any explicit signal to the monkey.

Bilateral area 46 deactivation impaired performance throughout both blocks, while bilateral area 9/46d deactivation did not affect performance. Surprisingly, bilateral deactivation of both areas (46 and 9/46d) impaired performance on anti-saccade trials but recovered performance on pro-saccade trials. These results present a causal relationship between area 46 and rule maintenance and provide evidence for functional dissociation between subregions in the dorsolateral PFC for rule-guided behavior.

**Key Words:** dorsolateral prefrontal cortex, rule maintenance, cooling, deactivation, regional specialization, principal sulcus

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## List of Abbreviations

| | |
|---|---|
| -in: | inches |
| °C: | degrees Celsius |
| ACC: | anterior cingulate cortex |
| AS: | arcuate sulcus |
| BOLD: | blood-oxygen-level-dependent |
| cm: | centimeter |
| DLPF: | dorsolateral prefrontal |
| DLPFC: | dorsolateral prefrontal cortex |
| DMS: | delayed match-to-sample |
| DR: | delayed-response |
| FEF: | frontal eye fields |
| Fig.: | figure |
| fMRI: | functional magnetic resonance imaging |
| LPFC: | lateral prefrontal cortex |
| mm: | millimeter |
| ms: | millisecond |
| PFC: | prefrontal cortex |
| pre-SMA: | pre-supplementary motor area |
| PS: | principal sulcus |
| RT: | reaction time |
| S-R: | stimulus-response |
| SEF: | supplementary eye fields |
| SMA: | supplementary motor area |
| VLPFC: | ventrolateral prefrontal cortex |
| WCST: | Wisconsin card sorting task |
| WM: | working memory |

## Section 1

# INTRODUCTION

## 1.1 Prefrontal cortex and Cognition.

Cognitive control enables us to flexibly guide our behaviour in an appropriate, context-dependent manner (Miller and Cohen, 2001). It allows one to simultaneously and selectively adapt working memory load, attention, stimulus comparisons and other processes necessary for appropriate response preparation. This type of control is crucial in everyday life to guide suitable actions when one is presented with a plethora of stimuli and possible responses. Cognitive control processes are distributed throughout multiple neural components in cortical and subcortical regions (Cole and Schneider, 2007).

Miller and Cohen's (2001) review of the prefrontal cortex (PFC) provides a thorough examination of its role in cognitive control. They suggest that executive functioning results from the representation of goals and means characterized by neural activity in the PFC. This results in competitive neural processing where actions with the strongest representations are successful in being implemented. As such, additional activity is needed for biasing away from prepotent, automatic actions to enable performance of more controlled and complex tasks. The PFC is thought to provide bias signals to other brain areas and assist with complex task performance. These PFC bias signals help guide the flow of activity between inputs and outputs. As such, the PFC is implicated in holding stimulus representations on-line and allows for performance of appropriate context-dependent behavioural responses. Accordingly, the PFC is also well positioned and connected to allow for this range of processing because it sends and

receives projections from most sensory and motor cortical and subcortical regions (See PFC connectivity; Petrides, 1995).

Additionally, Brutkowski's analysis of earlier work regarding the role of the PFC in cognition concluded that the PFC is critical for inhibitory functions (Brutkowski, 1965; Stanley and Jayne, 1948). This analysis examined PFC lesion studies, which have reported tendencies of ablated animals towards prepotent, automatic behaviours. He explained these effects as due to loss of general inhibition (disinhibition) resulting in perseverative tendencies. Thus, the PFC does not seem to be involved in the performance of automatic behaviours. Instead, it is activated during tasks that present a higher demand for control. Tasks that are directed by internal states (motivation, attention and goals) tend to reliably recruit the PFC. This is evident via PFC lesion studies that impair performance in tasks such as the Stroop Test and Wisconsin Card Sorting Task (WCST), both of which require performance of internally guided actions. These deficits will be discussed in detail later.

## 1.2 DLPFC: Anatomy, Cytoarchitecture, Connectivity and Functional Organization.

The PFC is the most distinguished and developed region in the primate brain in terms of size and connectivity. The PFC's position in the cortex supports its participation in a wide range of behaviors. The PFC can be differentiated into subregions based on differences in cytoarchitectonic composition (Brodmann, 1909; Petrides and Pandya, 1999; Petrides et al., 2012; Walker, 1940). The

diverse functionality of the PFC can be explained by the fact that the subregions of the PFC receive and send projections to virtually all cortical sensory and motor systems, with the exception of V1 and M1 (Goldman and Nauta, 1976). There are also local connections within and between subregions of the PFC allowing for functional integration (Pandya and Kuypers, 1969; Petrides, 2005; Yeterian et al., 2012). This enables the PFC to integrate and relay multimodal information.

### 1.2.1 Anatomical Location.

The PFC is a large structure in both humans and monkeys that spans several distinctive cytoarchitectural and functional regions. As such, it has been divided into several subregions based on these differences. For the purpose of our study, we will focus on the dorsolateral prefrontal cortex (DLPFC). In both humans and monkeys the DLPFC encompasses Brodmann's areas 9 and 46 (Figure 1).

In humans, the DLPFC comprises the middle part of the superior and middle frontal gyri (Petrides and Pandya, 1999; Petrides, 2005). Specifically, area 9 lies on the superior frontal gyrus extending dorsally to the midline and caudally to area 8. Ventrally, area 9 extends to area 9/46 (previously included as Brodmann's area 9). Area 9/46 lies in posterior portion of the middle frontal gyrus also extending caudally to area 8. Ventrally, area 9/46 adjoins the ventrolateral PFC at areas 44 and 45. Area 9/46 can be further subdivided into 9/46d and 9/46v representing the dorsal and ventral halves respectively. Area 46 also lies in the middle frontal gyrus, anterior to area 9/46. It is surrounded by area 9/46 at its

caudal, dorsal and ventral boundaries and connects to area 10 (frontopolar cortex) anteriorly.

In the macaque, the DLPFC extends from the lower limb of the arcuate sulcus (AS) to the midline in the mid-frontal cortex (Petrides et al., 2012). Area 46 lies within the principal sulcus (PS) and the gyri surrounding it at the anterior half of the PS. On the posterior banks of the PS lies area 9/46. Area 9/46 in the macaque is also divided into 9/46d and 9/46v. Area 9/46v lies on the ventral bank of the posterior PS and area 9/46d lies on the dorsal bank of the posterior PS. Area 9 lies on the dorsal boundaries of areas 46 and 9/46 and extends dorsally to the midline. Rostrally, areas 9 and 46 connect to the frontopolar cortex (BA 10).

All these areas have been identified and labeled based on cytoarchitectural differences in both the human and monkey cortices.

**1.2.2 Cytoarchitecture.**

Cytoarchitectonic differences in the prefrontal cortex of both humans and monkeys allow us to differentiate between the different regions within the DLPFC, namely areas 9, 46 and 9/46. Each of these areas has a distinguished cytoarchitectonic composition (Petrides and Pandya, 1999). Area 9 is characteristic of its narrow, not well-developed layer IV and large, deeply stained pyramidal neurons in layer IIIc (deepest part of level III). In contrast, area 46 does not contain these large pyramidal neurons in layer IIIc and consequently has a uniform appearance. Area 46 also has a very well developed and dense layer IV making it easy to identify within stained tissue under a microscope. Area 9/46 is interesting in that it has a cytoarchitectonic composition reflective of both

area 9 and area 46. Like area 46, area 9/46 possesses a dense, well-developed layer IV. As well, area 9/46 contains the large, deeply stained pyramidal neurons that are characteristic of area 9.

**1.2.3 Connectivity.**

As mentioned above, the PFC sends and receives projections from virtually all cortical sensory and motor areas. This accessibility to diverse information allows for the functional integration required for the PFC to implement control over executive functions (Miller and Cohen, 2000). While each subregion of the PFC has a unique pattern of connectivity, interconnections within and between these regions allow for interaction between information with different modalities.

In terms of connectivity with sensory cortical areas, the lateral PFC sends and receives projections to and from multiple sensory cortical hubs. This multimodal information comes from temporal and parietal cortices, which relay visual, somatosensory and auditory information (Jones and Powell, 1970; Pandya and Kuypers, 1969). Specifically, the DLPFC (areas 9, 9/46 and 46) receives inputs from multimodal sites like the cortex around the superior temporal sulcus, rostral superior temporal gyrus, cingulate cortex and retrosplenial cortex (Nauta, 1964; Pandya and Kuypers, 1969; Petrides, 2005). Thus, the DLPFC not only has access to multimodal information via its temporal projections, but it also has connections with paralimbic structures. Bidirectional connections with the retrosplenial region are the hallmark of areas 46 and 9/46, classically considered the mid-DPLFC (Petrides, 2005). This association with the retrosplenial region

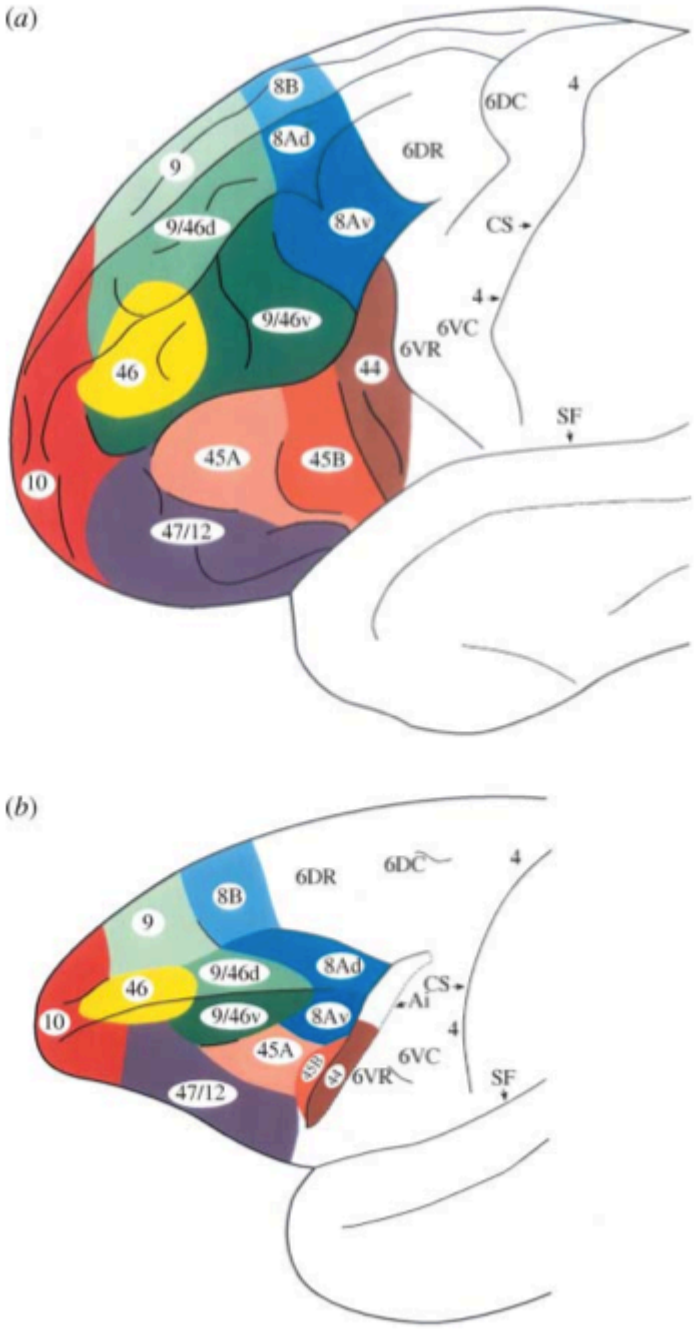


*Figure 1.* **Cytoarchitectonic map of the lateral prefrontal cortex by Petrides and Pandya, 2005.** (a) the human brain and (b) the macaque monkey brain. The DLPFC comprises of area 46 (yellow), area 9/46 and 9 (green).

allows for access to mnemonic information through the hippocampus (Morris, Petrides and Pandya, 1999). Additionally, areas 9/46 and 46 receive inputs from lateral and medial parietal cortex. These connections within the DLPFC show that it receives inputs from multiple sensory modalities as well as projections from regions that exhibit multimodal convergence themselves, thus allowing for complex multimodal integration.

In terms of connectivity with motor regions, the DLPFC is also connected with an array of motor-related sites that allow it to exert cognitive control. DLPFC (areas 9/46 and 46) sends projections to supplementary motor area (SMA), pre-supplementary motor area (pre-SMA), anterior cingulate cortex (ACC), premotor cortex, cerebellum and superior colliculus (Bates and Goldman-Rakic 1993; Goldman and Nauta, 1976; Leichnetz et al., 1981). The DLPFC also sends projections to the frontal eye fields (FEF) in area 8 (Yeterian et al., 2012). These extensive connections enable the DLPFC to exert flexible control for executive functioning (Miller and Cohen, 2000).

For both sensory and motor interconnections, the DLPFC does not interact with primary sensory cortex or primary motor cortex. Rather, the DLPFC is able to exert control via extensive connections with secondary cortical regions (Yeterian et al., 2012).

**1.2.4 Functional Organization.**

Based on distinctions in cytoarchitecture, anatomy and connectivity, there have been various models of functional organization in the lateral PFC. Specifically, functional organization within the lateral PFC has been extensively

studied and dorsal-ventral axes of organization have been suggested. First, work by Goldman-Rakic suggested modality-specific differentiation between dorsal (DLPFC) and ventral (VLPFC) regions. This model suggested that the DLPFC is responsible for spatial working memory while VLPFC is implicated in object related working memory tasks (Goldman and Rosvold, 1970; Goldman et al., 1971). This theory seems inconsistent with findings from experiments that report deficits in non-spatial working memory following DLPFC ablations and microstimulation (Bauer and Fuster, 1976; Stamm, 1969; Glick, Goldfarb and Jarvik, 1969). As well, multiple modalities converge within each subregion of the lateral PFC. Consequently, a model proposed by Owen and colleagues suggests distinct levels of executive control between the DLFPC and VLPFC not in terms of modality, but more generally in terms of task demands (Owen, Evans and Petrides, 1996; Petrides, 2005). They suggest that while DLPFC is recruited for monitoring and manipulation of multiple pieces of information in WM, VLPFC is crucial for encoding and retrieval within WM. The DLPFC is recruited when conscious active control or planned behavior and cognition are needed. The DLPFCs unique mode of interaction with the hippocampus provides an anatomical basis of control of WM from DLPFC (Morris, Petrides and Pandya, 1999b; Petrides and Pandya, 1999).

In addition to the dorsal-ventral axis of organization in the LPFC, research has shown a rostral-caudal axis of organization within the DLPFC. A selective lesion study by Petrides and colleagues found differential effects of caudal prefrontal lesions (areas 6 and 8) from mid-DLPFC (area 9/46 and 46) lesions

(Petrides et al., 1993). Caudal (area 8) lesions provide impairments in conditional tasks (tasks that require established stimulus-response pairings), while mid-DLPFC lesions impair working memory tasks.

### 1.3 DLPFC and Rule Switching.

Cognitive control enables us to flexibly guide our behaviour in an appropriate, context-dependent manner (Miller and Cohen, 2001). This allows for active maintenance of relevant rules in working memory while retaining the flexibility to switch between rules when faced with changing contingencies. This behavioral flexibility can be probed by rule-switching paradigms (Allport, Styles and Hsieh, 1994; Meiran, 2000; Monsell, 2003; Wylie and Allport, 2000; Yeung and Monsell, 2003; Yeung et al., 2006).

The Wisconsin Card Sorting Task (WCST) is a popular rule-switching paradigm used to probe rule-switching phenomena (Berg, 1948; Grant and Berg, 1948; Milner, 1963). In this task, subjects have to match a card according to color, shape or quantity. They have to acquire the classification rule in effect by evaluating feedback from recent trials. They then have to retain the relevant rule in working memory so that they can continue to apply it on subsequent trials. When the rule changes, subjects must shift to the alternative rule being reinforced. Thus, subjects have to update the strength of the relevant rule after each trial and retain flexibility to shift between rules. Human patients and monkeys with lesions of the prefrontal cortex (PFC) can acquire the initial rule but are unable to shift to a new rule (Milner, 1963). The dorsolateral PFC (DLPFC)

has been insinuated to play an important role in rule switching and maintenance by electrophysiological, fMRI and lesion studies (Milner, 1963; Monchi et al., 2001; Wallis, Anderson and Miller, 2001; Ravizza et al., 2010).

Milner observed performance of frontal lobe patients on WCST and found that only patients with DLPFC (areas 9, 9/46 and 46) lesions displayed impairment in WCST performance (Milner, 1963). These patients also made more perseverative errors than control subjects and patients with different lesions (orbital, ventrolateral), suggesting that patients with DLPFC lesions were less influenced by immediate consequences. Additionally, Monchi et al. observed prefrontal activity in human subjects during the distinct stages of a WCST analog using event-related functional MRI (Monchi et al., 2001). They found an increase in the BOLD response to the DLPFC (area 9/46) during the reinforcement period when subjects received positive or negative feedback, which is when subjects were required to update rule representation in working memory. These studies implicate the DLPFC in updating or manipulation of information in WM.

The WCST examines the relationship between the PFC and an arbitrary switch task, with equally represented stimulus-response (S-R) associations. In everyday life however, some S-R associations are stronger than others. Compatible or more familiar S-R associations are usually stronger and easier to execute than incompatible weaker S-R associations (Yeung and Monsell, 2003; Yeung et al., 2006). The Stroop task is a task-switching paradigm that differs from the WCST because it encompasses a dominance asymmetry, which means that the S-R mappings are not equally represented - one task is more dominant

than the other (Stroop, 1935; Wylie and Allport, 2000). In this task, subjects are presented with a coloured word as the stimulus. They are required to either read the word or name the colour of the word presented. Similar to the WCST, the relevant rule is acquired through feedback from previous trials and maintained until it no longer elicits positive feedback. However, word-reading is easier than colour-naming because it is more practiced, making it the prepotent, more dominant response. Human patients with prefrontal lesions are impaired in performing the Stroop task (Vendrell et al., 1995). Vendrell and colleagues associated neuroimaging results with findings from lesions while subjects performed the Stroop test. They found a correlation between activity in the lateral PFC (Areas 9 and 9/46) and error rates in Stroop colour-naming. Consistently, they found increased errors for colour-naming trials in patients with lesions in the right DLPFC. They attributed these findings to the role of the DLPFC in maintaining correct performance. These findings are consistent with the study by MacDonald et al. (MacDonald et al., 2000). MacDonald and colleagues found increased activity in the DLPFC during preparation for colour-naming compared to word-reading, which also suggests the role of the DLPFC in maintenance of task demands.

While these tasks have their differences, both tasks utilize processes that involve selective attention, WM, rule-based behavior, flexibility and behavioral inhibition. These functions depend on goal representation and can be seen in patterns of activity within the PFC (Miller and Cohen, 2001).

## 1.4 DLPFC and Working Memory.

Working memory (WM) allows for retrieval of relevant information and its active utilization to accomplish goal-directed behavior (Miller and Cohen, 2000; Baddeley, 2011; Baddeley, Chincotta and Adlam, 2001; Baddeley and Della Sala, 1996). This process has been called the "mental sketchpad" and is appropriate and active for a short period of time (Baddeley, 2011; Baddeley, Chincotta and Adlam, 2001; Baddeley and Della Sala, 1996). Working memory requires both inputs and outputs from long-term storage sites (Goldman-Rakic, 1987) and has been studied extensively through delayed-response (DR) paradigms. The DR paradigm necessitates subjects to retain information presented during the cue phase throughout a delay period prior to the test phase.

The PFC has been thought to play a role in WM since Jacobsen's experiments in 1935. Jacobsen (1935) showed that bilateral lesions in the PFC of monkeys significantly impaired their performance on a version of the DR paradigm. Since Jacobsen, it has been deduced that the region lining the principal sulcus (area 9/46 and 46) is necessary to cause this impairment in performance of the DR paradigm in monkeys (Goldman and Rosvold, 1970). As previously mentioned, the PS is part of area 46 and can be considered mid-DLPFC.

Initial evidence for the role of the DLPFC in WM came from experiments using spatial DR tasks (Hikosaka and Wurtz, 1983). In an oculomotor version of the classical DR task, the subject is shown a spatial location on a screen followed by a variable delay period after which the subject is required to choose

the correct location. The subject has to maintain the location in WM during the delay, presumably within the DLPFC. Thus, the correct response is internally guided by prior representation rather than externally via visual stimulus. Correct response ensures reward delivery.

Electrophysiological and imaging studies have determined a correlation between DLPFC and DR task performance (Fuster and Alexander, 1971; Stamm and Rosen, 1969; Owen, Evans and Petrides, 1996). The distinct temporal events within the spatial DR task allow for dissociation between different stages of neural processing, i.e. cue related (sensory processing), delay related (maintenance), response and reinforcement related. DLPFC neurons activated during the DR task consistently respond to distinct events during the task. While some DLPFC neurons respond to only one event of the DR task, most neurons in this area display activity during multiple events within the paradigm (i.e., during the cue, delay, and/or response periods). Additionally, the majority of DLPFC neurons exhibit changes in neuronal activity during the delay period, suggesting a role for the DLPFC neuron in mnemonic processing (Fuster and Alexander, 1970, 1971; Goldman-Rakic, 1995, 1996; Goldman and Rosvold, 1970). Microstimulation experiments show impairment in DR performance is greatest when electric current is applied to the DLPFC at the beginning of the delay period (Stamm and Rosen, 1969).

Furthermore, lesion and reversible deactivation studies have determined a causal relationship between the DLPFC and DR task performance (Fuster and Alexander, 1970; Alexander and Fuster, 1973). These studies found that DLPFC

ablations (areas 9, 46 and 9/46) impaired performance for DR paradigms but not for tasks lacking a delay period (conditional response tasks). Specifically PS lesions impaired DR task performance while lesions sparing the PS did not affect performance on DR tasks. As well, lesion and microstimulation studies have suggested that the mnemonic functioning of DLPFC is lateralized. Unilateral DLPFC ablation or electrical stimulation impairs performance on DR trials where the cue is presented on the contralateral side of the lesion. This hemispheric bias can be eliminated via an additional lesion to the DLPFC on the other hemisphere, which impairs task performance bilaterally (Funahashi, Bruce and Goldman-Rakic, 1993). Thus, the studies mentioned above have implicated a role for the DLPFC in spatial WM tasks.

In addition to spatial mnemonic processing, the DLPFC has been implicated in nonspatial mnemonic functions through electrophysiological, imaging and lesion studies. First, Miller and colleagues' electrophysiological study found that the majority of DLPFC neurons were active during the delay period of a delayed match-to-sample (DMS) task (Miller, Erickson and Desimone, 1996). For the DMS task, subjects have to maintain a cue object in WM through a delay period and select the same object during the response period. As well, Petrides and colleagues found an increase in regional cerebral blood flow to the mid DLPFC (areas 9, 9/46 and 46) in humans during performance of a self-ordered working memory task compared to a control task (Petrides et al., 1993). Finally, lesions of the region around the PS in monkeys impair performance on nonspatial tasks that require working memory (Bauer and Fuster, 1976; Petrides,

1995). Bauer and Fuster used cooling to deactivate area 9/46 while monkeys performed the DR task as well as a DMS task, which probed non-spatial WM (Bauer and Fuster, 1976). Cooling DLPFC impaired performance in both DR and DMS tasks, but did not impair performance in a simultaneous match-to-sample task that did not involve a mnemonic component. Similarly, Shindy and colleagues found cryogenic deactivations in monkey DLPFC (areas 9/46 and 46) produced deficits in performance of visual and haptic versions of the DMS task (Shindy, Posley and Fuster, 1994). Additively, these studies suggest that the DLPFC plays a general role during working memory tasks that is not specific to task modality (spatial versus non-spatial).

### 1.4.1 Cellular correlate of WM in DLPFC.

As seen above, the DLPFC has been implicated in WM through various electrophysiological, fMRI and lesion studies. In addition to knowing the DLPFC is involved in WM, it is important to know specifically how neurons in the DLPFC integrate and maintain information. The fact that neurons in the DLPFC are activated during the delay period of a delayed-response paradigm is the first clue to finding the cellular correlate of WM (Goldman-Rakic, 1988). As well as during the delay period, neurons in the DLPFC are activated during different phases (stimulus, response) of the DR task. Many neurons discharge during more than one phase and exhibit a composite profile reflective of its inputs from simpler one-dimensional cells (Goldman-Rakic, 1996). Thus, neurons in the DLPFC are differentially time locked. In addition, both interneurons and pyramidal neurons have specific memory fields reflected by maximal firing of neurons to specific

stimuli. For example, for the spatial DR paradigms, neurons display directional preferences for specific loci (Goldman-Rakic, 1995). These neurons also have an opponent memory field whereby the neurons have minimal activity for loci opposite to their memory field. This suggests some sort of regulatory interaction between neurons with opposite memory fields (Golman-Rakic, Cools and Srivastava, 1996). In fact, pyramidal neurons with compatible as well as opposing preferences are interconnected (opposing neurons interact via interneurons).

In addition to the directional preferences and connectivity between DLPFC neurons, DLPFC pyramidal neurons form a triad complex at spine synapses. This is where they receive input from sensory efferents and dopaminergic neurons allowing for direct dopaminergic modulation of inputs and outputs (Wang, Vijayraghavan and Goldman-Rakic, 2004; Vijayraghavan et al., 2007). The importance of dopaminergic modulation to WM is evident in cases where there is an observed deficit in WM in patients with Parkinson's Disease and in monkeys with dopamine depletion in DLPFC (Brozoski et al., 1979; Levin, Labre and Weiner, 1989).

## 1.5 DLPFC and Rule Selectivity.

The DLPFC comprises neurons that respond selectively to different stimuli, behavioral responses and a combination of both (Asaad, Rainer and Miller, 1998, 2000). These neuronal activity profiles suggest a role for the DLPFC in abstract

rule representation. Distinct rules represent different stimulus-response mappings. For instance, a single stimulus may elicit multiple responses and to know which response is relevant, we must know which abstract rule is in effect and attend to it (Rainer, Asaad and Miller, 1998). Neurophysiology studies in monkeys show that neurons in the DLPFC exhibit rule selectivity between tasks that follow different rules.

Asaad and colleagues recorded neuronal activity in DLPFC (areas 46 and 9/46) of monkeys while they performed an associative learning task (Asaad, Rainer and Miller, 1998). They found neurons that responded distinctively to different stimuli (cue) and neurons that responded selectively to different behavioral responses. Interestingly, they found the modal group of neurons responded preferentially to specific responses depending on the cue. Thus, some neurons responded to a specific stimulus-response pairing (rule). Another study by Asaad and colleagues used three tasks to assess neural activity in the lateral PFC (Asaad, Rainer and Miller, 2000). Two tasks shared common cue stimuli guiding different behavioral responses and two tasks shared common behavioral responses instructed by different cues. They found task dependent changes in baseline activity (prior to cue representation) as well as task dependent changes in stimulus or response related modulation regardless of the cue or behavioral response.

Furthermore, White and Wise compared prefrontal (areas 46 and 9/46) neuronal activity on spatial and conditional tasks (White and Wise, 1999). They found that prefrontal neurons had different firing rates based on the nature of the

task, i.e. conditional versus spatial. Similarly, Wallis and colleagues found rule related preferences in prefrontal neurons while monkeys performed an instructed matching versus non-matching task (Wallis, Anderson and Miller, 2001). Neuronal activity between the two tasks differed during the delay period, after the instruction had been given. The neuronal delay activity depended on the effective rule and allowed the monkeys to prepare for the upcoming response. Finally, oculomotor experiments using saccadic eye movements found DLPFC neurons that discharge differentially depending on whether monkeys look toward a peripheral stimulus or away from it (Everling and DeSouza, 2005; Johnston and Everling, 2006; Johnston et al., 2007).

Thus, rule selectivity has been observed in prefrontal neurons through several experiments utilizing different tasks (rules). This suggests a role for the DLPFC in executing rule-guided behavior. The presence of selectivity for stimuli, responses and tasks suggest a role for the DLPFC in implementing rule-guided behavior by bridging the gap between stimuli and responses.

## 1.6 DLPFC and Rule Maintenance.

Seeing that the DLPFC plays a role in WM and rule selectivity, it is only natural to expect that the DLPFC may be involved in maintaining abstract rules (or task-sets) across trials. Rule maintenance requires mnemonic processing to maintain relevant materials 'on-line' while discarding irrelevant information. Indeed, imaging, neurophysiological and lesion studies have found the DLPFC to be implicated in maintenance of abstract rules.

MacDonald and colleagues used event-related fMRI and a task-switching version of the Stroop task to examine distinct neural bases in specific aspects of cognitive control in human subjects (MacDonald et al., 2000). They found an increase in the blood-oxygen-level-dependent (BOLD) signal to the DLPFC during the preparatory period for color naming (more difficult task) compared to word reading. They also found individuals with the most DLPFC activation after color naming displayed the least Stroop interference effect. This study shows that the DLPFC plays a role in the maintenance of abstract rules by representing and maintaining the demands of the task during the preparatory periods.

Similarly, electrophysiological studies in monkeys have found rule selectivity present in DLPFC neurons within and between trials, suggesting rule maintenance in these neurons (Mansouri, Matsumoto and Tanaka, 2006; Johnston et al., 2007). Mansouri and colleagues recorded DLPFC neurons while a monkey performed an analog of the Wisconsin Card Sorting Task (Mansouri, Matsumoto and Tanaka 2006). Among other roles, they found that DLPFC neurons showed rule modulation within and between trials. The presence of rule selectivity during intertrial intervals suggests a role for the DLPFC in preparation for and maintenance of abstract rules. Furthermore, Johnston and colleagues (2007) recorded neurons around the PS while monkeys performed a task-switching paradigm using the anti-/pro-saccade task. They also found task selectivity in DLPFC neurons between pro- and anti-saccade tasks during the preparatory period before stimulus onset. Additionally, while rule modulation in the anterior cingulate cortex (ACC) decreased throughout a block (highest

immediately after switch), rule selectivity in neurons of the DLPFC was constant throughout blocks (Johnston et al., 2007). These experiments show that neuronal activity in the DLPFC is rule selective and is present between trials, allowing for the active maintenance of task rules.

Finally, while the above studies suggest a correlation between the DLPFC and rule maintenance, lesions studies are important in establishing a causal relationship. Consequently, Buckley and colleagues performed a lesion study that tested the effects of distinct lesions of the frontal cortex in performance of a WCST analog of monkeys (Buckley et al., 2009). They found that among all lesions, only lesions of the PS (area 46) impaired performance of the task throughout the blocks. This study suggests a causal relationship between the DLPFC area 46 and maintenance of abstract rules. Therefore, electrophysiological, imaging and lesions studies have implicated certain regions of the DLPFC in maintenance of abstract rules.

### 1.7 The anti-saccade task.

The oculomotor system is a very well understood system and is used extensively in systems neuroscience. Specifically, several paradigms using the saccadic system are used to quantify aspects of cognitive control. Saccadic eye movements enable us to gauge both automatic and controlled behaviours. The anti-saccade task has been used widely to assess cognitive control (Hallett, 1978; Leigh and Kennard, 2003). This task requires suppression of an automatic saccade towards a peripheral stimulus (pro-saccade) in favour of a saccade

away from the stimulus to its mirror location (Hallett, 1978; Munoz and Everling, 2004). Thus, correct anti-saccade performance relies on a two-fold implementation system, enabling experimenters to decouple stimulus-related processes from response-related processes. Since pro-saccades toward target stimuli are the prepotent response, anti-saccades must be guided by internal states, like attention, intention and motivation. Thus, performance of this task utilizes and allows us to probe the function of a number of different cortical and subcortical regions involved in response inhibition and vector inversion.

### 1.7.1 DLPFC and the anti-saccade.

Imaging and electrophysiological experiments measuring differences between pro- and anti-saccades display contrasting neural activity between the two tasks (DeSouza, Menon and Everling, 2003; Everling et al., 1999; Everling and Munoz, 2000; Sweeney et al., 1996).

The imaging study by DeSouza and colleagues used fMRI to differentiate between pro- and anti-saccade processing while temporally separating preparatory periods from motor periods (DeSouza, Menon and Everling, 2003). This study found an increase in the BOLD response bilaterally to the FEF and the DLPFC during the preparatory period on anti-saccades compared to pro-saccades. The SEF and DLPFC probably underlie suppression of pre-target activity (Munoz and Everling, 2004; Koval, Lomber and Everling, 2011). Consistently, an increase in the BOLD response is observed in the PFC during anti-saccade performance compared to pro-saccade performance in normal subjects but not in schizophrenic patients (McDowell et al., 2002; McDowell and

Clementz, 2001). Additively, these studies display differences in preparatory neural activity between anti- and pro-saccades and indicate greater cortical control during the more complex anti-saccade task (Curtis and D'Esposito, 2003; Johnston, DeSouza and Everling, 2009). In fact, patients with frontal lobe damage, specifically the DLPFC have more difficulty in performing anti-saccades than control subjects (Gaymard et al., 1998; Guitton, Buchtel and Douglas, 1985; Pierrot-Deseilligny et al., 1991; Ploner et al., 2005). Guitton and colleagues proposed that impairment in anti-saccade performance might be due to a decrease in rate of processing in frontal areas that lead to the cancellation of reflexive pro-saccade. Thus, the cancellation signal is slightly delayed, leading to an entirely inappropriate automatic pro-saccade. Similarly, Fukushima and colleagues found frontal lobe related deficiencies in anti-saccade performance of schizophrenic patients (Fukushima et al., 1988, 1990, 1994). They found only patients with frontal atrophy (and not patients with intact frontal lobes) displayed difficulty in suppressing a reflexive pro-saccade and initiating a voluntary anti-saccade. While these studies display a relationship between prefrontal regions and anti-saccade performance, it is unclear which subregions are crucial for anti-saccades (for alternative, see Ploner et al., 2005). On the other hand, Koval and colleagues studied the effects of bilateral localized reversible prefrontal lesions on anti-saccade performance (Koval, Lomber and Everling, 2011). Bilateral deactivation of area 46 significantly impaired anti-saccade performance by reducing task-selective activity in the SC, with stronger effects during the memory condition.

## 1.8 Reversible Deactivations.

While electrophysiological and imaging studies help establish a correlation between a brain area and behavior, lesion studies allow us to establish a causal relationship between the two. Traditionally, lesion studies were performed via permanent ablations to cortical areas. However, permanent ablations come with a multitude of disadvantages that can be avoided with the use of reversible deactivation techniques (Lomber, Payne and Horel, 1999). Pharmacological and cryogenic manipulations are two means to achieve reversible cortical and subcortical deactivations.

For our purposes, pharmacological deactivations present certain disadvantages. First, because of the injection's localized action, multiple penetrations are often required to deactivate a region long enough to observe behavioural effects, which increases tissue damage (Wardak, Olivier and Duhamel, 2002). Additionally, different pharmacological agents have unique shortcomings: Lidocaine also deactivates fibers of passage causing unrestricted deactivations and muscimol deactivates tissue for several hours, making it difficult to obtain post deactivation data.

Several studies have used cooling to reversibly deactivate cortical regions (Fuster and Alexander, 1970; Alexander and Fuster, 1973; Bauer and Fuster, 1976; Shindy, Posley and Fuster, 1994; Chafee and Goldman-Rakic, 2000). Cryogenic techniques include cooling with thermoelectric coolers resting on the dura. Contrary to pharmacological injections, thermoelectric coolers deactivate a larger area. However, the thermoelectric coolers do not allow for deactivation in

sulcul tissue. An alternative method for cryogenic depression is the cryogenic cooling loop (Lomber, 1999).

The cryoloop consists of hypodermic tubing that can be shaped to fit the structure intended for deactivation. Pumping chilled methanol through the cryoloop lumen decreases temperature in and deactivates adjacent cortical tissue. The drop in temperature disrupts local synaptic activity but spares activity in axonal fibers (Lomber, Payne and Horel, 1999). By monitoring activity of neurons before, during and after cooling, Lomber showed that cooling cortical cells between 20 and 24°C significantly reduces neural activity while reducing temperature below 20°C diminishes neural activity completely (Lomber, Payne and Horel, 1999; Benita and Conde, 1972). Action potentials diminished when the cooling pumps were turned on and return to normal when pumps are turned off. Thus, the effects of cooling are completely reversible.

## 1.9 Rationale and Hypothesis.

The various imaging, electrophysiological and lesion studies mentioned above have implicated regions of the DLPFC in rule maintenance and dynamic updating of immediate consequences. For example, Milner's study found patients with DLPFC lesions displayed perseverative tendencies (Milner, 1963). Although these studies have found the DLPFC to play a role in rule switching and maintenance, it is important to differentiate between different subregions and examine their specific roles on rule maintenance. As such, Buckley and colleagues examined the effects of distinct PFC lesions during a WCST analog

for monkeys (Buckley et al., 2009). They found impairment in rule maintenance with area 46 lesions, whereas combined area 9 and 9/46d lesions did not alter task performance. While Buckley found no relationship between area 9/46d and rule maintenance, other studies have found neurons in this region to be rule selective during an anti-/pro-saccade task-switching paradigm (Everling and DeSouza, 2005; Johnston et al., 2007). This discrepancy may be due to differences between tasks (presense/absence of dominance asymmetry between S-R pairings) or between techniques (permanent ablation versus simultaneous recordings). We hypothesized that area 46 is involved in general rule maintenance and area 9/46d is additionally recruited specifically for maintenance during asymmetric task-sets.

Here, we used cooling to test the role of areas 46 and 9/46d on rule maintenance and switching while monkeys performed a rule-switching version of the anti-/pro-saccade tasks. Based on findings from Buckley and colleagues, we expected area 46 cooling to impair rule maintenance for both rules. Based on the discrepancy in results between area 9/46d lesion and electrophysiology studies for rule maintenance, we expected area 9/46d cooling to effect rule maintenance specific to asymmetric task sets (Buckley et al., 2009; Everling and DeSouza, 2005; Johnston et al., 2007). It follows that combined cooling of area 46 and 9/46d was expected to impair maintenance of both rules (area 46 cooling) with additional asymmetric effects resulting from area 9/46d deactivation.

## Section 2

# METHODS

## 2.1 Surgeries.

Data were collected from two male rhesus monkeys (*Macaca mulatta*) weighing 10 and 12 kg. Animals were handled in accordance with the guidelines of the Canadian Council on Animal Care policy on the use of laboratory animals and a protocol approved by the Animal Use Subcommittee of the University of Western Ontario Council on Animal Care.

Ketamine hydrochloride was administered intramuscularly to sedate the monkeys for surgeries (10–15 mg/kg). Bradycardia and salivary secretions were reduced by subcutaneous administration of atrophine (0.05 mg/kg). Propofol was used to initiate (2.0 mg/kg) and maintain (0.2 mg/kg/min) anesthesia. Midazolam (0.35 mg/kg/min) was also given throughout the surgery via an intravenous cannula. Heart rate, blood pressure, respiratory rate, and body temperature were monitored closely for the duration of the surgery. Animals received analgesics and antibiotics postoperatively and were closely monitored by a university veterinarian. They received a daily dose of amoxicillin (antibiotic) orally to prevent infection and intramuscular injections of buprenorphine (analgesic) hydrochloride (0.01 mg/kg) to relieve discomfort for a period of 10 days postoperatively. Health status and weight were recorded daily to ensure the animals' well being.

A head implant was fixed to the skull with titanium screws for each monkey during the first surgery. The head implants were made of dental acrylic. Both animals were then implanted with a plastic head restraint each. After being trained on both versions of the anti-/pro-saccade switch task (cued and uncued) to a performance criterion level of ~75%, both animals underwent a second

surgery for the permanent implantation of stainless steel cryoloops (Fig.3). In both monkeys, the cryoloops were implanted bilaterally into the posterior third of the principal sulcus (caudal area 46) and bilaterally on the gyrus adjacent to the principal sulcus dorsally (caudal area 9/46d). The cryoloops were 6 mm by 3 mm and were constructed from 23- gauge hypodermic stainless steel tubing. Lomber, Payne and Horel describe the technical procedures for crafting, surgery, and use of cryoloops (Lomber, Payne and Horel, 1999).

**2.2 Behavioral Tasks.**

Monkeys were trained to perform alternating blocks of pro- and anti-saccades (Fig. 4). Each trial was initiated with the presentation of a 0.2° fixation spot at the center of a CRT monitor screen. Monkeys were required to fixate on it within a 0.5° x 0.5° window for a random period of 1100 to 1400 ms. A 0.2° white peripheral visual stimulus was then presented with equal probability 8° to the left or 8° to the right of the fixation spot. Monkeys had to generate a saccade to the stimulus location on pro-saccade blocks or to the mirror location away from stimulus on anti-saccade blocks within 500 ms to obtain a liquid reward. The reward was presented 200 ms after saccade cessation on successful trials in which the animals used the appropriate rule. After animals had performed between 15 to 25 correct responses, the task switched (from pro- to anti-saccades or vice versa) randomly without any explicit signal. The fixation spot in the uncued version of the task was always white. Thus, the monkeys had to maintain the relevant rule on “repeat trials” or switch to the alternate rule on

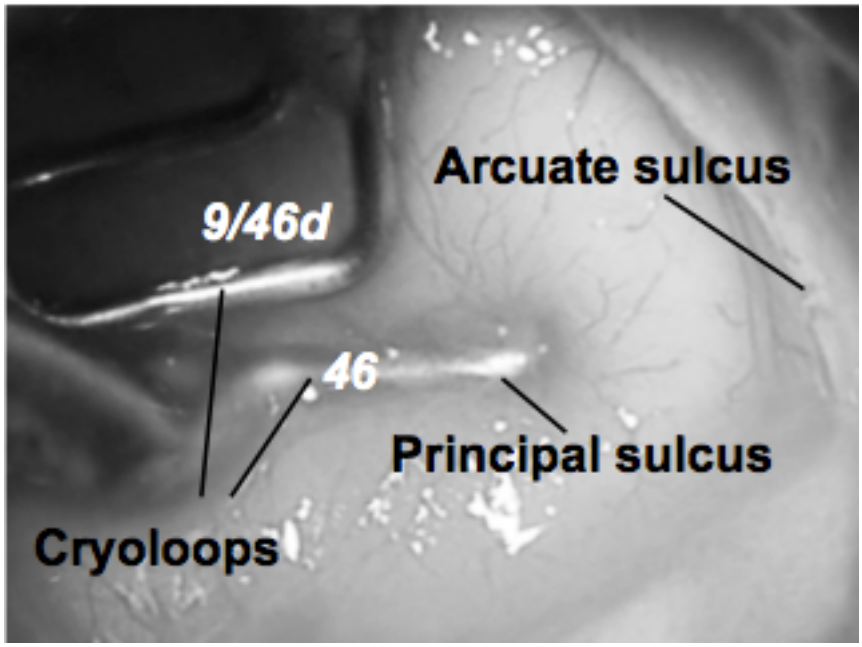


*Figure 3*. **Chronic implantation of cryoloops.** This photo shows cryoloop locations in the right prefrontal cortex of monkey B. The cryoloop in area 46 was situated in the posterior third of the principal sulcus and the area 9/46d cryoloop was implanted on the dorsal bank of the posterior third of the principal sulcus.

"switch trials" based on reward outcome for the uncued task. The fixation spot in the cued version of the task was green for pro-saccade trials and red for anti-saccade trials for monkey G and reversed for monkey B. Therefore, the monkeys were instructed to maintain or switch the relevant rule based on the color of the fixation spot reducing mnemonic demands of working memory. Cued and uncued versions of the switch task were run on separate days. On average, monkeys performed 50 task switches per day. The experimental paradigm was presented by running the CORTEX program on two Pentium PCs. The program also monitored the animals' behavior and controlled the reward delivery. An Eyelink II system recorded horizontal and vertical eye positions at 500 Hz (SR Research, Kanata, Canada).

**2.3 Prefrontal Deactivations.**

Several studies have used cryogenic depression to reversibly deactivate cortical regions (Adey, 1974; Koval, Lomber and Everling, 2011; Fuster and Alexander, 1970; Alexander and Fuster, 1973; Bauer and Fuster, 1976; Shindy, Posley and Fuster, 1994). The cryoloop consists of hypodermic tubing that can be shaped to fit the cortical structure intended for deactivation. Cooling occurred by turning on cooling pumps that initiated the passage of methanol through the cooling apparatus. Room temperature methanol was pumped from a reservoir via Teflon tubing through a methanol ice bath where it was chilled. The methanol ice bath was maintained at subzero temperatures by adding dry ice. Finally, the chilled methanol was passed through chronically implanted cryoloops where it

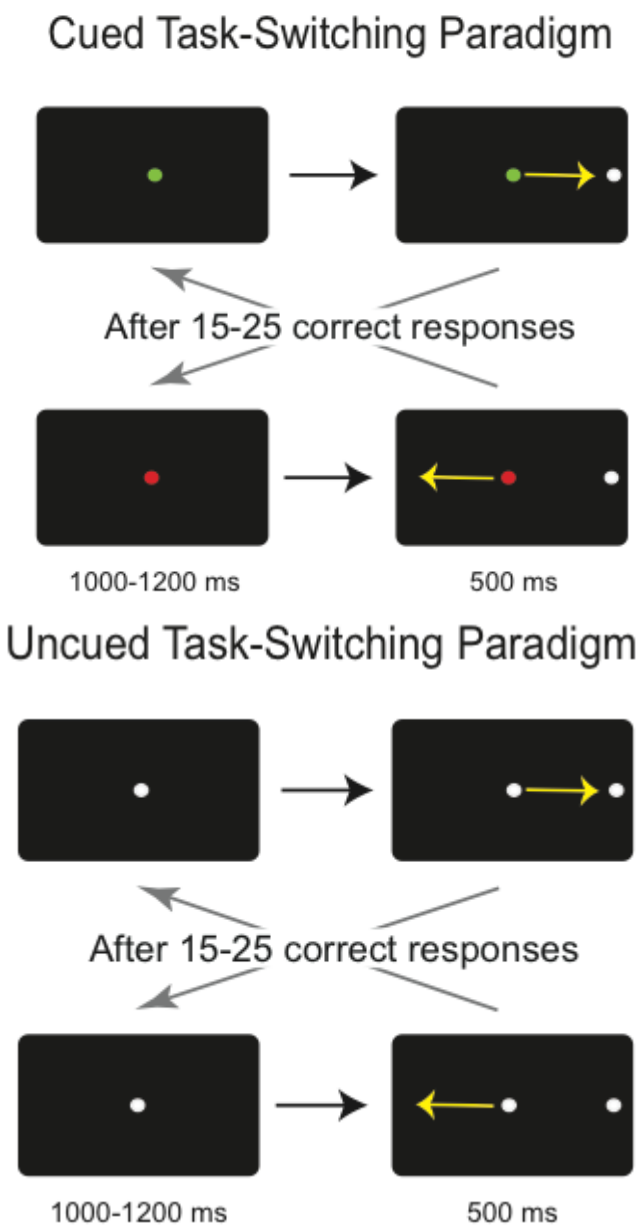


*Figure 4*. **Experimental Paradigms.** Monkeys alternated between blocks of pro-saccades and anti-saccades. In the cued condition, the color of the central fixation point instructed the animals which task to perform. In the uncued condition, monkeys were not instructed on the relevant task. Instead, they had to acquire and maintain the current task rule based on reward feedback.

reduced cortical temperature and returned back to the reservoir at room temperature.

Cryoloop temperature was monitored by an attached microthermocouple and manipulated by adjusting the rate of flow of the pump. In this manner, cryoloop temperature was maintained in the range of 1-5°C. We chose this range because it allowed us to deactivate as large an area of cortical tissue as possible while avoiding potentially harmful subzero cortical temperatures. Cortical temperatures around 20°C serve as the threshold for deactivation (Benita and Conde, 1972; Jasper, Schacter and Mountplaisir, 1970). When cryoloop temperature is between 1-3°C, the extent of deactivated tissue (tissue that is under 20°C) is limited to a radius of ~2 mm (Lomber, Payne and Horel, 1999).

Data were collected from a total of 103 sessions. Cooling sessions alternated with control sessions to control for behavioral adaptation to the paradigm. We obtained data for 4 different conditions, which were: (1) no deactivation (control), (2) bilateral deactivation of caudal principal sulcus (area 46), (4) bilateral deactivation of the caudal region of the dorsal bank of the principal sulcus (area 9/46d) (4) bilateral deactivation of both cortical regions (areas 46 and 9/46d). Condition (1) required no pumps, conditions (2) and (3) required use of 2 pumps and condition (4) required use of 4 pumps. On average, it took 85 s to reduce cryoloop temperature to 3°C. The experimental task began 3-5 minutes after turning on the cooling pumps and experimental sessions lasted between 60-70 minutes. Monkeys received liquid until satiation post-session and were returned to their home cages. Daily records of the weight and health status

of the monkeys were kept, and additional fruit was provided.

## 2.4 Daily Sessions and Data Analysis.

After monkeys were guided into a primate chair, they were brought into an experimental room where their heads were restrained. They were then placed in a sound-attenuating chamber 42 cm away from a 21-in. computer screen. A liquid-spout was positioned in their mouth for reward delivery. Monkeys watched movies during the setup and tasks were presented on the same screen.

After data acquisition, we used custom-designed software in Matlab (Mathworks) for analysis. Based on the rule in effect and saccade direction, each trial was classified as correct or error. For analyses, we excluded skipped trials (no fixation) and trials in which monkeys did not maintain fixation (broken fixation trials). We also excluded anticipation trials in which reaction times fell below 80 ms and no response trials in which latency surpassed 1000 ms.

We computed the mean pro- and anti-saccade performance and reaction time for each trial of each experimental session. We then averaged the performance values across all sessions. Because reaction times were consistent throughout the blocks, we computed mean reaction times of all correct pro- and anti-saccades for each session (one value for pro-saccades and one for anti-saccades for each session) and averaged across sessions.

## Section 3

# RESULTS

Data were obtained over a total of 78 experimental sessions (n=20 for non-cooling, n=20 for area 46 cooling, n=20 for area 9/46d cooling and n=18 for cooling both areas). Although none of the deactivation conditions altered the number of skipped trials (4.1% vs. 8.3% vs. 2.6% vs. 5.7%; one-way ANOVA: $p > 0.05$) or no response trials (1.4% vs. 1.4% vs. 3.7% vs. 3.4%; student's t-test: $p > 0.017$), the percentage of broken fixation trials increased with area 46 cooling (23.1% vs 9.4%, $p < 0.0001$, student's t-test) and combined cooling of areas 46 and 9/46d (25.8% vs 9.4%, $p < 0.0001$, student's t-test). Despite this increase in broken fixation trials, monkeys continued to perform the task during both conditions.

**3.1 Effects of DLPFC deactivation on uncued task performance.**

Figure 5 displays performance (in percentage of correct trials) of both monkeys' on the uncued task for the various conditions (n = 17 for all conditions). The dashed lines (x = 0) represent a switch from anti- to pro-saccades (Fig. 5A) and pro- to anti-saccades (Fig. 5B). Performance immediately preceding the switch as well as 15 trials following a switch is presented.

During control sessions when no cortical area was deactivated, performance of anti-saccades was at ~75% before the task-switch and dropped to ~25% during the switch trials (Fig. 5A). This is expected due to the lack of instruction pre-switch. On the second pro-saccade trial after switch, performance recovered to ~50% and recovery continued until the sixth post-switch pro-saccade trial, where it plateaued at ~85%. The dark grey line represents

performance on sessions when caudal area 46 was deactivated bilaterally. During this condition, performance of pre-switch anti-saccade was only ~60% and post-switch, pro-saccade performance only recovered to ~70%. Although there was an observable decrease in the post-switch performance, recovery occurred at the same rate. This means that recovery was complete and reached a plateau by trial 6 post-switch. These effects were not observed in the other deactivation conditions. Performance during bilateral deactivation of caudal area 9/46d (medium grey line) or bilateral deactivation of caudal area 46 and 9/46d together (light grey line) did not differ from performance during control sessions.

Figure 5B displays performance of both monkeys' on the uncued task when it switches from pro-saccades to anti-saccades. Pro-saccades performance immediately before switch was at ~85% for control sessions. When the rule switched to anti-saccades, performance dropped to ~15%, which is expected. On the second trial after switch, performance recovered to ~50%. Recovery continued until the fifth post-switch trial, where it plateaued at ~75%. Bilaterally inactivating caudal area 46 reduced the anti-saccade performance plateau from ~75% in control to ~60% without altering rate of post-switch improvement. Performance during bilateral deactivation of caudal area 9/46d did not differ from control performance. On the other hand, deactivation of both caudal areas 46 and 9/46d yielded deficits similar to deactivation of caudal area 46 alone, where the anti-saccade performance plateaued at ~60%.

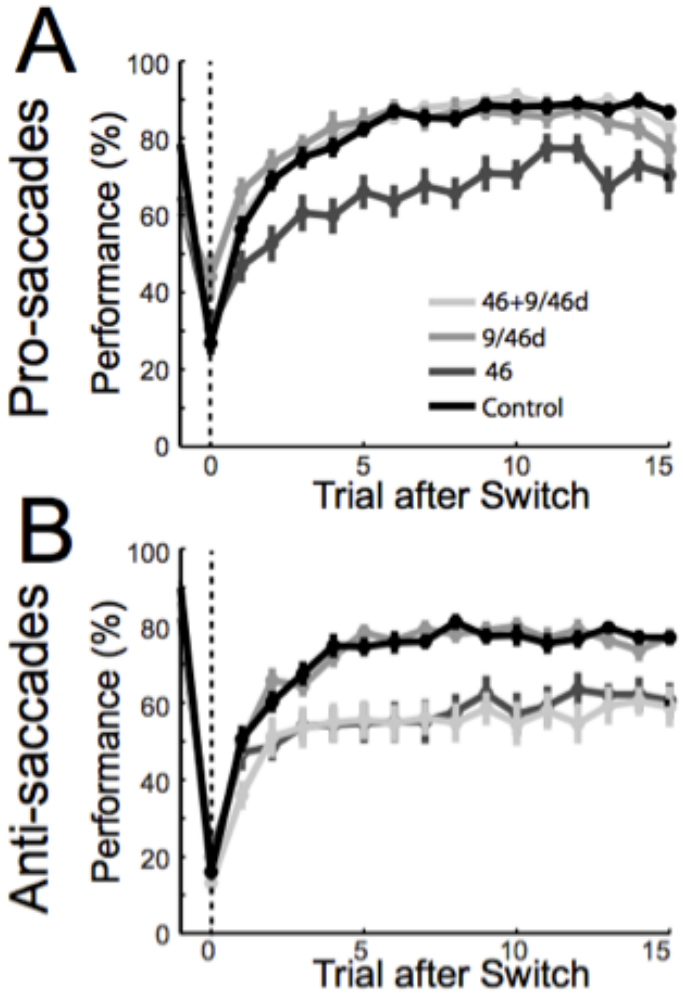


*Figure 5*. **Effects of dorsolateral deactivations on performance in uncued task.** Each line represents performance of both monkeys during different conditions (black line = control; dark grey line = bilateral deactivation of caudal area 46; medium grey line = bilateral deactivation of caudal area 9/46d; light grey line = combined bilateral deactivation of caudal area 46 and 9/46d; n=17 for each condition). The dashed line represents switch trials and the x-axis presents each post-switch trial. Performance is measured in percentage of correct trials.

### 3.2 Effects of DLPFC deactivation on rule maintenance.

To test effects of deactivation on rule maintenance, we had to eliminate results from effects of switching. Since post-switch recovery for pro-saccades was complete at 6 trials after which performance plateaued, we used post-switch trials 6 through 15 to statistically measure effects of cooling on rule maintenance. We calculated one mean error rate for trials 6-15 because performance remained relatively consistent after trial 6 for each condition (Fig. 6).

Figure 6A shows error rates for all conditions on pro-saccade blocks. Subsequently, we performed a one-way ANOVA to test for a significant difference on error rates between different conditions. This showed a significant effect of deactivation on pro-saccade error rates ($F(3) = 13.99$, $P<0.0001$). There were three degrees of freedom due to the 4 experimental conditions (n=4). Conducting planned two sample t-tests as post-hoc comparisons between control and each deactivation condition determined that deactivation of caudal area 46 significantly increased error rates ($P<0.00001$). Contrastingly, deactivation of caudal area 9/46d ($P=0.83$) or the combination of caudal areas 46 and 9/46d ($P=0.32$) did not significantly alter error rates. In fact, there was a significant increase in pro-saccade error rates for area 46 deactivation compared to combined deactivation ($P<0.0001$). Deactivations displayed consistent effects on uncued pro-saccade performance between monkeys (Fig. 7).

The same analyses were conducted for anti-saccade blocks (Fig. 6B). A one-way ANOVA between conditions revealed significant effects of deactivations on anti-saccade error rates ($F(3) = 13.99$, $P<0.000001$). Post-hoc comparison

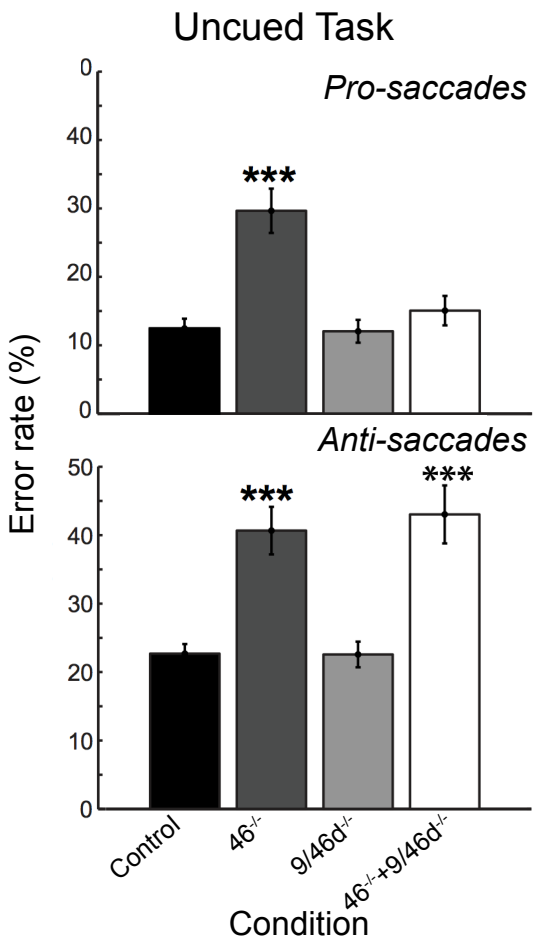


*Figure 6*. **Effects of dorsolateral deactivations on error rates in uncued task for both monkeys.** Bars display error rates of both monkeys from post-switch (a) pro-saccade and (b) anti-saccade trials 6 through 15 during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=17 for each condition). Asterisks represent significant differences between deactivation condition and control sessions illustrated by planned post-hoc analyses ($P$<0.00001).

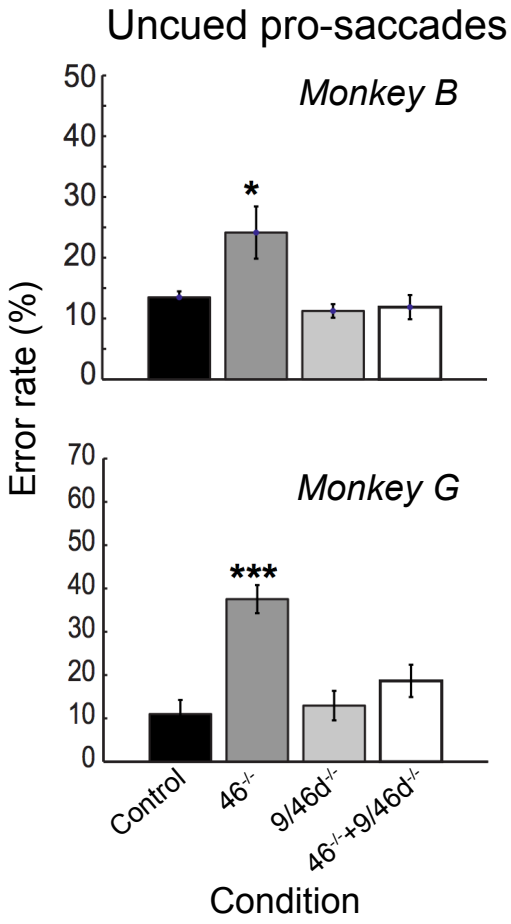


*Figure 7*. **Effects of dorsolateral deactivations on error rates in uncued pro-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in pro-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=17 for each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons (1 asterisk = 0.001, 3 asterisks = 0.00001).

between the control condition and deactivation of caudal area 46 established a significant increase in anti-saccade error rates for the latter condition ($P$<0.0001). Interestingly, there was a significant increase in error rates for the combined deactivation of caudal areas 46 and 9/46d ($P$<0.0001). Deactivation of caudal area 9/46d alone did not affect anti-saccade performance. Again, effects of deactivations on uncued anti-saccade performance were consistent between monkeys (Fig. 8).

We also measured effects of cooling on saccadic reaction times for trials 6 through 15. For statistical analyses, we converged these values because reaction time remained consistent throughout this interval. A one-way ANOVA between conditions revealed no significant differences in reaction times between the 4 groups for pro-saccade blocks (Fig. 9A, $F(3) = 2.01$, $P$=0.12). On the other hand, there was a significant effect of deactivation on anti-saccade reaction times (Fig. 9B, $F(3) = 3.8$, $P$=0.014). A two-sample t-test post-hoc further revealed a significant increase in anti-saccade reaction times during the combined cooling of caudal areas 46 and 9/46d ($P$=0.002). Plotting saccadic reaction times for both monkeys exposed slight differences between subjects (Fig. 10 and 11).

Overall, our results display impairments in pro- and anti-saccade performance without altering reaction times during bilateral deactivation of caudal area 46. Contrastingly, bilateral deactivations of adjacent caudal area 9/46d did not alter performance or reaction times. Surprisingly, combined deactivation of both caudal areas 46 and 9/46d only impaired performance and increased reactions times on anti-saccades and spared pro-saccade performance and

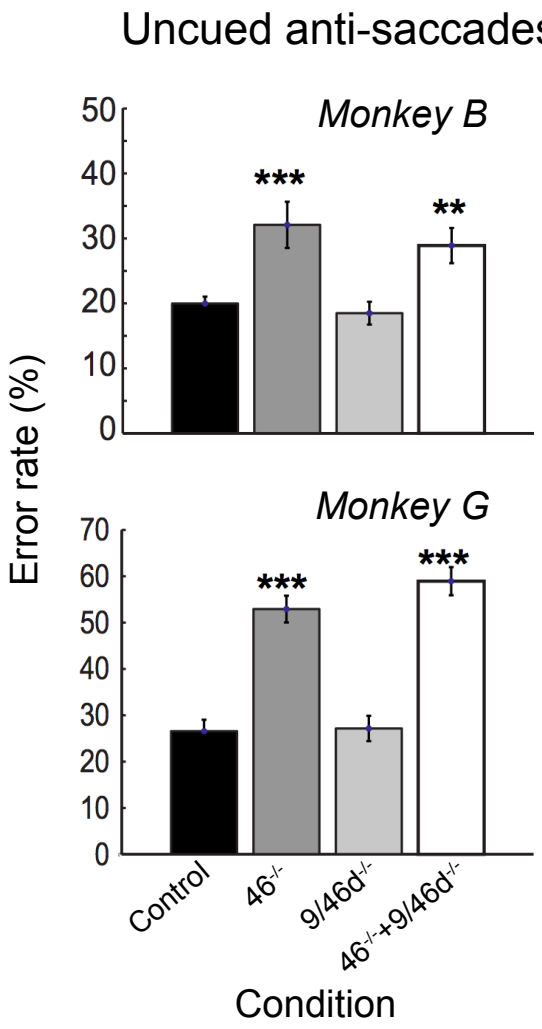


*Figure 8*. **Effects of dorsolateral deactivations on error rates in uncued anti-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in anti-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=17 for each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons.

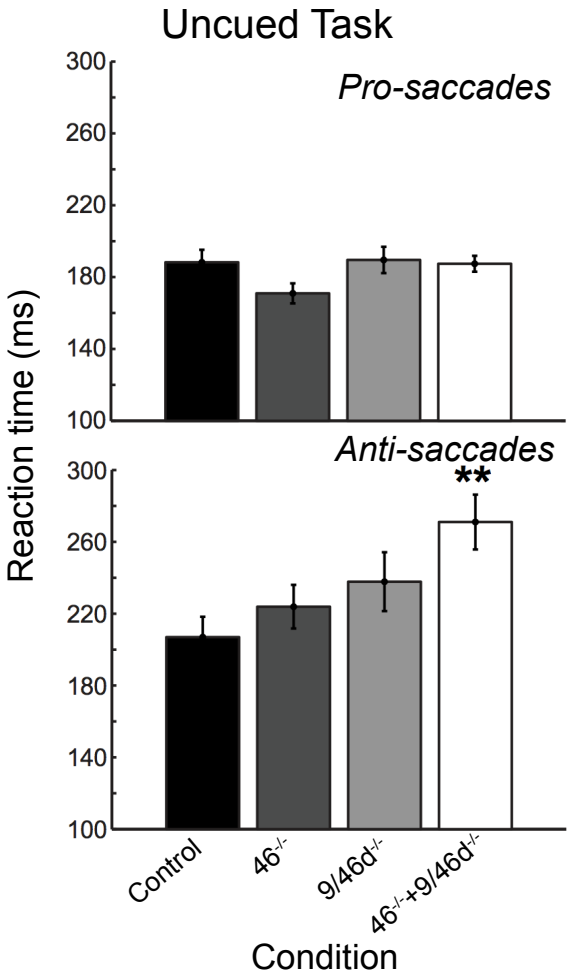


*Figure 9*. **Effects of dorsolateral deactivations on reaction time during uncued task for both monkeys.** Bars display reaction times of both monkeys for post-switch (a) pro-saccade and (b) anti-saccade trials 6 through 15 during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=17 for each condition). Asterisks represent significant differences between deactivation condition and control sessions illustrated by planned post-hoc analyses.

reaction times.

### 3.3 Effects of DLPFC deactivation on rule switching.

To evaluate the effect of DLPFC deactivations on rule switching, we analyzed performance in percentage correct on the first trial after a switch trial error. A one-way ANOVA revealed no significant differences in performance after switch between conditions for both pro- to anti-saccade and anti- to pro-saccade switches ($F(3) = 1.72$, $P=0.17$; and $F(3) = 2.48$, $P=0.07$, respectively). Thus, dorsolateral deactivations did not produce any switch related alterations.

### 3.4 Effects of DLPFC deactivation on cued task performance.

To confirm effects of dorsolateral prefrontal deactivations were due to impairment of rule maintenance in working memory, we tested the monkeys on a similar task that did not require rule maintenance. The cued task was identical to the uncued task except it provided monkeys with instruction for the relevant rule on every trial (by the colour of the fixation point). Thus, this task still required monkeys to retrieve rules from long-term memory and switch between rules but does not require monkeys to maintain relevant rules across trials in WM.

Figure 12 displays performance of both monkeys' on the cued task for the various conditions (n = 5 for all conditions). Performance immediately preceding the switch as well as 15 trials following a switch is presented. During control sessions when no cortical area was deactivated, performance of anti-saccades was at ~95% before switch and did not drop drastically during switch trials (Fig.

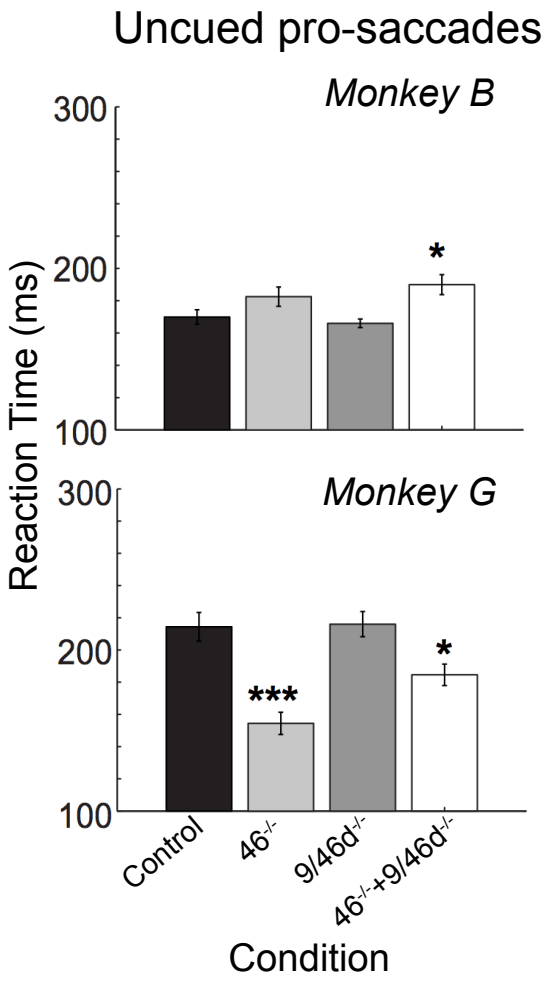


*Figure 10*. **Effects of dorsolateral deactivations on reaction times in uncued pro-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in pro-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=17 for each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons.

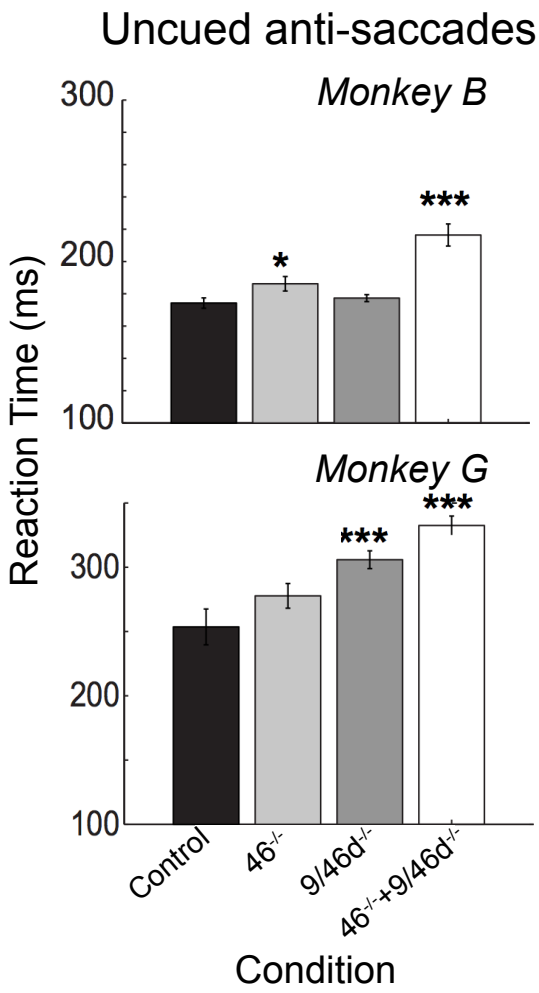


*Figure 11*. **Effects of dorsolateral deactivations on reaction times in uncued anti-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in anti-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=17 for each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons.

12A). Instead, instruction for the relevant rule allowed monkeys to perform pro-saccades at ~100% immediately following switch. Figure 12B displays performance of both monkeys' on the cued task when it switches from pro-saccades to anti-saccades. Pro-saccades performance immediately preceding the switch trial was at ~100% for control sessions. When the rule switched to anti-saccades, performance only dropped to ~95%, which was the average performance for anti-saccades.

Similar to the analysis for the uncued task, we pooled error rates and reaction time values for trials 6 through 15 for each condition. A one-way ANOVA demonstrated no significant differences in error rates between conditions for pro-saccades (Fig. 13A; $F(3) = 1.66$, $P=0.20$, one-way ANOVA). Effects between monkeys were relatively consistent for cued pro-saccade blocks (Fig. 14). A one-way ANOVA revealed a significant effect of DLPFC deactivation on error rates during cued anti-saccade blocks (Fig. 13B; $F(3) = 3.3$, $P=0.03$). Post-hoc t-tests analyses revealed a significant increase in error rates for the combined deactivation of caudal areas 46 and 9/46d ($P=0.02$). Effects between monkeys were relatively consistent for cued anti-saccade blocks (Fig. 15).

Next, we measured the effects on dorsolateral prefrontal deactivations on saccadic reaction times for the cued task. A one-way ANOVA illustrated no significant differences between conditions for pro-saccade reaction times (Fig. 16A; $F(3) = 2.07$, $P=0.13$) but revealed significant differences in reaction time between groups for anti-saccade blocks (Fig. 16B; $F(3) = 3.97$, $P<0.05$). Post-hoc t-tests demonstrated significant increases in reaction time associated with

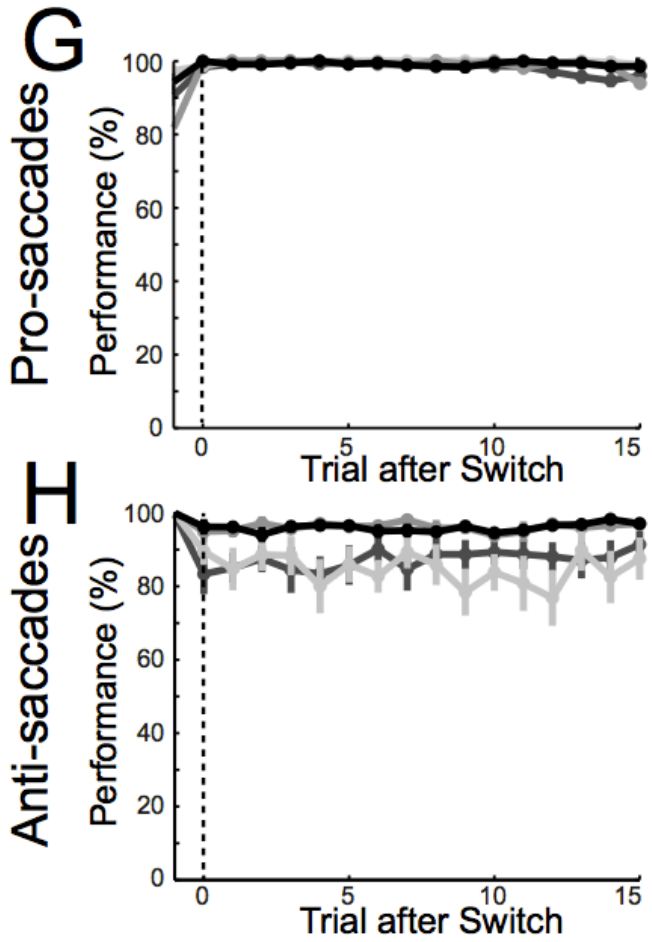


*Figure 12*. **Effects of dorsolateral deactivations on performance in cued task.** Each line represents performance of both monkeys during different conditions (black line = control; dark grey line = bilateral deactivation of caudal area 46; medium grey line = bilateral deactivation of caudal area 9/46d; light grey line = combined bilateral deactivation of caudal area 46 and 9/46d; n=10 for each condition). The figure shows performance during (a) post-switch pro-saccade trials and (b) post-switch anti-saccade trials. The dashed line represents switch trials and the x-axis presents each post-switch trial. Performance is measured in percentage of correct trials.

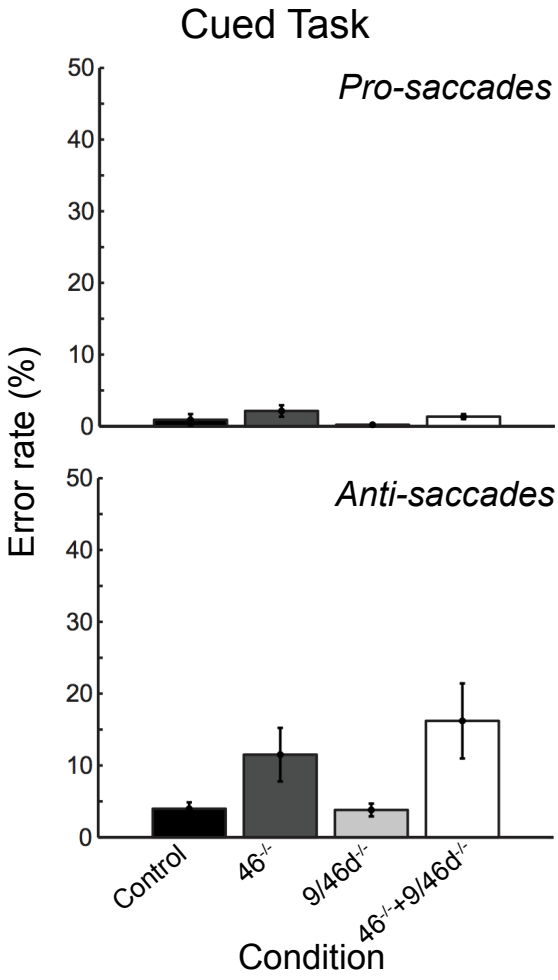


*Figure 13*. **Effects of dorsolateral deactivations on error rates in cued task for both monkeys.** Bars display error rates of both monkeys from post-switch (a) pro-saccade and (b) anti-saccade trials 6 through 15 during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=10 for each condition). Asterisks represent significant differences between deactivation condition and control sessions illustrated by planned post-hoc analyses ($P$<0.00001).

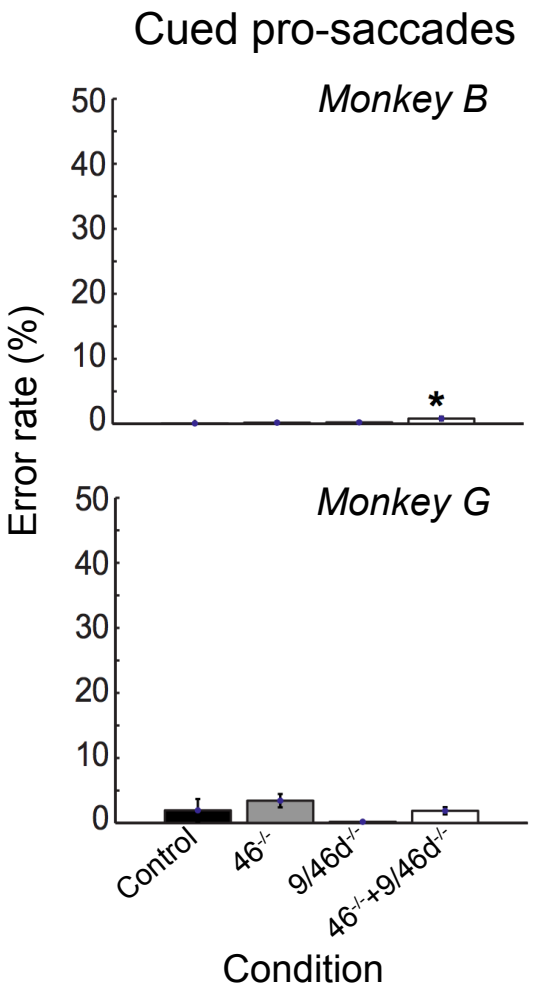


*Figure 14*. **Effects of dorsolateral deactivations on cued error rates in pro-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in pro-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=5 for each monkey at each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons.

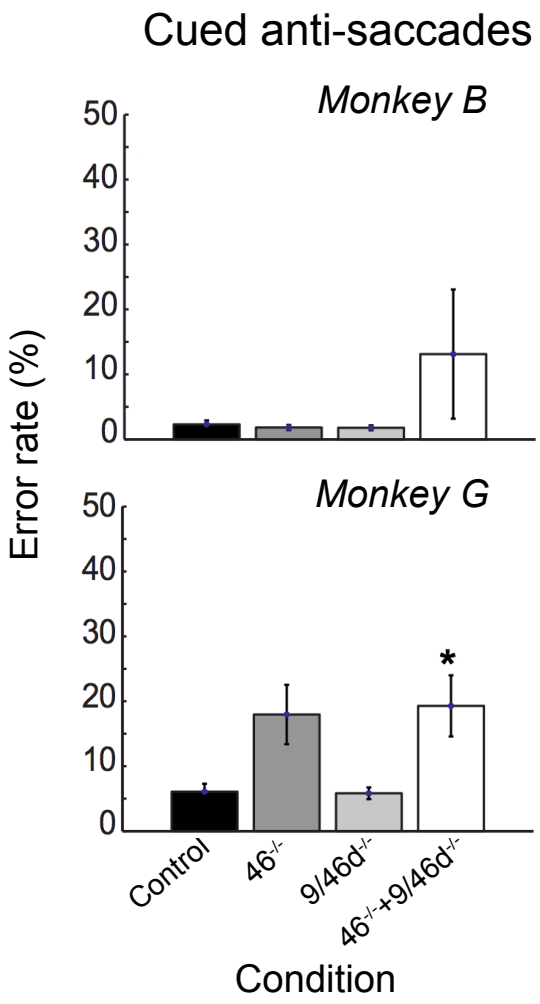


*Figure 15*. **Effects of dorsolateral deactivations on error rates in cued anti-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in anti-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=5 for each monkey at each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons.

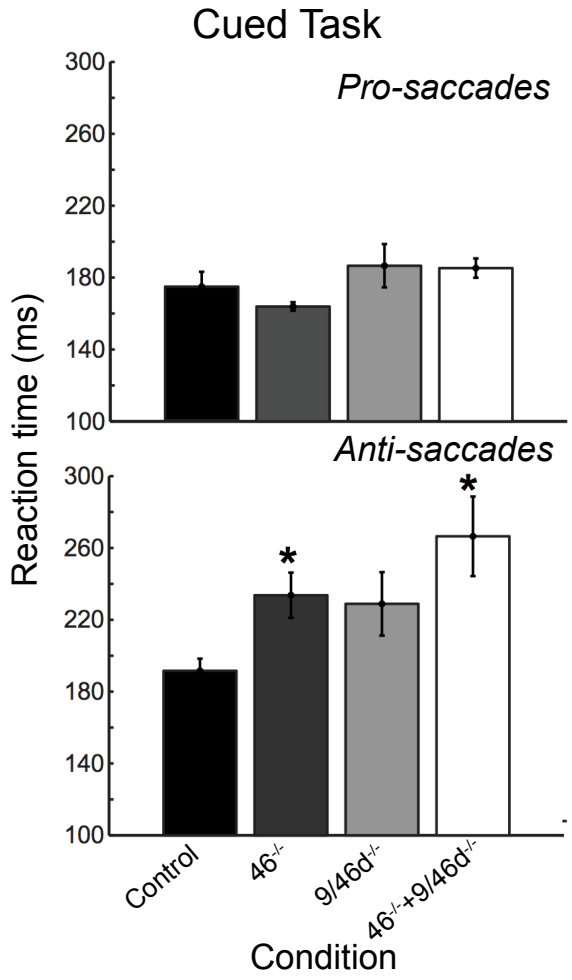


*Figure 16*. **Effects of dorsolateral deactivations on reaction time during cued task for both monkeys.** Bars display reaction times of both monkeys for post-switch (a) pro-saccade and (b) anti-saccade trials 6 through 15 during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=10 for each condition). Asterisks represent significant differences between deactivation condition and control sessions illustrated by planned post-hoc analyses.

deactivation of caudal area 46 and during combined cooling of caudal areas 46 and 9/46d ($P$=0.01 and $P$<0.005, respectively). Effects of deactivations on pro-saccade reaction times between monkeys were slightly inconsistent (Fig. 17) and effects on anti-saccade reaction times had similar trends (Fig. 18).

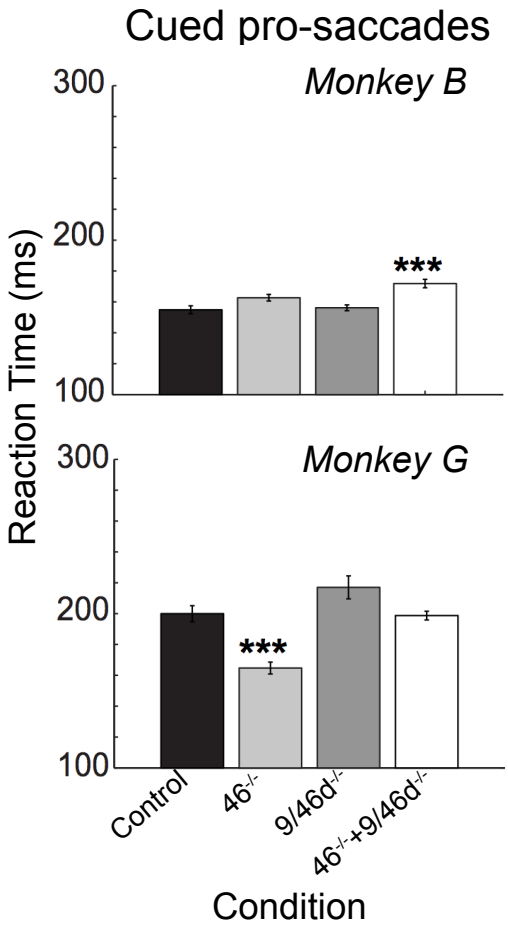


*Figure 17*. **Effects of dorsolateral deactivations on reaction times in cued pro-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in pro-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=5 for each monkey at each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons.

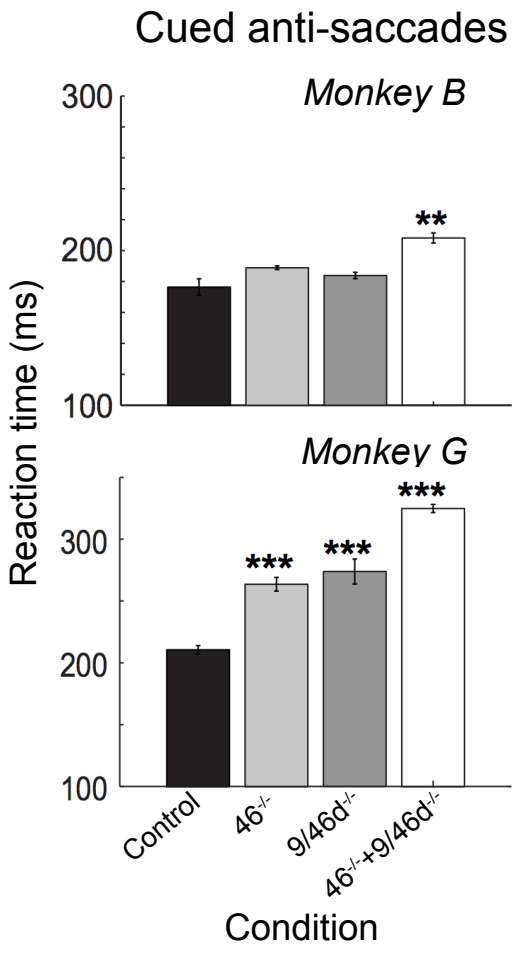


*Figure 18*. **Effects of dorsolateral deactivations on reaction times in cued anti-saccade blocks for each monkey.** Bars display error rates of each monkey from post-switch trials 6 through 15 in anti-saccade blocks during different conditions (black bar = control; dark grey bar = bilateral deactivation of caudal area 46; medium grey bar = bilateral deactivation of caudal area 9/46d; light grey bar = combined bilateral deactivation of caudal area 46 and 9/46d; n=5 for each monkey at each condition). Asterisks represent significant differences between deactivation condition and control sessions revealed by post-hoc comparisons.

## Section 4

# DISCUSSION

Monkeys performed an oculomotor version of the switch task, which required them to alternate between blocks of pro- and anti-saccades. This allowed us to distinguish between externally guided pro-saccades and internally guided anti-saccades for uncued and cued versions of the same task. For the uncued version, animals were required to determine the relevant rule by trial and error based on reward feedback. Once they discovered the relevant rule, the monkeys had to maintain it until it no longer elicited positive feedback at which point they were required to switch to the alternate rule. For the cued version, the colour of the fixation point provided monkeys with the relevant rule in addition to reward feedback (also provided in uncued version). Thus, the cued condition eliminates the intertrial mnemonic demands of the uncued condition.

Bilateral caudal areas 46 and 9/46d of the DLPFC were deactivated independently and in combination to determine their relationship with rule maintenance and rule switching. Evaluating the effects of the differential deactivations on performance and reaction times (RT) revealed functional specialization within subregions of the DLPFC during rule-guided behaviour. Deactivating caudal area 46 (principal sulcus) impaired performance of monkeys on both pro- and anti-saccade blocks in the uncued condition, but only slightly impaired anti-saccade performance in the cued condition. Effects on cued anti-saccades are consistent with the study by Koval, Lomber and Everling (2011), which measured effects of deactivating area 46 on randomly interleaved (cued) pro- and anti-saccades. On the other hand, deactivation of caudal area 9/46d alone (directly dorsal to area 46) did not alter task performance for pro- or anti-

saccades in either task condition. Deactivating both areas 46 and 9/46d selectively impaired performance on anti-saccades and spared pro-saccade performance for both task conditions. Similarity in deactivation effects between both task conditions suggests the impairment produced by combined cooling was independent of mnemonic processes.

**4.1 Effects of deactivating caudal area 46.**

Deactivating caudal principal sulcus impaired performance of both pro- and anti-saccades throughout blocks in the uncued condition. This effect was seen by computing error rates from post-switch trials 6 through 15 for pro- and anti-saccades. Increased error rates were observed with deactivation of area 46 consistently in both monkeys. While deactivation increased error rates, it did not alter RTs in either pro- or anti-saccades in the uncued condition. These deactivation effects on RTs in the uncued condition were similar between monkeys for anti-saccades but differed slightly for pro-saccades. Deactivating area 46 decreased pro-saccade RT for monkey G on both conditions but did not alter pro-saccade RT for monkey B.

In switch paradigms, there is a *mixing cost* associated with performing two tasks within the same session. This mixing cost represents the difference in RT between performing a session with just one rule and performing a session with multiple rules (Monsell, 2003). This means that a monkey's RT for pro-saccades will be higher when the pro-saccades run in the same session as anti-saccades than when pro-saccades are the only role in the session. This mixing cost arises

from the fact that sessions with multiple rules require maintenance of all possible actions. This leads to *proactive interference* between tasks. Thus, when performing pro-saccades, monkeys still have to maintain anti-saccade processes in WM. These processes require inhibition of saccadic tendencies (Barton et al., 2006), which would increase RT for pro-saccade blocks. Furthermore, Bengtsson et al. have suggested that after a task rule has been generated, the DLPFC may be implicated in keeping rules online in WM and protecting it from distractions (Bengtsston et al., 2009). Thus, the decrease in pro-saccade RT may be due to a general loss of persistent inhibition in the saccade generating system due to distracting processes from the anti-saccade task. The discrepancies between monkey B and G may be due to differences in baseline cognitive potential of the monkeys. Monkey B consistently exhibited better overall performance. So, while deactivation causes a decrease in pro-saccade RT for monkey G, control sessions for monkey B could be exhibiting a floor effect.

**4.2 Effects of deactivating caudal area 9/46d.**

Deactivating caudal area 9/46d did not alter performance on either the uncued or the cued condition. This is consistent with findings from Buckley and colleagues where lesions of areas 9/46d and 9 in monkeys did not impair performance on an analog of the WCST (Buckley et al., 2009). In fact, they included the areas 9 and 9/46d lesion group in the control group for analytic purposes. These results were consistent between both monkeys for error rates.

In contrast, RT data revealed slight differences between monkeys during

cooling of caudal area 9/46d alone. When looking at RT of both monkeys for control and deactivation conditions, there were no significant differences between the conditions. However, while monkey B exhibited no alteration in RT on either pro- or anti-saccades for both conditions, monkey G revealed an increase in RT for anti-saccades on both cued and uncued task conditions. This again could be due to monkey B being relatively proficient in anti-saccades, so proficient that cooling of caudal area 9/46 alone does not provide an impairment. Monkey B has shown a lack of impairment with cooling in previous experiments that have reported impairments in other monkeys (Koval, Lomber and Everling, 2011). The increase in anti-saccade RT for monkey G during deactivation suggests a difficulty in generating the internally guided anti-saccades. If there were difficulty with inhibiting the reflexive pro-saccade, we would expect an increase in anti-saccade error rates due to a pro-saccade bias. Thus, the impairment in monkey G seems to be selective for the generation of an anti-saccade and not the initial inhibition of a pro-saccade.

### 4.3 Effects of simultaneously deactivating caudal areas 46 and 9/46d.

Simultaneously deactivating caudal areas 46 and 9/46d produced an interesting effect. Like deactivation of caudal area 46 alone, combined cooling increased anti-saccade error rates for the uncued condition. However, unlike deactivation of caudal area 46, combined cooling did not alter uncued pro-saccade error rates. Effects on error rates for the uncued condition were consistent between both monkeys, with impairment on anti-saccade blocks but

not pro-saccades. Combining the effects of deactivating both areas independently suggests impairment in rule maintenance (cooling area 46) and increased difficulty generating internally guided anti-saccades (cooling area 9/46d). Thus, although there is an impairment in rule maintenance, the increased difficulty with anti-saccades produced a bias towards pro-saccades in the uncued condition.

Additionally, combined cooling increased RT for anti-saccades without altering pro-saccade RT in the uncued condition. For the cued condition, anti-saccade RTs were increased consistently with no differences in error rates and pro-saccade RTs. Differences between monkeys are discussed further. Both monkeys individually exhibited an increase in RT for uncued anti-saccade blocks and showed similar trends for cued anti-saccades. On the contrary, monkeys displayed opposing effects for uncued pro-saccade RT. While monkey G displayed a decrease in uncued pro-saccade RT during deactivation (same effect as deactivating caudal area 46 alone), monkey B demonstrated a slight but significant increase in uncued pro-saccade RT. The reaction time effects on pro-saccades for monkey G are selectively present only in the uncued condition, suggesting a maintenance related process. Since effects of combined cooling are consistent with deactivating caudal area 46 alone for monkey G, the same explanation may apply. Thus, deactivation could cause a decrease in general inhibition of the saccade generating system due to lack of maintenance allowing neural activity for externally generated pro-saccades to reach initiation threshold faster (Barton et al., 2006; Munoz and Everling, 2004). On the other hand,

monkey B displayed an increase in uncued pro-saccade RT. As well, pro-saccade RT effects of monkey B were present in both uncued and cued task conditions, suggesting an effect unrelated to rule maintenance. These effects are consistent with another study at our laboratory where monkey B had to perform randomly interleaved pro-saccades and anti-saccades (Koval, Lomber and Everling, 2011). Analogous to our results, deactivation of the DLPFC in monkey B increased RT for both pro- and anti-saccades. Their results accompanied a decrease in preparatory activity in the SC. This results in a longer RT once a stimulus appears because it takes longer for activity to accumulate towards saccade initiation threshold. Thus, while monkey G displayed a maintenance related decrease in pro-saccade RT, monkey B displayed a general increase in RT present in multiple tasks.

### 4.4 Rule maintenance.

We found that cooling the caudal principal sulcus produced robust effects on rule maintenance. This effect can be explained by the results from single neuron recording studies in nonhuman primates. These studies have demonstrated delay related activity, task selective activity as well as task selective delay activity in DLPFC neurons (Asaad, Rainer and Miller, 1998, 2000; Wallis, Anderson, and Miller, 2001; Wallis and Miller, 2003; White and Wise, 1999; Genovisio et al., 2005; Johnston and Everling, 2006; Johnston et al., 2007; Everling and DeSouza, 2005). Furthermore, imaging studies have reported increased activity in the DLPFC during maintenance of abstract rules (Crone et

al., 2006; Sakai and Passingham, 2003). Additionally, the lesion study performed by Buckley et al. (2009) revealed the importance of area 46 (principal sulcus) in maintenance of abstract rules via WCST analog. Their results showed that the principal sulcus was crucial for the performance of tasks that required rule maintenance. Thus, our findings were consistent with Buckley et al.'s study and demonstrated deactivation of caudal area 46 selectively impairs performance in tasks that do not provide the subject with instruction and depend on maintenance of rules.

Our inference that area 46 is crucial for rule maintenance is further supported by the lack of an effect of cooling area 46 on performance of cued pro-saccade and anti-saccade blocks. This finding has also been supported by dorsolateral lesion studies in the macaque that produce no impairment in tasks that rely on stimulus-response associations (Gaffan and Harrison, 1989; Petrides, 1982). On the other hand, ventral and orbital prefrontal lesions seem to impair performance on conditional tasks (Bussey, Wise and Murray, 2001; Murray, Bussey and Wise, 2000; Passingham, Toni and Rushworth, 2000; Wang, Zhang and Li, 2000). Further support for this functional specialization within the PFC comes from imaging studies where there is increased activation in the DLPFC during self-ordered tasks (Frith et al., 1991; Deiber et al., 1991; Bengtsson et al., 2009) and increased activity in ventral prefrontal regions during tasks that require retention of stimulus-response associations (Toni, Rushworth and Passingham, 2001).

Although there was no effect of deactivation on cued pro-saccades,

deactivation of caudal area 46 did slightly impair performance of cued anti-saccades. Consistently, the aforementioned study by Koval and colleagues (2011) found increased error rates and RTs on randomly interleaved pro- and anti-saccades during bilateral deactivation of caudal area 46. These behavioural results were in concert with alterations in preparatory, visual and motor responses in the SC, which may provide a neural correlate of the deficits produced by DLPFC deactivation.

### 4.5 Rule switching.

None of our deactivation conditions affected the monkeys' ability to switch to the alternate rule. This is consistent with previous findings from electrophysiological studies at our laboratory. Johnston and colleagues (2007) found low rule selectivity in DLPFC neurons (areas 46 and 9/46d) following a rule switch, while rule selectivity increased after a rule switch in the anterior cingulate cortex, suggesting a minor role for the DLPFC in rule switching. In addition, imaging studies have demonstrated an increase in activity in the pre-SMA and ACC during task-set reconfiguration (Crone et al., 2006), strongly implicating medial PFC structures in rule switching.

### 4.6 Internal generation of actions.

Previous studies have implicated the DLPFC in response inhibition and generation of internally guided actions (Guitton, Buchtel and Douglas, 1985; Frith et al., 1991). We found that deactivation of caudal area 9/46d did not affect

performance of either pro- or anti-saccades, which is consistent with the study by Buckley and colleagues (2009). However, combined deactivation of caudal areas 46 and 9/46d prolonged anti-saccade reaction time but spared pro-saccades. Since anti-saccade performance relies on inhibition of stronger pro-saccade tendencies and internal generation of willed anti-saccades, these results may be due to a deficit in response inhibition or internal generation with the additional caudal area 9/46d lesion. If deactivation impaired response inhibition, we would expect an increase in anti-saccade error rates due to insufficient inhibition of pro-saccades. This is not the case suggesting that the increase in anti-saccade reaction time may be due to increased difficulty in generating internally guided actions. In addition, we found a slight increase in anti-saccade reaction time during deactivation of caudal area 9/46d alone for monkey G. This may be due to fewer goal-directed DLPFC anti-saccade bias signals reaching downstream saccadic centres. Deactivation of this subregion did not completely take away these bias signals because the intact area 46 recovered this function.

Frith and colleagues (1991) conducted a PET experiment and contrasted regional cerebral blood flow while subjects performed willed versus automatic actions. Consistent with our findings, Frith and colleagues found an increase in DLPFC activity during willed actions compared to routine actions for multiple modalities.

In their study, Passingham, Toni and Rushworth (2000) suggest that activity of a neuron within a given frontal region may be derived from it's connections with other frontal regions and that only lesion studies can determine whether a

particular region is essential for a given behavior. Following this argument, our data speak against a role of caudal 9/46d in rule maintenance and in the suppression of automatic responses.

**4.7 Functional specialization.**

Although deactivation of caudal area 46 impaired uncued pro- and anti-saccade performance and cooling caudal area 9/46d did not affect performance on either cued or uncued conditions, combined cooling selectively impaired anti-saccade performance while sparing pro-saccades. Therefore, simultaneous deactivation of caudal area 9/46d reversed the uncued pro-saccade impairment produced by deactivation of caudal area 46 alone. This suggests that while deactivation of caudal area 46 alone produces a general deficit in maintenance of uncued rules, additional deactivation of caudal area 9/46d produces a specific deficit associated with performance of the more complex task. Nonetheless, our results support the hypothesis that the DLPFC is involved in rule maintenance. Area 46 is implicated in general rule maintenance whereas area 9/46d may be additionally recruited when rules require overwriting strong, well-established tendencies (Bunge, 2004). Consistently, the DLPFC has been involved in response inhibition during anti-saccade performance (Guitton, Buchtel and Douglas, 1985; Pierrot-Deseilligny et al., 1991; Ploner et al., 2005).

Accordingly, caudal area 46 is involved in maintenance of both automatic (pro-saccades) and controlled (anti-saccades) tasks. Thus, deactivation of this subregion results in an increase in errors for anti- and pro-saccades during the

uncued condition. Additionally, deactivation of caudal area 9/46d alone did not impair performance on either pro- or anti-saccades. This may be due to intactness of caudal area 46 maintaining general task processes associated with both rules. As well, the slight increase in anti-saccade RT for monkey G might be due to fewer dorsolateral processes providing anti-saccade bias signals downstream. Simultaneous deactivation of both subregions revealed effects consistent with our hypothesis. Thus, combined deactivation selectively impaired anti-saccades (via an increase in RT) without affecting pro-saccade performance because of a general deficit in rule maintenance as well as impairment in control of the complex task. This is consistent with Fuster's characterization of prefrontal involvement in 'least automatic' actions that require planning and deliberation and not in reflexive actions (Fuster, 1981). As well, Holmes suggested frontal centres are implicated in controlling or inhibiting inappropriate reflexes resulting in frontal lobe patients being confined to reflexive tendencies (Holmes, 1938). Analogously, our results demonstrate that combined deactivation impairs performance of the controlled anti-saccade and spares performance of the reflexive pro-saccade.

Therefore, cooling area 46 alone impaired performance on both pro- and anti-saccade for the uncued condition but not for the cued condition. This implicates the principal sulcus in rule maintenance but not in conditional association tasks. Interestingly, while cooling area 9/46d alone had no effect on performance of either task, combined cooling of areas 46 and 9/46d impaired performance of anti-saccades (by increasing RT). Thus, additional cooling of

area 9/46d recovered pro-saccade performance, which was impaired during area 46 deactivation alone. This suggests that while area 46 is essential for rule maintenance, area 9/46d may be additionally recruited when task demands are asymmetric. In addition, both areas together seem to be involved in inhibitive processes that control production of automatic pro-saccades.

## Section 5

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