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Investigating Cognitive Control And Task Switching Using The Macaque Oculomotor System

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ABSTRACT

Cognitive control is crucial to voluntary behaviour. It is required to select appropriate goals and guide behaviour to achieve the desired outcomes. Cognitive control is particularly important for the ability to adapt behaviour to changes in the external environment and internal goals, and to quickly switch between different tasks. Successful task switching involves a network of brain areas to select, maintain, implement, and execute the appropriate task. Uncovering the neural mechanisms of this goal-directed behaviour using lesions, functional neuroimaging, and neurophysiology studies is central to cognitive neuroscience.

The oculomotor system provides a valuable framework for understanding the neural mechanisms of cognitive control, as it is anatomically and functionally well characterized. In this project, pro-saccade and anti-saccade tasks were used to investigate the contributions of oculomotor and cognitive brain areas to different stages of task processing. In Chapter 2, non-human primates performed cued and randomly interleaved pro-saccade and anti-saccade tasks while neural activity was recorded in the superior colliculus (SC). In Chapter 3, non-human primates performed cued and randomly interleaved pro-saccade and anti-saccade tasks while local field potential activity was recorded in the SC and reversible cryogenic deactivation was applied to the dorsolateral prefrontal cortex (DLPFC). In Chapter 4, non-human primates performed uncued and cued pro-saccade and anti-saccade switch tasks while reversible cryogenic deactivation was applied to the dorsal anterior cingulate cortex (dACC).

The first study clarifies that macaque monkeys demonstrate similar error rate and reaction time switch costs to humans performing cued and randomly interleaved pro-saccade and anti-saccade tasks. These switch costs were associated with switch-related differences in stimulus-related activity in the SC that were resolved by the time of saccade onset. The second study

shows that bilateral DLPFC deactivation decreases preparatory beta and gamma power in the superior colliculus. In addition, the correlation of gamma power with spike rate in the SC was attenuated by DLPFC deactivation. Lastly, bilateral dACC deactivation in the third study impairs anti-saccade performance and increases saccadic reaction times for pro-saccades and anti-saccades. Deactivation of the dACC also impairs the ability to integrate feedback from the previous trial.

Overall, these findings suggest unique roles for the dACC, DLPFC, and SC in cognitive control and task switching. The dACC may monitor feedback to select the appropriate task and implement cognitive control, the DLPFC may maintain the current task-set and modulate the activity of other brain areas, and the SC may be modulated by task switching processes and contribute to the production of switch costs.

KEYWORDS:

Anti-saccade, cortical deactivation, local field potential, oculomotor control, prefrontal cortex, single-neuron electrophysiology, superior colliculus, task switching, top-down control

CO-AUTHORSHIP STATEMENT

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As author of this thesis and the primary author of the three experimental chapters, Jason Chan

was responsible for designing the experiments, collecting the data (Chapter 4), data analysis, and

writing the completed thesis and manuscripts. Michael Koval collected the data for Chapters 2

and 3. Thilo Womelsdorf assisted in data analysis for Chapter 3. Kevin Johnston assisted with

revisions for Chapter 2 and performed the surgical procedures and assisted in data collection for

Chapter 4. Stephen Lomber designed and performed the surgical procedures to implant the

cryoloops for Chapters 3 and 4. Stefan Everling supervised all stages of this thesis and assisted in

experimental design, data analysis, and manuscript revisions for all three experimental chapters.

"If it seems to neurologists that our present understanding of the brain and the mind of man is hardly more than a beginning of science it may be reassuring to recall that our task is the ultimate one. The problem of neurology is to understand man himself."

– Dr. Wilder Penfield, 1965

program advisory committee. It would have been difficult to embark on a PhD program in neuroscience without having an idea of what research entails. I would like to thank Drs. Joseph DeSouza, Martin Paré, and Michael Dorris for introducing me to a career in science and encouraging my involvement in research.

Throughout graduate school, I have had the opportunity to interact with friends and colleagues at the University of Western Ontario, across the province and country, and around the world. I would like to thank them for their insight, perspective, and for keeping life interesting. In particular, I would like to thank Dr. Aaron Kucyi for his continuing friendship and brilliant discussions, since we both started on our respective journeys in research ten years ago.

Finally, I would like to thank my family – my parents, grandparents, and brother – for a lifetime of support. Although there was never any suggestion or expectation that I pursue graduate school or extended post-secondary education, this would not have been possible without their continuing support.

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ACC	Anterior cingulate cortex
BOLD	Blood oxygen level-dependent
CCZ	Caudal cingulate zone
CMAd	Dorsal cingulate motor area
CMAr	Rostral cingulate motor area
CMAv	Ventral cingulate motor area
dACC	Dorsal anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
ERP	Event-related potential
EVC	Expected value of control
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
iMLF	Interstitial nucleus of the medial longitudinal fasciculus
IPS	Intraparietal sulcus
LFP	Local field potential
LIP	Lateral intraparietal
MCC	Midcingulate cortex
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
PPC	Posterior parietal cortex
PPRF	Paramedian pontine reticular formation
pre-SMA	Pre-supplementary motor area
RCZa	Anterior rostral cingulate zone
RCZp	Posterior rostral cingulate zone
RF	Response field
ROC	Receiver operating characteristic
RSC	Retrosplenial cortex
SC	Superior colliculus
SEF	Supplementary eye field
SMA	Supplementary motor area
SRT	Saccadic reaction time
TPJ	Temporal parietal junction

CHAPTER 1

Introduction

1.1 Cognitive Control

In everyday life, our behaviour is driven by the pursuit of various goals. Consider a writer who is sitting at a desk working on a lengthy essay as an example. At times, successive sentences are readily composed. At others, focusing on writing may be difficult as feelings of hunger or the desire to take a break emerge. Goals can be short-term, such as eating food when hungry, or long-term, such as finishing the essay. Multiple goals can be elicited by the same external stimulus and the appropriate goal to pursue depends on the current context. A computer monitor can prompt writing, or trigger checking incoming emails, reading the news, or watching a movie. The presence of an immediately impending deadline for the essay or fatigue would likely determine whether the writer continues working or takes a break. Ultimately, cognitive control is required to select appropriate goals and guide behaviour to achieve the desired outcomes.

Cognitive control plays a crucial role in our lives, particularly with regard to voluntary behaviour, and consequently is a central research topic in experimental psychology and cognitive neuroscience. Notably, cognitive control is not a single unitary process. Instead, it refers to a set of different cognitive functions that together enable goal-directed behaviour. Cognitive functions include, but are not limited to, the ability to attend to behaviourally relevant information, maintain information in working memory, select and inhibit responses, make decisions, plan a series of steps to achieve a goal, and monitor whether actions have their intended consequences (Logan, 1985; Stoet and Synder, 2009; Botvinick and Braver, 2015). The capacity to flexibly

adapt behaviour to changes in the external environment and internal goals is a hallmark of cognitive control.

1.1.1 Rule-Guided Behaviour

Much of our behaviour is guided by rules, or learned associations between stimuli, contexts, actions, and outcomes (Bunge, 2004). Rules vary in their level of abstraction and enable us to act in an appropriate manner. Simple and concrete rules, or stimulus-response associations, can be learned and applied quickly. For example, drivers know that a green light means go whereas a red light means stop. Arbitrary associations between stimuli and responses, however, are difficult to apply to other situations. Outside of driving, green-go and red-stop do not readily provide information about which behaviour is appropriate. In contrast, complex and abstract rules are not constrained by specific stimuli or responses, and can be generalized and applied to familiar and novel situations (Wallis et al., 2001; Buschman and Miller, 2014). For example, drivers know that in order to drive a motor vehicle, the engine must be started, regardless of where the ignition is located or the method used to start the engine. Depending on the goal, single or multiple concrete or abstract rules may be required to guide the appropriate behaviour.

A concept related to rules is that of a "task-set." Each behaviour or task that is performed is associated with a task-set, or task-specific configuration of mental processes and resources (Monsell, 2003; Sakai, 2008). As such, a task-set consists of task-relevant information about stimuli, responses, and rules, as well as the sensory, attentional, and motor processes required for performing the task. Like rules, task-sets are actively maintained for task performance. Overall,

cognitive control is required to select, maintain, implement, and execute the appropriate rules and task-sets.

1.1.2 Attention

Attention is integral to cognitive control and its importance in everyday life is generally understood and accepted. As a phenomenon, William James (1890) described attention as follows:

> "Everyone knows what attention is. It is taking possession by the mind in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought... It implies withdrawal from some things in order to effectively deal with others."

Accordingly, at any given moment, the total amount of attentional and cognitive resources available for information processing is limited (Kahneman, 1973). Although multiple sensations, tasks, emotions, and thoughts may occur concurrently, attention selectively allocates resources to information that is behaviourally relevant, while inhibiting the processing of information that is behaviourally irrelevant.

How attention is allocated depends on bottom-up and top-down factors (Corbetta and Shulman, 2002; Knudsen, 2007). Bottom-up or exogenous attention is involuntarily driven by novel, salient, or unexpected stimuli in the sensory environment. In contrast, top-down or endogenous attention is voluntarily driven by an individual's knowledge, experience, and current goals. To illustrate these factors, take for example a writer working on an essay. If a fire alarm starts ringing and flashing, attention would be immediately and involuntarily drawn to the alarm in a bottom-up manner and the writer would be compelled to act on this novel and salient

stimulus. Using previous experience and meaning associated with the alarm, the writer may choose to stop working and focus on evacuating the building. Alternatively, if the writer knew beforehand that the alarm is a test, attention may instead be maintained on writing in a top-down manner while ignoring the alarm. Bottom-up and top-down processes interact with each other to dynamically shift and maintain attention. The top-down allocation of attentional and cognitive resources, also referred to as executive attention, is a critical component of cognitive control and particularly important for goal-directed behaviour.

1.1.3 Working Memory

Behaviourally relevant information is temporarily maintained and manipulated online by working memory, which provides an interface between perception, long-term memory, and action (Baddeley, 1986; Baddeley, 2003). A key feature of working memory is its ability to maintain information in the absence of sensory stimulation and motor output. Consequently, it is critical for the active maintenance of goals and task rules, and for the implementation of cognitive control and goal-directed behaviour. Notably, there is a close functional relationship between working memory and attention, especially at the executive level. The central executive of working memory proposed by Baddeley (1986) to coordinate and process information for the control of behaviour mirrors the supervisory attentional system proposed by Norman and Shallice (1986) for attentional control. Furthermore, working memory and attention both have a limited capacity for information processing and the content of both are often identical, such that working memory can be considered to represent the contents of attention (Knudsen, 2007). Given the similarities between working memory and attention for goal-directed behaviour, Fuster

(2008) described working memory for psychological and neural investigation as "sustained attention focused on an internal representation."

1.2 Brain Systems for Cognitive Control

Uncovering the neural mechanisms underlying cognitive control is a central aim of cognitive neuroscience. Numerous lesion, functional neuroimaging, and neurophysiological studies have associated cognitive control, including the central executive of working memory and supervisory attentional system, with the frontal lobes (Stuss and Knight, 2002; Fuster, 2008). Functional neuroimaging has also shown that broad networks of brain areas are simultaneously activated with the frontal lobes for cognitive control.

The bottom-up control and top-down control of attention are generally accepted to be associated with the ventral attention network and dorsal attention network respectively. The ventral attention network includes the temporal parietal junction (TPJ) and ventral prefrontal cortex, and is lateralized to the right hemisphere in humans (Corbetta and Shulman, 2002). The role of these brain areas in the bottom-up control of visual attention is evident when a lesion to the right hemisphere produces left-sided spatial neglect (Corbetta and Shulman, 2002). Furthermore, transient activation with functional magnetic resonance imaging (fMRI) is elicited in the ventral attention network when behaviourally relevant, salient, or unexpected stimuli are presented, regardless of the modality of the stimuli (Corbetta et al., 2000; Downar et al., 2000). In non-human primates, neurons in area 7a, which may correspond to the human TPJ (Patel et al., 2015), respond to stimuli that are behaviourally relevant and presented to previously unattended locations (Bushnell et al., 1981; Robinson et al., 1995; Steinmetz and Constantinidis, 1995).

Whereas the ventral attention network orients attention to salient stimuli in the sensory environment, the dorsal attention network, which includes the frontal eye field (FEF) and intraparietal sulcus (IPS), is implicated in the endogenous control of attention (Fig. 1.1) (Corbetta and Shulman, 2002). With regard to visual attention, sustained activation with fMRI is elicited bilaterally in these brain areas when attention is covertly directed to a peripheral location, with stronger activation contralateral to the attended visual field (Kastner et al., 1999; Corbetta et al., 2000; Hopfinger et al., 2000). In non-human primates, FEF and IPS neurons increase in activity in anticipation of the onset of a stimulus (Bushnell et al., 1981; Colby et al., 1996) and encode stimuli features that are behaviourally relevant (Seagraves and Goldberg, 1987; Toth and Assad, 2002). In addition, the FEF and IPS are implicated in working memory and the control of eye movements (Corbetta and Shulman, 2002). This convergence and integration of sensory, attentional, and motor information in frontoparietal cortex is critical for goal-directed behaviour.

More generally, frontoparietal brain areas are implicated in a variety of cognitive functions, including attention, working memory, task representation, response selection, inhibition, planning sequences of actions, and decision making (Duncan and Owen, 2000; Corbetta and Shulman, 2002; Duncan, 2010). The lateral prefrontal cortex, anterior insula, anterior cingulate cortex (ACC), pre-supplementary motor area (pre-SMA), and IPS are commonly activated together with fMRI for cognitive tasks and tests of fluid intelligence (Duncan and Owen, 2000; Duncan, 2010). Accordingly, neurons in these brain areas have demonstrated the ability to encode task-relevant information and reorganize information rapidly when the context changes (Asaad et al., 2000; Wallis et al., 2001; Stoet and Snyder, 2004; Johnston et al., 2007; Duncan, 2010). The unique contributions of each brain area to cognitive
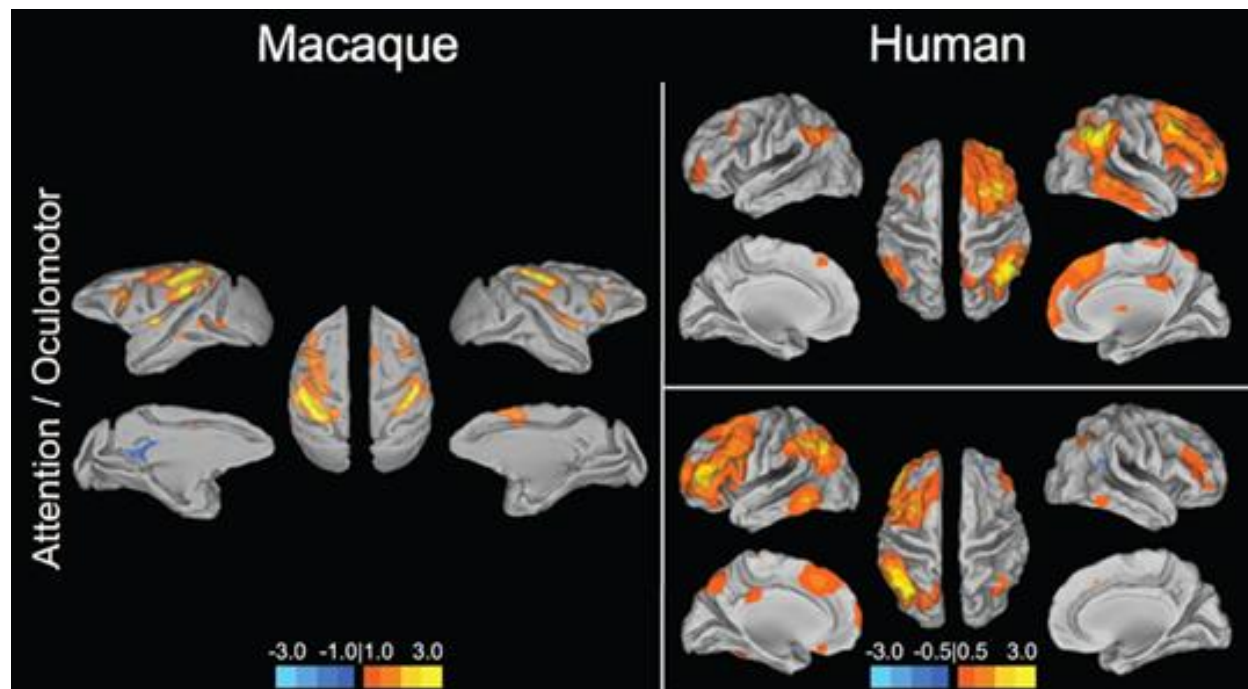
Figure 1.1. Dorsal attention and oculomotor network. Frontoparietal networks of macaque monkeys and humans are mapped using independent component analysis of resting-state functional magnetic resonance imaging data. Brain areas in this network include the FEF, IPS, DLPFC, and ACC. Reproduced with permission from: Hutchison RM, Everling S (2012) Monkey in the middle: why non-human primates are needed to bridge the gap in resting-state investigations. Front Neuroanat 6:29.

control in this multiple-demand network (Duncan, 2010), however, remain unclear. Although brain areas outside the frontal lobe are certainly involved in cognitive control, the prefrontal cortex (PFC) has long been recognized to play a particularly important role.

1.2.1 Prefrontal Cortex

The PFC, located in the anterior part of the frontal lobes, is a neocortical region that is highly developed and expanded in primates, especially humans. Although the entire PFC receives projections from the mediodorsal nucleus of the thalamus, it can be further subdivided into distinct regions based on cytoarchitecture and connectivity (Brodmann, 1909; Petrides and Pandya, 1999; Petrides, 2005; Fuster, 2008; Hutchison and Everling, 2014). These regions are interconnected and many receive converging inputs from multiple sensory modalities (Pandya and Kuypers, 1969; Jones and Powell, 1970; Chavis and Pandya, 1975; Petrides, 2005). As a result, the PFC performs a diverse set of functions that are interrelated and complement each other. Overall, the PFC receives and sends projections to a variety of cortical sensory and motor-related areas, and subcortical areas (Pandya and Kuypers, 1969; Jones and Powell, 1970; Miller and Cohen, 2001; Fuster, 2008), making it well positioned to coordinate neural processes and integrate information for complex purposeful behaviour.

Within the PFC, the dorsolateral prefrontal cortex (DLPFC) and dorsal anterior cingulate cortex (dACC) are two areas that are often associated with each other and with cognitive control. The DLPFC and dACC are highly and reciprocally connected (Barbas and Pandya, 1989; Bates and Goldman-Rakic, 1993; Morecraft and Van Hoesen, 1993; Paus et al., 2001; Petrides, 2005), and functional neuroimaging studies have consistently demonstrated co-activation for a variety of cognitively demanding tasks (Duncan and Owen, 2000). Although their relative roles in

cognitive control remain poorly understood, anatomical and physiological studies suggest distinct contributions for the DLPFC and dACC.

1.2.1.1 Dorsolateral Prefrontal Cortex

Anatomically, the DLPFC consists of Brodmann areas 9, 9/46, and 46 and is defined from other regions in the PFC by a well-developed granular layer IV, particularly in areas 9/46 and 46 (Petrides and Pandya, 1999; Petrides, 2005). In humans, this corresponds to the superior frontal gyrus and middle frontal gyrus. In macaque monkeys, the DLPFC is located anterior to the arcuate sulcus and includes the banks of the principal sulcus, the cortex surrounding the anterior portion of this sulcus, and the cortex extending dorsally to the midline (Petrides and Pandya, 1999).

The DLPFC receives converging visual, auditory, and somatosensory inputs from the occipital, temporal, and parietal cortices (Jones and Powell, 1970; Petrides and Pandya, 1984; Seltzer and Pandya, 1989), including from multimodal areas such as the superior temporal sulcus, superior temporal gyrus, cingulate cortex, and retrosplenial cortex (Chavis and Pandya, 1976; Seltzer and Pandya, 1989; Petrides and Pandya, 1999; Petrides, 2005). Through reciprocal connections with the retrosplenial cortex, orbitofrontal, and medial prefrontal cortex, the DLPFC also has access to the limbic system for the processing of long-term memory, affect, and motivation (Morris et al., 1999; Miller and Cohen, 2001; Petrides, 2005). This diverse set of inputs allows for complex multimodal processing and integration. The DLPFC's projections to the supplementary motor area (SMA), pre-SMA, premotor cortex, FEF, ACC, cerebellum, and superior colliculus (SC) (Goldman and Nauta, 1976; Selemon and Goldman-Rakic, 1988; Bates

and Goldman-Rakic, 1993; Lu et al., 1994) likely enable it to exert cognitive control over behaviour.

Functionally, the DLPFC is broadly thought to encode representations of rules and goals, and bias other brain areas to achieve the desired outcome (Miller and Cohen, 2001). Representations require the maintenance of information and consequently, the DLPFC has long been implicated in working memory. The role of the DLPFC in working memory has been extensively studied using a variety of tasks, especially delayed-response tasks where stimulus information must be retained over a delay period prior to executing an appropriate behavioural response.

Jacobsen (1935) first demonstrated that bilateral PFC lesions induce delayed-response impairments in monkeys. Subsequent lesion studies further delineated the anatomical substrate of delayed-response performance. Unilateral PFC lesions also produce deficits (Warren et al., 1969) and DLPFC lesions in particular impair the ability to retain spatial information and the integration of this information over time (Mishkin et al., 1969; Fuster and Alexander, 1970; Goldman and Rosvold, 1970). In humans, DLPFC lesions increase accuracy errors with delayed-response tasks (Lewinsohn et al., 1972; Milner et al., 1985; Pierrot-Deseilligny et al., 1991a). Notably, deficits produced by DLPFC lesions occur regardless of sensory modality.

Studies investigating delayed-response and other memory tasks with neuroimaging techniques such as fMRI and positron emission tomography (PET) have consistently shown DLPFC activation (Duncan and Owen, 2000; Curtis and D'Esposito, 2003; Wager and Smith, 2003). This activation increases with the number of items retained in working memory (Jaeggi et al. 2002; Kirschen et al., 2005). Neuroimaging studies also consistently demonstrate that working memory tasks activate other brain areas simultaneously, including the parietal cortex,

and provide support that the DLPFC is part of a larger network underlying working memory. Neurophysiological investigations provide insight into the specific role of the DLPFC in working memory.

Early single-unit recordings in the principal sulcus of monkeys performing delayed-response tasks demonstrated neurons with increased and sustained activity during the delay period (Fuster and Alexander, 1971; Fuster, 1973). These neurons were termed "memory cells" because their activity, which bridges the temporal gap between stimulus and response, is thought to be a neural correlate of working memory. Appropriately, the level of activity during the delay period is correlated with correct task performance (Fuster, 1973). Visual working memory tasks preferentially activate memory cells in the inferior convexity of the principal sulcus, whereas spatial working memory tasks preferentially activate cells in the superior convexity (Fuster et al., 1982; Wilson et al., 1993). With regard to spatial working memory, neurons are grouped for distinct locations in visual space and are preferentially activated for the contralateral hemifield (Funahashi et al., 1989). Unlike receptive fields in visual brain areas, however, memory fields in the DLPFC are not clearly topographically organized.

Although delay period activity is generally accepted as a neural correlate of working memory, the information that is represented by this activity remains unclear. DLPFC responses may represent remembered stimulus information, such as stimulus location, or motor information, such as the direction of an upcoming movement (Hasegawa et al., 1998; Constantinidis et al., 2001). DLPFC responses may also be associated with diverse processes supporting task performance, such as attention, task representation, and task preparation (Asaad et al., 2000; Wallis et al., 2001; Lebedev et al., 2004). Regardless of the information contained in

DLPFC signals, the DLPFC is thought to influence neural activity in other brain areas to perform the appropriate task.

Recent investigations using local field potentials (LFPs), which reflect the average postsynaptic activity of a population of neurons (Buzaki et al., 2012), further support the DLPFC's role in working memory and the implementation of cognitive control. In particular, oscillations in the beta (12-30 Hz) frequency band have been implicated in working memory maintenance (Engel and Fries, 2010; Salazar et al., 2012; Spitzer et al., 2014). Task-specific neural ensembles can be formed in the DLPFC by beta synchronization (Buschman et al., 2012) and enhanced beta coherence between the DLPFC and other brain areas, such as the posterior parietal cortex, is thought to facilitate top-down control (Buschman and Miller, 2007; Donner et al., 2007; Siegel et al., 2012). Overall, both direct neuronal outputs and neuronal oscillations likely enable the DLPFC to exert control over distant brain areas, and ultimately behaviour.

1.2.1.2 Dorsal Anterior Cingulate Cortex

The cingulate cortex is located immediately above the corpus callosum in the medial wall of the cerebral hemispheres, and can be divided into four regions based on cytoarchitecture, connectivity, and function: the anterior cingulate cortex (ACC), midcingulate cortex (MCC), posterior cingulate cortex (PCC), and retrosplenial cortex (RSC) (Fig. 1.2) (Vogt et al., 2005; Vogt, 2009). Although the ACC is variably defined in the literature, here, the dACC will refer to the MCC and its anterior portion in particular. In macaque monkeys, the dACC consists of Brodmann area 24 and is located in the cingulate gyrus and sulcus. In humans, the dACC consists of Brodmann areas 24 and 32' and corresponds to the cingulate gyrus dorsal to the corpus callosum and paracingulate gyrus when present (Cole et al., 2009; Procyk et al., 2016).
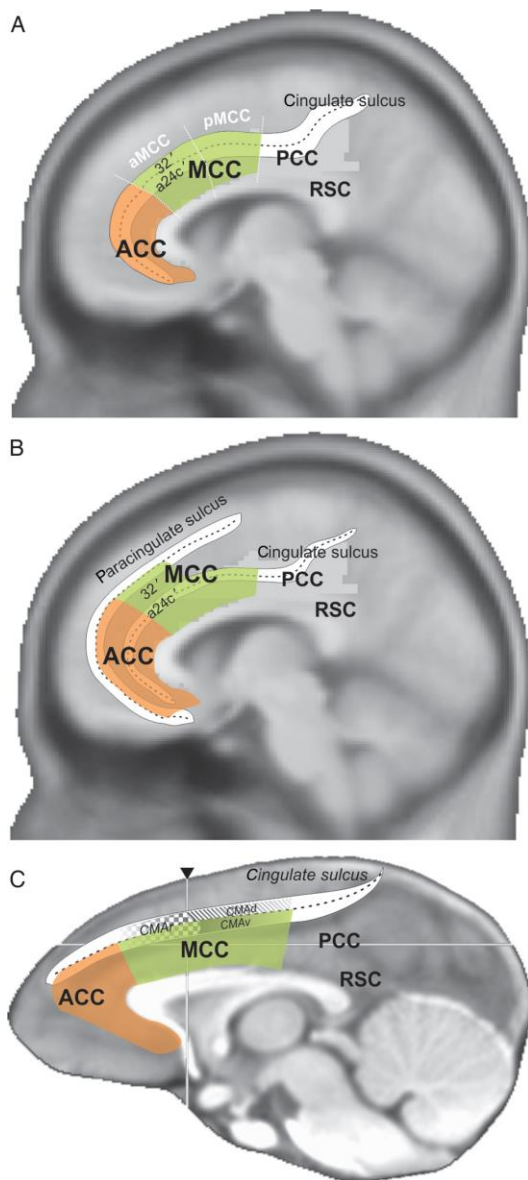
Figure 1.2. Regions of the cingulate cortex. Representations of the anterior cingulate cortex (ACC), midcingulate cortex (MCC), posterior cingulate cortex (PCC), and retrosplenial cortex (RSC) in the human brain in the absence (***A***) and presence (***B***) of a paracingulate sulcus, and in the macaque brain (***C***). Reprinted with permission from: Procyk E, Wilson CR, Stoll FM, Faraut MC, Petrides M, Amiez (2016) Midcingulate motor map and feedback detection: Converging data from humans and monkeys. Cereb Cortex 26:467-476.

As a whole, the dACC includes the rostral, ventral, and dorsal cingulate motor areas (CMAr, CMAv, and CMAd), as defined in monkeys by intracortical microstimulation and connectivity, and the homologous anterior rostral cingulate zone (RCZa), posterior rostral cingulate zone (RCZp), and caudal cingulate zone (CCZ) respectively in humans (Fig. 1.3) (Picard and Strick, 1996; Amiez and Petrides, 2014). The dACC and cognitive control are particularly associated with CMAr, which is situated on the dorsal and ventral banks of the cingulate sulcus anterior to the arcuate sulcus.

The dACC receives input from the temporal cortex, parietal cortex, and insula, and is highly and reciprocally connected with the DLPFC (Vogt and Pandya, 1987; Barbas and Pandya, 1989; Bates and Goldman-Rakic, 1993). It sends projections to motor areas such as the premotor cortex, FEF, primary motor cortex, and ventral horn of the spinal cord (Dum and Strick, 1991; Picard and Strick, 1996; Wang et al., 2004). However, microstimulation of the dACC does not strongly evoke movement and suggests that it does not play a direct role in motor control (Luppino et al., 1991; Picard and Strick, 1996).

Instead, the dACC is strongly implicated in cognitive control. Numerous functional imaging studies have demonstrated dACC activation with a variety of cognitive functions, including attention, task conflict, action selection, working memory, episodic memory, decision making, problem solving, reward processing, pain processing, emotion, and motivation (Duncan and Owen, 2000; Shackman et al., 2011; Shenhav et al., 2013). Nonetheless, precise mechanisms for dACC function have been difficult to elucidate because of discrepancies between lesion, functional imaging, and neurophysiological studies, and between species (Fellows and Farah, 2005; Cole et al., 2009).

A Human motor cingulate regions

Case 1: no paracingulate sulcus

Case 2: paracingulate sulcus

- 🔴 Saccade regions
- 🟡 Tongue regions
- 🟢 Hand regions
- 🔵 Foot regions
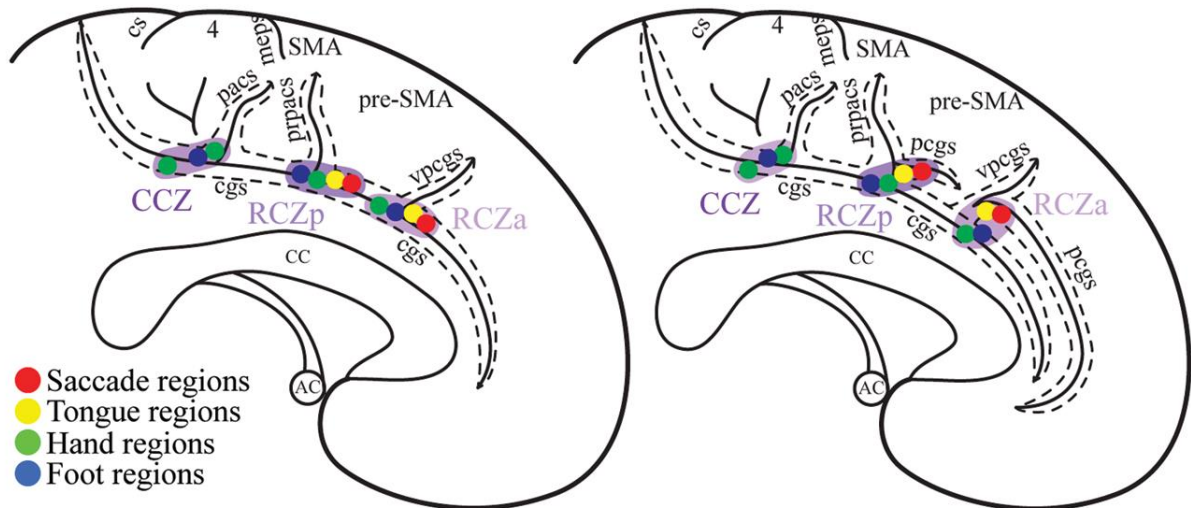
B Monkey motor cingulate regions
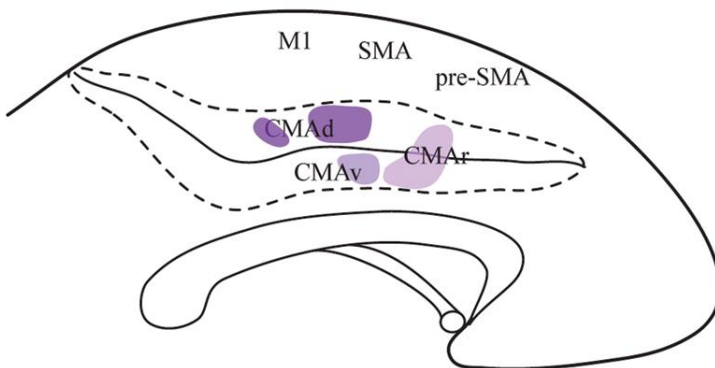
Figure 1.3. Cingulate motor regions. *A*, Representations of the anterior rostral cingulate zone (RCZa), posterior rostral cingulate zone (RCZp), and caudal cingulate zone (CCZ) in the human brain in the absence and presence of a paracingulate sulcus. *B*, Representations of the rostral, ventral, and dorsal cingulate motor areas (CMAr, CMAv, and CMAd) in the macaque brain. Reprinted with permission from: Amiez C, Petrides M (2014) Neuroimaging evidence of the anatomo-functional organization of the human cingulate motor areas. Cereb Cortex 24:563-578.

Early theories of dACC function were based on electrophysiological and functional imaging studies in humans. Error-related negativity, or a negative deflection in the event-related potential (ERP) immediately after an erroneous response, has been localized to the ACC and is thought to be associated with conflict monitoring or performance monitoring (Falkenstein et al., 1991; Gehring et al., 1995; Botvinick et al., 2001). The conflict monitoring hypothesis proposes that the dACC detects conflict, defined as the co-activation of two or more competing processes by a single stimulus, and subsequently signals an increase in cognitive control to resolve the conflict and improve task performance (Botvinick et al., 2001). In humans, investigations with fMRI and single-unit recordings have shown that the dACC responds to conflict during tasks that produce conflict, such as the Stroop task, and predicts adjustments in behaviour (Carter et al., 2000; MacDonald et al., 2000; Botvinick et al., 2001; Kerns et al., 2004; Davis et al., 2005). However, studies involving the monkey dACC have been unable to produce evidence of conflict-related signals.

For example, the countermanding task, where subjects must withhold a planned movement immediately prior to execution in response to a stop signal, has been shown to produce conflict-related dACC activation in humans (Curtis et al., 2005), but was not associated with conflict-related responses in monkeys (Ito et al., 2003; Emeric et al., 2008). Studies involving other tasks and dACC lesions have also failed to associate the monkey dACC with conflict monitoring (Nakamura et al., 2005; Mansouri et al., 2007). Rather, monkey studies have demonstrated that dACC neurons and LFPs signal erroneous responses, rewarded responses, and unrewarded responses (Shima and Tanji, 1998; Ito et al., 2003; Nakamura et al., 2005; Emeric et al., 2008). Furthermore, the dACC has been shown to monitor feedback for changes in behaviour and is thought to associate value with actions (Kennerley et al., 2006; Johnston et al., 2007;

Quilodran et al., 2008; Amiez et al., 2012). Beyond conflict monitoring, both human and monkey data are consistent with a role of the dACC in performance monitoring.

Another theory of dACC function proposes that the dACC predicts error-likelihood, which incorporates both conflict and error detection (Brown and Braver, 2005). Activity in the dACC is thought to be proportional to the likelihood of an error, such that more cognitive control is recruited for increased task demands. Task demands increase during task switching and task selectivity in dACC neurons has been shown to be strongest after a task switch, thereby reflecting the implementation of increased cognitive control (Johnston et al., 2007). Neurons in the dACC also encode cognitive demand and are modulated by the demands of the previous trial to mediate behavioural adaptations (Sheth et al., 2012). Thus, the dACC functions to both monitor performance and implement cognitive control.

To reconcile the diversity of findings regarding the dACC, Shenhav et al. (2013) proposed that the dACC estimates the expected value of control (EVC) of a task in order to allocate cognitive control. As such, the dACC functions to monitor and integrate information, such as task demands, processing capacity, motivation, and positive and negative outcomes, to determine the EVC. Based on the estimated EVC, the dACC also functions to specify which task to allocate control to and how much control to allocate to maximize the EVC. In this model of dACC function, control signals specified by the dACC are implemented by brain areas like the DLPFC, which are responsible for regulating the information processing required for task performance. Accordingly, changes in task demand have been shown to increase task selectivity and LFP power in the dACC prior to more sustained responses in the DLPFC, which are thought to be involved in maintaining behaviour (Johnston et al., 2007; Rothé et al., 2011).

1.3 Task Switching

The ability to flexibly engage in goal-directed behaviour in response to changes in the external environment and internal goals is a hallmark of cognitive control. Cognitive control is required to select, maintain, implement, and execute the appropriate task-set. Furthermore, the act of task switching itself is associated with an increase in cognitive demand. Thus, task switching paradigms have become an attractive method to investigate cognitive control and task processing.

1.3.1 Task Switching Paradigms

Jersild (1927) first used a task switching paradigm to examine cognitive control by asking participants to perform a series of trials where they either repeated a single task or alternated between two. Original task switching studies were limited to investigating the effects of task switching on behaviour, but since the development of functional imaging, the number of task switching experiments has increased dramatically and many variations of task switching paradigms have been designed (Monsell, 2003).

Although Jersild's paradigm enabled comparison between task switching and task repetition (Jersild, 1927; Spector and Biederman, 1976), the method of alternating tasks from trial to trial required the maintenance of multiple tasks and a task sequence in working memory and thereby imposed an additional cognitive load (Monsell, 2003). Many contemporary task switching paradigms avoid this confound by increasing the number of trials before a switch or signalling when a task switch will occur. Consequently, paradigms may be designed with alternating blocks of a single task, where the task switch is signalled by a pre-specified number of trials, stimulus cue, or change in reward. Alternatively, paradigms may be designed with

multiple tasks that are interleaved and cued from trial to trial. Other features of paradigms, such as preparation time and performance feedback, can also be manipulated to enable specific aspects of cognitive control to be investigated. Regardless of the variations, all paradigms have periods where the task either remains the same or changes from one trial to the next. Performance on or after switch trials can provide insight into cognitive control and task processing.

1.3.2 Task Switching Phenomena

Task switching is ubiquitously associated with switch costs, or increases in reaction times and error rates on trials where the task is switched compared to trials where the task is repeated (Allport et al., 1994; Monsell, 2003). To successfully switch tasks, task-relevant information must be selected and maintained over task-irrelevant information. Task-set reconfiguration requires shifting attention to the new task-set while inhibiting the prior task-set. Switch costs may arise from the time required to complete task-set reconfiguration and accordingly, switch costs can be reduced if sufficient preparatory time is allowed for reconfiguration (Monsell, 2003). Interestingly, long preparatory periods do not eliminate switch costs and these residual costs are thought to be due to the inability to complete task-set reconfiguration before stimulus onset. A component of reconfiguration may depend on the presence of external stimuli (Rogers and Monsell, 1995) or reconfiguration may only be successful before stimulus onset on a proportion of trials in an all-or-none manner (De Jong, 2000).

The persistence of the previous task-set, or task-set inertia, may also contribute to switch costs. Interference from task-set inertia is particularly evident when switching from a non-dominant task to a dominant task, such as colour naming and word naming with Stroop stimuli

respectively. Switching to the more practiced and habitual dominant task is counterintuitively associated with a greater switch cost and can be attributed to increased cognitive control during performance of the non-dominant task carrying over and interfering with preparation for the dominant task-set (Allport et al., 1994; Monsell, 2003). Task-set inertia is supported by evidence that longer periods of time between the performance of the previous task and instruction for the current task reduce switch costs, which suggests dissipation of the competing previous task-set (Meiran et al., 2000). In addition, task-set inertia may contribute to residual switch costs.

1.3.3 Human and Non-Human Primate Task Switching

Task switching behaviour and switch costs have been consistently demonstrated in humans. Non-human primates, particularly macaque monkeys, have been widely used in lesion, functional neuroimaging, and neurophysiological studies as a model for cognitive control, but whether they show switch costs is less clear. One comparative study between humans and monkeys found that monkeys only had switch costs with short intertrial intervals and suggested that although monkeys experience task-set inertia, the previous task-set dissipates quickly (Stoet and Snyder, 2003). The absence of a persistent residual switch cost was taken to suggest that monkeys can complete task-set reconfiguration before stimulus onset. In contrast, another comparative study found that humans and monkeys had comparable and robust reaction time and error rate switch costs (Caselli and Chelazzi, 2011). Although studies demonstrate conflicting results regarding switch costs in non-human primates, monkeys, like humans, are able to perform complex cognitive tasks and switch between tasks. Thus, the macaque monkey remains a suitable model for studying the neural basis of task processing.

1.3.4 Neural Basis of Task Switching

1.3.4.1 Task-Set Representation

Successful task switching requires a network of brain areas to select, maintain, implement, and execute the appropriate task-set. Although a task-set is a psychological construct, it may be possible for task-sets to be represented in the brain. The neural correlates of a task-set can be considered task-specific neural activity. Single-unit recordings in monkeys have identified multiple brain areas with task-specific activity, including the DLPFC (White and Wise, 1999; Asaad et al., 2000; Wallis et al., 2001; Everling and DeSouza, 2005; Mansouri et al., 2006; Johnston and Everling, 2006; Johnston et al., 2007), dACC (Johnston et al., 2007), premotor cortex (Wallis and Miller, 2003), and posterior parietal cortex (PPC) (Stoet and Snyder, 2004; Kamigaki et al., 2009). Among these brain areas, the DLPFC is thought to be particularly important for encoding and maintaining task representations, and modulating other brain areas for task performance (Miller and Cohen, 2001). Task-related information has also been shown to be represented in the activity of neural populations (Stokes et al., 2013) and LFP activity (Buschman et al., 2012).

In humans, fMRI is often used to investigate task processing. When a task is performed, specific areas are more active than others due to the types of stimuli, processing, and responses that are required. Conventional univariate analysis can identify which brain areas are involved with task performance, but are unable to distinguish task representations in the same brain areas. Alternatively, studies using multivariate pattern analysis have demonstrated that task representations can be identified from blood oxygen level-dependent (BOLD) activity in frontoparietal cortex (Bode and Haynes, 2009; Woolgar et al., 2011; Chan et al., 2015). Although frontoparietal cortex is known to represent different types of task-related information, including

stimuli colour and responses, task rule was found to be the most strongly represented feature

(Woolgar et al., 2011). Taken together, the encoding of task representations in the brain can be

demonstrated using a variety of techniques, from single-unit recordings to whole-brain functional

imaging.

1.3.4.2 Task-Set Selection and Interference

In human fMRI studies, preparatory activation during trials where the task is switched is

often compared to activation during trials where the task is repeated to identify brain areas

involved in selecting, establishing, and maintaining task-sets. Although brain areas exclusively

activated by switch trials are consistently absent (Ruge et al., 2013), a network of frontoparietal

brain areas, including the DLPFC, ACC, and PPC, is more strongly activated for switch trials

compared to repeat trials (Sohn et al., 2000; Braver et al., 2003; Liston et al., 2006; Chiu and

Yantis, 2009; Ruge et al., 2013). Switch-related prefrontal activation may be related to the

preparation of response-directed intentional task-sets, whereas parietal activation may be related

to the preparation of stimulus-directed attentional task-sets (Ruge et al., 2013). Increased

processing in these brain areas, as demonstrated by increased activation, may reflect task-set

reconfiguration and the maintenance of the new task-set. Consistent with this, task-related

information in the PFC and PPC has been shown to increase after presentation of the instruction

cue (Bode and Haynes, 2009). This is similar to the presence of task-specific activity in PFC,

ACC, and PPC neurons during the preparatory period (Asaad et al., 2000; Wallis et al., 2000;

Everling and DeSouza, 2005; Johnston et al., 2007; Stoet and Snyder, 2004). While the DLPFC

is thought to maintain task information, the ACC and PPC have been implicated in signalling

that a task switch has occurred and selecting the new task (Johnston et al., 2007; Kamigaki et al., 2009).

Interference from the previous task-set may manifest as task-specific activity that persists on switch trials. Task-set inertia can be demonstrated with functional imaging by using two tasks that activate distinct brain areas. When participants were asked to switch between a face categorization and a word categorization task, activation in brain areas for the irrelevant task was positively correlated with the reaction time switch cost (Yeung et al., 2006). Thus, at the whole brain level, processing for the previous task may compete with preparation for the new task. Unfortunately, single-unit recording studies in monkeys have not yet addressed differences in neural activity between switch trials and repeat trials and the mechanisms of task-set inertia.

1.3.4.3 Task-Set Implementation

The PFC, with connections to motor areas such as the SMA, pre-SMA, premotor cortex, FEF, cerebellum, and SC (Goldman and Nauta, 1976; Selemon and Goldman-Rakic, 1988; Lu et al., 1994), is well situated to implement the tasks it encodes. Human functional imaging and monkey neurophysiological studies have demonstrated that task-specific activity in the PFC influences activity in brain areas that are more involved in task execution and this activity is negatively correlated with reaction times (Johnston and Everling, 2006; Sakai and Passingham, 2006). Unsurprisingly, motor areas such as the premotor cortex and SC encode behavioural responses more strongly than the PFC (Everling et al., 1999; Wallis and Miller, 2003).

1.3.4.4 Task and Performance Monitoring

Once a task is performed, the outcome of the task must be monitored to determine whether the task should be repeated or switched. Of the brain areas implicated in task switching, the dACC may be best positioned to integrate task-related information with task outcomes. The dACC encodes task-related information (Johnston et al., 2007) and has been shown to respond to task conflict (Carter et al., 2000; MacDonald et al., 2001; Botvinick et al., 2001), changes in task demand (Johnston et al., 2007; Sheth et al., 2012), and positive and negative feedback (Shima and Tanji, 1998; Ito et al., 2003; Nakamura et al., 2005). Integration of monitored information may enable the dACC to determine the appropriate task to allocate cognitive control to (Shenhav et al., 2013).

1.4 Investigating Cognitive Control Using the Oculomotor System

Eye movements are integral to human behaviour. In particular, saccadic eye movements, which involve conjugate, ballistic movements of the eyes, are frequently performed to direct gaze to objects of interest in the visual world. To generate a saccade, one must decide when to look, where to look, and whether to look. Consequently, saccades are goal-directed movements that require cognitive control and are influenced by attention, working memory, inhibition, decision making, long-term memory, and learning (Hutton, 2008). Sensory input to the oculomotor system can be precisely manipulated and its output, produced by six distinct extraocular muscles, is simple compared to movements of other parts of the body and can be easily and accurately measured. The oculomotor system is well characterized anatomically and functionally, and notably, many of the same brain areas are also implicated in cognitive control

(Liversedge et al., 2011). Thus, the oculomotor system serves as an attractive model for investigating cognitive control.

1.4.1 Oculomotor Neurophysiology

1.4.1.1 Brainstem

In order to generate saccadic eye movements, position and velocity signals are sent by motor neurons from the oculomotor nuclei (cranial nerve III), trochlear nuclei (cranial nerve IV), and abducens nuclei (cranial nerve VI) in the brainstem to the extraocular muscles. Burst neurons in the paramedian pontine reticular formation (PPRF) and interstitial nucleus of the medial longitudinal fasciculus (iMLF) produce phasic signals to initiate horizontal and vertical saccades respectively (Cohen and Henn, 1972; Keller, 1974; Büttner et al., 1977; King and Fuchs, 1979). Eye position is maintained by tonic activity from the nucleus prepositus hypoglossi for horizontal saccades and from the interstitial nucleus of Cajal for vertical saccades (Sparks, 2002). These motor signals are ultimately controlled by the cerebral cortex through the SC, which projects to contralateral brainstem saccade generators.

1.4.1.2 Superior Colliculus

The SC is a laminated structure in the dorsal midbrain that is critical to oculomotor control. Functionally, the SC is divided into the superficial layers and the intermediate or deep layers. These layers contain topographic sensory and motor maps that are similarly aligned, which facilitate the SC's role in sensorimotor transformation (Sparks, 1986). Overall, the SC

receives multisensory, motor, and cognitive inputs from various brain areas and is well situated

to integrate information for the control of eye movements and other orienting behaviours.

The superficial layers of the SC are made up of the three dorsal most layers and receive

direct projections from the retina, visual cortex, and FEF (Hubel et al., 1975; Fries, 1984).

Neurons in the superficial layers respond to the appearance of a visual stimulus in their response

field (RF) and produce a topographic map of the contralateral visual hemifield (Schiller and

Koerner, 1971; Cynander and Berman, 1972; Goldberg and Wurtz, 1972). The fovea and

periphery are mapped on to the rostral and caudal SC, respectively, while the upper and lower

visual fields are mapped onto the medial and lateral SC, respectively. In addition, superficial

layer neurons respond to the intensity of a stimulus, but demonstrate minimal preference for the

features of a stimulus. These characteristics implicate the superficial layer of the SC in visual

salience mapping and bottom-up processing (Fecteau and Munoz, 2006). Accordingly, the

superficial layers may influence visual processing through projections to the pulvinar nucleus

and lateral geniculate nucleus of the thalamus (Harting et al., 1978; Stepniewska et al., 2000).

Outputs to the intermediate layers of the SC may facilitate sensorimotor processing (Isa, 2002).

The intermediate layers of the SC are made up of the four deeper layers and receive

inputs from the superficial layers (Isa, 2002), and a variety of cortical and subcortical areas,

including the FEF, DLPFC, supplementary eye field (SEF), ACC, lateral intraparietal (LIP) area,

and substantia nigra pars reticulata of the basal ganglia (Goldman and Nauta, 1976; Leichnetz et

al., 1981; Hikosaka and Wurtz, 1983; Lynch et al., 1985; Stanton et al., 1988b; Shook et al.,

1990). In contrast to the superficial layers, the intermediate layers contain visual, auditory,

somatosensory, and motor maps (Schiller and Koerner, 1971; Robinson, 1972; Wurtz and

Goldberg, 1972; Sparks, 1986; Stein and Stanford, 2008). The map of contralateral saccade vectors is closely aligned to the map of the contralateral visual hemifield.

Saccades to positions proximal to the fovea are mapped onto the rostral SC, while saccades to positions distal to the fovea are mapped onto the caudal SC (Schiller and Koerner, 1971; Robinson, 1972; Wurtz and Goldberg, 1972). In the rostral pole of the SC, fixation-related neurons discharge tonically during visual fixation in the presence and absence of a visual stimulus and pause for most saccades, and are thought to maintain visual fixation and inhibit saccade generation (Munoz and Wurtz, 1993a, b; Dorris and Munoz, 1995). Rostral pole neurons also encode microsaccades, or small-amplitude fixational saccades (Hafed et al., 2009; Hafed and Krauzlis, 2012). Saccade-related neurons in the remainder of intermediate layers discharge a burst of action potentials before and during saccades of varying amplitudes and directions (Wurtz and Goldberg, 1972; Sparks et al., 1976; Munoz and Wurtz, 1995). These neurons can be subdivided into motor neurons, which only discharge for a saccade, and visuomotor neurons, which also discharge for stimuli in their RF. In addition, buildup neurons are distinguished from burst neurons by low-frequency activity prior to the appearance of a stimulus (Munoz and Wurtz, 1995). Buildup activity is thought to be associated with motor preparation and higher-level processing.

The interaction between visual, motor, and cognitive information in the intermediate layers is consistent with a role in priority mapping, where visual salience is integrated with the behavioural relevance of a stimulus (Fecteau and Munoz, 2006). An example of integrating salience and relevance is saccade target selection, where neurons discriminate a target from distractors by suppressing distractor-related activity while enhancing target-related activity (Horwitz and Newsome, 2001; McPeek and Keller, 2002). Similarly, neural activity is modulated

by visual stimuli that are associated with reward (Ikeda and Hikosaka, 2003). Taken together, the SC is well suited to integrating information for the flexible control of behaviour.

Outputs from the intermediate layers to the PPRF and iMLF in the brainstem enable the generation of saccades (Sparks, 2002). The intermediate layers also send projections to the FEF through the mediodorsal nucleus of the thalamus (Lynch et al., 1994; Sommer and Wurtz, 2004). This pathway enables the transmission of a corollary discharge, or an internal copy of the motor signal, to cortex to enable monitoring of the forthcoming saccade and visual stability.

1.4.1.3 Frontal Eye Field

The FEF is located at the junction of the precentral and superior frontal sulci in humans and in the anterior bank of the arcuate sulcus in macaque monkeys. It receives inputs from the SC, substantia nigra pars compacta of the basal ganglia, and dentate nucleus, and is reciprocally connected with the occipital, temporal, parietal, and prefrontal cortices (Maioli et al., 1984; Huerta et al., 1987; Lynch et al., 1994). Consistent with a role in saccade generation, the FEF influences SC activity through direct projections to the SC and basal ganglia (Leichnetz et al., 1981; Stanton et al., 1988a, b). FEF neurons also project to the brainstem saccade generators (Stanton et al., 1988b).

FEF neurons, like SC neurons, are topographically organized for saccade vectors and contralateral visual stimuli. Microstimulation of lateral and medial FEF evokes small- and large-amplitude saccades, respectively (Robinson and Fuchs, 1969; Bruce et al., 1985). Accordingly, the lateral FEF projects to the intermediate layers of the rostral SC while the medial FEF projects to the caudal SC (Stanton et al., 1988b). In addition to saccade-related neurons, the FEF contains visual neurons and visuomotor neurons that discharge for stimuli in their RF (Bruce and

Goldberg, 1985; Seagraves and Goldberg, 1987). Visual responses in the FEF are thought to

facilitate covert visual attention while saccade-related responses are thought to underlie the

orientation of overt visual attention (Thompson et al., 2005). As a key cortical node in the

oculomotor network, the FEF is particularly important for the generation of volitional and goal-

directed saccades (Schall, 2002). Beyond the FEF, cortical oculomotor brain areas are not

directly involved in generating saccades, as discussed below.

1.4.1.4 Posterior Parietal Cortex

The PPC, specifically the medial bank of the posterior IPS in humans and the lateral bank

of the IPS (LIP) in macaque monkeys, has been implicated in oculomotor processing (Grefkes

and Fink, 2005). It receives inputs from various visual areas (Andersen et al., 1990; Baizer et al.,

1991) and sends projections to the FEF and SC (Lynch et al., 1985; Schall et al., 1995).

However, the PPC does not participate directly in saccade generation. PPC lesions do not impair

saccade generation (Lynch and McLaren, 1989) and microstimulation with high currents is

required to evoke saccades (Their and Andersen, 1998). Instead, neural activity in the PPC is

enhanced by attended or behaviourally relevant stimuli (Bushnell et al., 1981; Colby et al., 1996;

Gottlieb et al., 1998). Thus, the PPC is thought to serve as an interface between the visual and

oculomotor systems that mediates visual attention and guides saccadic behaviour.

1.4.1.5 Dorsolateral Prefrontal Cortex

The DLPFC is associated with a diverse set of cognitive functions and has been

implicated in the cognitive control of saccades, rather than saccade generation. Unlike the

neighbouring FEF, microstimulation at low currents does not evoke saccades in the DLPFC (Bruce et al., 1985). Consistent with a role in working memory, DLPFC neurons are spatially tuned to visual stimuli and exhibit sustained delay period activity that facilitates saccades to remembered spatial locations (Funahashi et al., 1989, 1990, 1991). Signals for visual stimuli location, saccade direction, and oculomotor task have been shown to be sent directly from the DLPFC to the SC (Johnston and Everling, 2006). Although the DLPFC has long been thought to suppress saccades by inhibiting the oculomotor system, DLPFC deactivation and pharmacological manipulation studies suggest that the DLPFC's influence is excitatory in nature (Condy et al., 2007; Wegener et al., 2008; Koval et al., 2011; Everling and Johnston, 2013; Johnston et al., 2014). Thus, erroneous saccades are a result of the DLPFC's inability to maintain and implement task rules, rather than a failure to inhibit inappropriate responses.

1.4.1.6 Dorsal Anterior Cingulate Cortex

The dACC, like the DLPFC, has been implicated in the cognitive control of saccades. Its direct projections to oculomotor brain areas such as the FEF (Wang et al., 2004) and SEF (Huerta and Kaas, 1990) suggest the existence of cingulate eye fields. However, saccades are only evoked by dACC microstimulation at a small number of sites (Mitz and Godschalk, 1989) and visual response latencies in the dACC are considerably longer than in the FEF or SEF (Pouget et al., 2005). In addition, unilateral dACC deactivation does not affect the reaction times, velocity, or duration of saccades (Koval et al., 2014). Thus, the dACC is unlikely to be directly involved in saccade generation. Given the dACC's strong association with a diversity of cognitive functions, its connections with oculomotor brain areas likely serve to modulate eye movements based on cognitive and behavioural context.

1.4.2 Investigating Cognitive Control

Saccades, as a goal-directed behaviour, have become a useful model for investigating cognitive control. Given the close association between saccades and attention, the FEF and PPC have been shown to be involved in the dorsal attention network (Corbetta and Shulman, 2002). Furthermore, frontoparietal brain areas in the oculomotor system are implicated in a variety of cognitive functions, including attention, working memory, task representation, response selection, response inhibition, planning sequences of actions, and decision making (Duncan and Owen, 2000; Corbetta and Shulman, 2002; Duncan, 2010). Consequently, oculomotor tasks can be used in a laboratory setting to study the neural mechanisms of cognitive control. For example, memory-guided saccade tasks can be used to examine spatial working memory and the anti-saccade task can be used to examine stimulus-response mapping and task processing.

1.5 The Anti-saccade Task

The anti-saccade task, where a saccade is generated away from a peripheral stimulus to the mirror opposite location, has been extensively used in conjunction with the pro-saccade task, where a saccade is generated towards a peripheral stimulus, to investigate cognitive control (Fig. 1.4) (Hallett, 1978; Munoz and Everling, 2004). These tasks are particularly useful because they have distinct stimulus-response associations and behaviour is consistent and comparable between humans and monkeys. Successful anti-saccade performance first requires the inhibition of the prepotent response to look at the peripheral stimulus, then the inversion of the stimulus vector to generate a saccade away from the stimulus. Thus, anti-saccades require additional processing compared to pro-saccades and are associated with greater reaction times (Fischer and Weber, 1992; Amador et al., 1998; Everling et al., 1999; Bell et al., 2000). Anti-saccades are also
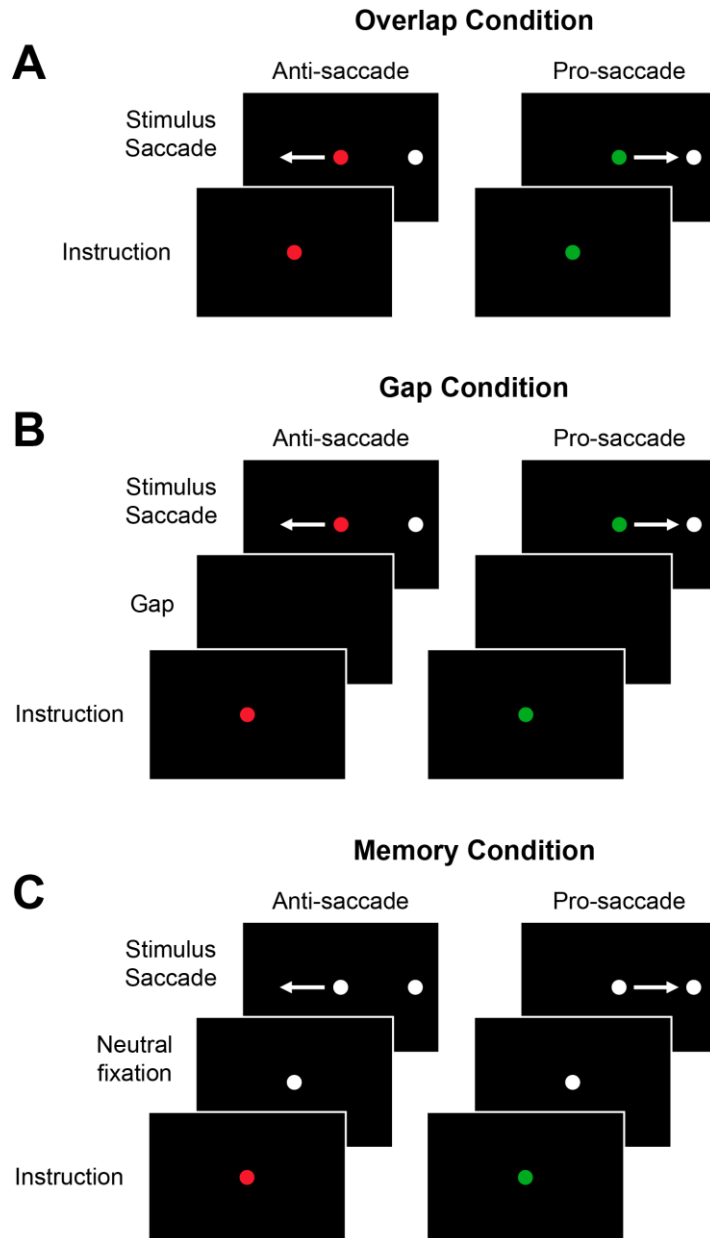
Figure 1.4. The anti-saccade task. A successful anti-saccade trial involves generating a saccade away from a peripheral stimulus to the mirror opposite location, whereas a successful pro-saccade trial involves a saccade towards a peripheral stimulus. *A*, In the overlap condition, the fixation point remains visible throughout the trial. *B*, In the gap condition, the fixation point is removed at least 200 ms prior to stimulus onset. *C*, In the memory condition, the task instruction is removed and must be maintained in working memory.

associated with direction errors, or saccades generated in the incorrect direction. These errors have shorter latencies than correct responses, can be corrected after short intersaccdic intervals, and are thought to be due to the failure to inhibit the prepotent response (Amador et al., 1998; Everling et al., 1998; Fischer et al., 2000; Munoz and Everling, 2004).

Variations of the anti-saccade task place different demands on task performance. In the overlap condition, the fixation point provides the task instruction, remains visible throughout the trial, and overlaps with the onset of the peripheral stimulus (Fig. 1.4A). However, in the gap condition, the fixation point is removed at least 200 ms before peripheral stimulus onset (Fig. 1.4B). Preparation during the gap results in a decrease in reaction times and increase in direction errors (Fischer and Weber, 1997; Everling et al., 1999; Bell et al., 2000), and is thought to require increased inhibitory control for correct anti-saccade performance (Curtis et al., 2001). Similarly, pro-saccade reaction times are decreased by the gap condition. In the memory condition, the task instruction is removed, must be maintained in working memory, and has been shown to increase direction errors for anti-saccades and pro-saccades (Fig. 1.4C) (Koval et al., 2011). The anti-saccade task can be used with the pro-saccade task in alternating blocks or with the tasks interleaved. With alternating blocks, the tasks can be either cued or uncued to test the ability to maintain a task in working memory and switch tasks based on reward feedback. In contrast, interleaving anti-saccade trials with pro-saccade trials requires frequent changes in behaviour.

1.5.1 Neurophysiology

As an oculomotor task, anti-saccade performance relies on the anatomically and functionally well characterized oculomotor system. The SC receives converging input from

various cortical and subcortical brain areas and is strongly modulated by the anti-saccade task (Everling et al., 1999; Munoz and Everling, 2004). Fixation during anti-saccade preparation is associated with increased fixation-related neuron activity and decreased saccade-related neuron activity (Fig. 1.5), and stimulus-related and saccade-related activity is generally reduced (Everling et al., 1999). Similarly, stimulus-related and saccade-related activity is reduced in the FEF (Everling and Munoz, 2000). Prestimulus activity in both these areas is predictive of whether or not an anti-saccade is performed correctly, and suggests that successful performance requires the inhibition of saccade-related neurons and thus, the prepotent pro-saccade (Everling et al., 1998; Everling and Munoz, 2000). Other brain areas play a role in modulating saccade generation in the SC and FEF for anti-saccade performance.

On anti-saccade trials, IPS neurons with response fields aligned to the direction of the upcoming saccade transiently discharge 50 ms after the arrival of visual information in the contralateral IPS (Zhang and Barash, 2000). Thus, the PPC may be involved in switching sensorimotor transformations. The SEF, which sends projections to the SC and FEF (Huerta et al., 1987; Shook et al., 1990), contains visual-related and movement-related neurons that increase their activity on anti-saccade trials and may contribute to anti-saccade generation (Schlag-Rey et al., 1997; Amador et al., 2004). The SEF also sends projections to omnipause neurons in the brainstem (Shook et al., 1998) and contains fixation-related neurons that increase their activity during the anti-saccade instruction period (Amador et al., 2004), which suggest a role in facilitating saccade inhibition.

A critical area for anti-saccade performance is the DLPFC. Human patients with DLPFC lesions consistently demonstrate increased anti-saccade errors and reaction times (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991b, 2003; Ploner et al., 2005). Neurons in the DLPFC have
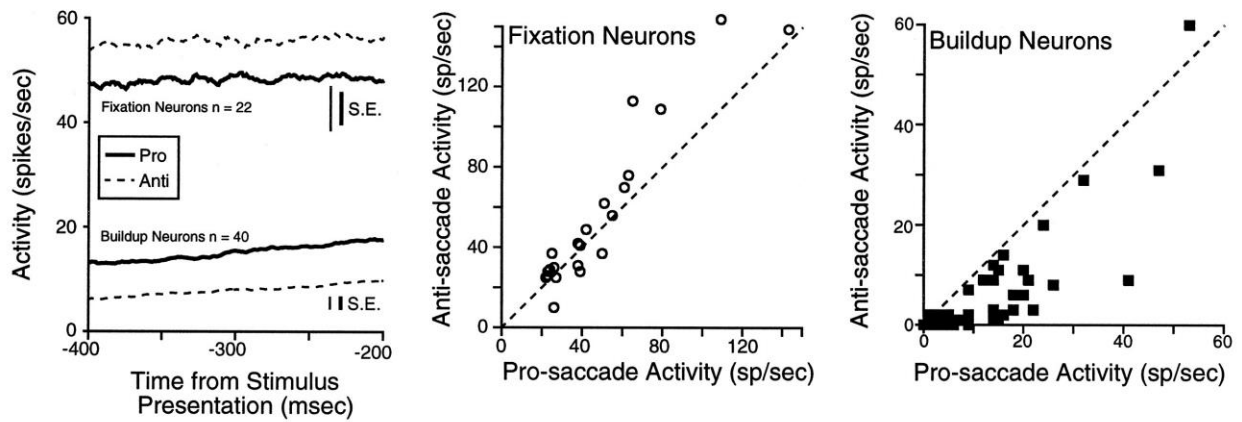
Figure 1.5. Task-selective SC activity during the instruction period. Fixation-related neuron activity is higher and saccade-related buildup neuron activity is lower during preparation for anti-saccades than pro-saccades. Reproduced with permission from: Everling S, Dorris MC, Klein RM, Munoz DP (1999) Role of the primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. J Neurosci 19:2740-2754.

demonstrated task-specific activity for anti-saccades and pro-saccades (Funahashi et al., 1993; Everling and DeSouza, 2005; Johnston and Everling, 2006; Johnston et al., 2007) and the DLPFC sends outputs to the SC and FEF (Goldman and Nauta, 1976; Selemon and Goldman-Rakic, 1988). In particular, the DLFPC has been shown to send task-specific information to the SC (Johnston and Everling, 2006). Accordingly, DLPFC deactivation in monkeys has demonstrated increases in anti-saccade errors and reaction times that are accompanied by decreases in SC preparatory activity and increases in SC stimulus-related activity (Koval et al., 2011). Like the DLPFC, the dACC also contains neurons that show task-specific activity for anti-saccades and pro-saccades (Johnston et al., 2007). The dACC likely works with the DLPFC to implement cognitive control for anti-saccade performance.

Human experiments investigating anti-saccade performance with fMRI are largely consistent with single-unit recording studies in monkeys. Greater activation in the DLPFC, FEF, SEF, ACC, and IPS for anti-saccades compared to pro-saccades during the preparatory and stimulus-response periods is reliably observed and is thought to reflect task-specific neural processing (Kimmig et al., 2001; Connolly et al., 2002; DeSouza et al., 2003; Ford et al., 2005; Brown et al., 2007). Furthermore, monkey fMRI has demonstrated activation in the same brain areas for anti-saccades compared to pro-saccades (Ford et al., 2009). Similarities between monkeys and humans make the anti-saccade task useful for understanding the neural basis of oculomotor and cognitive control in both species.

1.5.2 Task Switching

The anti-saccade task and pro-saccade task have distinct stimulus-response associations, which make them useful for investigating task switching. Switch costs are consistently observed

with randomly interleaved anti-saccade and pro-saccade tasks in humans (Cherkasova et al., 2002; Barton et al., 2006; Weiler and Heath, 2012; Chan and DeSouza, 2013; Weiler and Heath 2014, Yeung et al., 2014). In particular, these tasks involve switching between a non-dominant task and dominant task and commonly result in unidirectional pro-saccade reaction time switch costs. Consistent with other task switching experiments, this unidirectional switch cost has been attributed to interference from task-set inertia (Weiler and Heath, 2014). Reduced BOLD activation in the FEF and SEF for pro-saccade trials preceded by anti-saccade trials (Manoach et al., 2007) may reflect the effects of task-set inertia and contribute to pro-saccade switch costs. Interestingly, while anti-saccade behaviour has been extensively studied in humans and monkeys, task switching with cued switch tasks, such as randomly interleaved anti-saccades and pro-saccades, in monkeys is poorly understood. Consequently, cued and randomly interleaved anti-saccades and pro-saccade tasks in monkeys would be a valuable approach to investigating the neural mechanisms underlying frequent changes in behaviour.

1.6 Lesion Studies

1.6.1 Investigating Brain Function Using Lesions and Reversible Deactivation

Lesion studies with human patients and animals have been long used to infer and localize brain function. Since Paul Broca (1861) reported an association between a lesion of the posterior inferior frontal gyrus and the ability to produce speech, numerous causal relationships between brain areas and function, including language, memory, vision, and motor control, have been established based on deficits due to lesions. In a laboratory setting, permanent lesions are

commonly created surgically by excision or aspiration. Unfortunately, surgical lesions are imprecise, and often involve damage to surrounding cortical tissue or white matter and disruption of blood supply to adjacent areas (Lomber, 1999). Permanent lesions created by chemical ablation using neurotoxins, such as ibotenic or kainic acid, or electrolytic ablation (Winn, 1991) can avoid excessive tissue damage. Nonetheless, the spread of neurotoxins is variable and electrolytic ablations are limited to small lesion sizes. All permanent lesions are associated with a recovery of function, where deficits diminish over time as intact brain areas compensate for the lesioned brain area (Newsome and Paré, 1988; Lomber, 1999).

In comparison, reversible deactivation techniques can test relationships between brain areas and function while avoiding these limitations (Lomber, 1999). Temporary periods of deactivation allow brain tissue to be fully functional at baseline. As a result, there is no need for behavioural or neural adaptation to lasting deficits, and the function of a brain area can be tested at the time of deactivation. In addition, each subject serves at its own control, subjects can be retrained on other tasks for other experiments, and deficits can be reliably reproduced regardless of time between deactivation. Reversible deactivation is commonly achieved by chemical or cryogenic deactivation.

Reversible chemical deactivation involves the injection of deactivating agents, including sodium channel blockers such as lidocaine, divalent cations such as cobalt or magnesium, and receptor modulators such as γ-aminobutyric acid (GABA) or muscimol, into surface or deep brain structures (Malpeli, 1999; Martin and Ghez, 1999). Unfortunately, the duration of deactivation and the time to recovery range from minutes to hours and are variable. Another drawback to chemical deactivation is that diffusion of the deactivating agent is variable between applications and is limited to brain volumes less than 2.0 mm³ (Lomber, 1999; Malepi, 1999).

Larger deactivations can be achieved with multiple injections, but can increase the amount of permanent tissue damage. Issues associated with the replicability of deactivation parameters such as duration, recovery time, and size can be avoided with reversible cryogenic deactivation.

1.6.2 Reversible Cryogenic Deactivation

Reversible cryogenic deactivation or cooling can be conducted with thermoelectric cooling plates, cryotips, or cryoloops. Cooling plates have been widely used in behavioural and electrophysiological studies and can be acutely attached and placed in contact with the dura mater (Fuster and Alexander, 1970; Lomber, 1999). However, cooling plates do not conform readily to the shape of the cerebral cortex and may deactivate cortical tissue beyond the target area or provide insufficient coverage. Alternatively, cryotips are needle-like devices with coolant filled tubing that localizes cooling to the tip and are designed to deactivate deep brain structures (Zhang et al., 1986; Campeau and Davis, 1990). Similar to the application of chemical deactivation, cryotips are associated with damage to overlying brain tissue. Although cryoloops are limited to surface brain structures, they can be designed to conform to the cortical surface, including sulci (Lomber, 1999; Lomber et al., 1999). Cooling is typically conducted by passing chilled methanol through a cryoloop to deactivate adjacent cortical tissue.

As temperature decreases, neuronal firing frequency decreases and action potentials widen and decrease in amplitude (Jasper et al., 1970; Gahwiler et al., 1972; Moseley et al., 1972). Below 20°C, neuronal firing ceases (Jasper et al., 1970; Bénita and Condé, 1972; Lomber et al., 1994). Cooling is thought to block synaptic transmission by interfering with membrane permeability, active ion transport, and the opening of presynaptic voltage-gated calcium channels, while leaving the axonal transmission of action potentials unaffected (Jasper et al.,

1970; Moseley et al., 1972; Adey, 1974; Lomber et al., 1999). Complete deactivation and recovery of function can be achieved within minutes.

Although the specific extent of deactivation is dependent on the cooling technique, the 20°C thermocline at which neurons are deactivated is stable and remains consistent between applications. For cryoloops, thermal and metabolic measurements demonstrate that deactivation is restricted to 1-3 mm on either side of the loop and that cooling reliably deactivates all layers of the cerebral cortex (Lomber et al., 1999; Payne and Lomber, 1999). Notably, the spread of cooling is influenced by the direction of blood flow and may be asymmetric. Incoming warm blood opposes cooling and restricts the spread to approximately 1.5 mm from the loop, whereas blood flow away from the loop facilitates the spread of cooling up to 2.5 mm (Lomber et al., 1999; Payne and Lomber, 1999). Irreversible structural, biochemical, or functional damage has not been shown with brain tissue cooled to above 0°C (Lomber et al., 1999; Yang et al., 2006), and supports the safety and long-term use of reversible cryogenic deactivation.

1.7 Objectives

Brain areas in the oculomotor system contribute distinctively to oculomotor control, from the direct generation of saccades to the modulation of saccades based on cognitive processes. Many of these brain areas are also implicated in cognitive control and task switching. Oculomotor task switching paradigms can be used to examine the unique contributions of oculomotor and cognitive brain areas to different stages of task processing. Successful task switching requires a network of brain areas to select, maintain, implement, and execute the appropriate task, and each stage may be attributed to a specific brain area. Brain areas closer to the generation of movements, such as the SC, may be associated with the implementation or

execution of tasks while prefrontal areas, such as the DLPFC and dACC, may be associated with the selection and maintenance of tasks. Here, the role of the SC, DLPFC, and dACC at different stages of task processing will be investigated using single-unit activity, LFPs, and reversible cryogenic deactivation in macaque monkeys performing pro-saccade and anti-saccade tasks.

1.7.1 Examine the effects of saccadic task switching on neural activity in the superior colliculus

Many brain areas, including the DLPFC, ACC, PPC, and SC demonstrate task selectivity which may be critical for task switching (Everling et al., 1999; Wallis et al., 2001; Stoet and Snyder, 2004; Everling and DeSouza, 2005; Johnston et al., 2007; Kamigaki et al., 2009). Frontoparietal brain areas are thought to select and encode task rules and exert cognitive control to perform the appropriate task (Monsell, 2003; Stoet and Snyder, 2009), but the role of brain areas closer to the execution of tasks in task switching is unclear. The SC integrates information from various brain areas to generate saccades and is likely influenced by task switching. In this study, behavioural switch costs in monkeys performing cued and randomly interleaved pro-saccade and anti-saccade tasks will be clarified and the activity of saccade-related neurons in the SC will be examined from task preparation to task execution to identify changes associated with task switching. If switch costs are produced by the time required to complete task-set reconfiguration or task-set inertia, and SC activity is a potential neural signature of the task-set, SC activity for switch trials should differ from that on repeat trials.

1.7.2 Examine the effects of bilateral dorsolateral prefrontal cortex deactivation on superior colliculus local field potential activity

The SC receives and integrates task-relevant information from various brain areas to generate saccades and perform oculomotor tasks. In particular, the DLPFC, which is thought to encode task representations and bias other brain areas to perform the appropriate task (Miller and Cohen, 2001), contains neurons that project directly to and send task-selective signals to the SC (Goldman and Nauta, 1976; Johnston and Everling, 2006). However, the mechanisms by which the DLPFC modulates the SC and other brain areas are poorly understood. Beyond spiking activity, communication between distant brain areas may be mediated by LFPs and neuronal oscillations (Fries, 2005; Siegel et al., 2012). In this study, LFP activity in the SC of monkeys performing cued and randomly interleaved pro-saccade and anti-saccade tasks will be examined without and with bilateral DLPFC deactivation. If LFPs and neuronal oscillations are a mechanism by which the DLPFC exerts top-down control, bilateral DLPFC deactivation should reduce LFP activity in the SC.

1.7.3 Examine the effects of bilateral dorsal anterior cingulate cortex deactivation on saccadic task switching behaviour

The DLPFC and dACC are two interconnected brain areas that are thought to play a critical role in cognitive control (Duncan and Owen, 2000). Whereas the DLPFC is generally accepted to encode task representations and bias other brain areas to perform the appropriate task, the dACC's role in cognitive control is less clear. The dACC has been implicated in a broad range of cognitive functions, including conflict monitoring, performance monitoring, action selection, working memory, episodic memory, decision making, problem solving, emotion, and

motivation (Duncan and Owen, 2000; Shenav et al., 2013). In particular, neurons in the dACC have been shown to increase task selectivity following a task switch (Johnston et al., 2007) and suggest that the dACC may implement cognitive control in response to a change in task demand. In this study, behaviour in monkeys performing uncued and cued pro-saccade and anti-saccade switch tasks will be examined without and with bilateral dACC deactivation. If the dACC is involved in signalling a task switch, bilateral dACC deactivation should impair performance on the trial following a switch. If the dACC is involved in task maintenance, bilateral dACC deactivation should impair performance throughout a task block.

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CHAPTER 2

Neural correlates for task switching in the macaque superior colliculus

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2.1 Introduction

A hallmark of cognitive control is the ability to flexibly engage in goal-directed behavior. When external demands or internal goals change, certain behaviors become more appropriate than others for achieving the desired outcome. To switch successfully from one task to another, the appropriate task-set – the rules governing appropriate performance of the task at hand – must be selected over competing task sets. Difficulties in the ability to accurately switch between tasks are consistently reflected by increased error rates and increased reaction times on correct trials (Allport et al., 1994; Monsell, 2003). Such "switch costs" are thought to arise from persistence of the task-set from previous trials and consequent interference with task-set reconfiguration – the ability to implement a new task-set in advance of subsequent trials (Monsell, 2003; Keisel et al., 2010). To date, the neural mechanisms of task switching and their relationship to behavioral switch costs remain unclear.

Paradigms requiring participants to switch between tasks have been used extensively to investigate switch costs and concomitant brain activity in humans. Functional neuroimaging studies have found a network of frontoparietal brain areas that are more strongly activated on trials on which the task is switched than repeated, including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and posterior parietal cortex (PPC) (Sohn et al.,

2000; Braver et al., 2003; Forstmann et al., 2005; Liston et al., 2006; Chiu and Yantis, 2009; Jamadar et al., 2010; Ruge et al., 2010). Similarly, task-selective single-unit activity has been observed in homologous cortical areas in rhesus macaques (Stoet and Snyder, 2004; Everling and DeSouza, 2005; Mansouri et al., 2006; Johnston et al., 2007; Kamigaki et al., 2009). Although uncued switch tasks, in which changes in task requirements are signalled by error feedback, have commonly been used to study task switching in macaques, task and feedback processing are difficult to dissociate and the process of switching may occur over several trials (Stoet and Snyder, 2009). Paradigms in which tasks are explicitly cued and randomly interleaved provide an alternative approach to investigating the neural mechanisms underlying frequent changes in behavior. Such tasks have been shown to incur switch costs in human studies (Cherkasova et al., 2002; Manoach et al., 2007; Chan and DeSouza, 2013), though more variable results have been obtained in macaques (Stoet and Snyder, 2003; Caselli and Chelazzi, 2011)

Saccade tasks provide a simple and direct means of investigating the processes underlying task switching. The pro-saccade task, in which subjects generate a saccade towards a peripheral stimulus, and anti-saccade task, where subjects generate a saccade away from a peripheral stimulus to the mirror opposite location (Hallett, 1978), have distinct stimulus-response associations, which makes them useful for investigating task switching. Different conditions can also be applied to these tasks to vary task difficulty. The use of a gap condition, in which the fixation point is removed before peripheral stimulus onset, has been shown to increase direction errors and decrease saccadic reaction times (SRTs) for anti-saccades (Fischer and Weber, 1997; Bell et al., 2000), and is thought to create an increased "inhibitory load" for anti-saccades (Curtis et al., 2001). The use of a memory condition, in which the task instruction is visible briefly and then removed, and thus must be maintained in working memory to support

correct task performance, has been shown to increase direction errors for pro- and anti-saccades (Koval et al., 2011).

The oculomotor system provides an ideal model for investigating the neural basis of task switching. It is well characterized anatomically and functionally, and includes brain areas implicated in the instantiation of task-sets and modulated by the cognitive requirements of previous trials, including the DLPFC (Everling and DeSouza, 2005; Johnston and Everling, 2006; Johnston et al., 2007; Koval et al., 2011; Chan et al., 2014; Hussein et al., 2014; Johnston et al., 2014), frontal eye field (FEF) (Everling and Munoz, 2000), ACC (Johnston et al., 2007; Phillips et al. 2011), and PPC (Gottlieb and Goldberg, 1999; Zhang and Barash, 2010). The superior colliculus (SC) is a midbrain structure critical for saccade initiation that receives direct projections from many of these prefrontal and posterior parietal areas (Leichnetz et al., 1981; Paré and Wurtz, 1997; Johnston and Everling, 2004). SC neurons exhibit characteristic patterns of discharge on pro- and anti-saccade trials (Everling et al., 1999). The convergent cortical inputs to this area, the well characterized responses of SC neurons on pro- and anti-saccade trials, and the long established role of this area in saccade initiation render this area ideal for investigating neural processes related to task-switching.

Here, we recorded single-unit activity in the SC while macaque monkeys performed randomly interleaved cued pro- and anti-saccade trials, to investigate behavioral switch costs and their neural correlates in SC activity. Overlap, gap, and memory conditions were used to examine task switching under different task difficulty and cognitive demand. We reasoned that switch costs would increase with cognitive demand and that these behavioral changes would be reflected in SC activity. On anti-saccade trials, preparatory, stimulus-related, and saccade-related SC activity are lower than on pro-saccade trials (Everling et al., 1999). This reduced activity

prevents SC activity from reaching threshold and triggering an incorrect reflexive saccade toward, rather than away from, the visual stimulus (Munoz and Everling, 2004). It has been proposed that switch costs are a result of task-set inertia (Allport et al., 1994), manifested in residual activity from preceding trials affecting that on the current trial (Kiesel et al., 2010; Yeung et al., 2006) and interfering with task-set reconfiguration. Here, we can consider SC activity a potential neural signature of the task-set. In this context, SC activity for pro- and anti-saccade switch trials should differ from that on repeat trials. Neural activity on switch trials on which an anti-saccade is preceded by a pro-saccade would be expected to be higher than on anti-saccade repeat trials, since higher pro-saccade activity persists into the following anti-saccade trial following a switch. In this case, task switches would be expected to result in an increased proportion of errors and reduced SRTs for correct trials, since activity is closer to saccade threshold. Conversely, activity on switch trials on which a pro-saccade is preceded by an anti-saccade would be expected to be lower than on pro-saccade repeat trials, due to residual suppression of activity from the previous anti-saccade trial. We did not predict a change in error rate in this condition, since a delay in activity reaching threshold should affect only SRT, but not the ability to generate a correct saccade toward the visual stimulus. These predictions were evaluated by comparing SC activity on pro- and anti-saccade switch and repeat trials.

2.2 Materials and Methods

All procedures were conducted in accordance with 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.

2.2.1 Surgical Procedures

Three adult male macaque monkeys (*Macaca mulatta*) weighing 9-16 kg were prepared

for single-neuron recordings in the SC using previously described techniques (Johnston and

Everling, 2006). A recording chamber was implanted in each animal, centered on the midline

and tilted 38° posterior of vertical to allow for recordings from neurons in the SC. Data from

these animals have been previously reported by Johnston et al. (2014) and Koval et al. (2011) for

the effects of unilateral and bilateral DLPFC deactivation respectively on pro-saccade and anti-

saccade behavior and SC spiking activity. For these deactivation studies, stainless steel cryoloops

were also implanted bilaterally into the posterior principal sulci in each animal for reversible

cryogenic deactivation (Johnston et al., 2014; Koval et al., 2011). Monkeys received analgesics

and antibiotics postoperatively and were closely monitored by a university veterinarian.

2.2.2 Gap Paradigm

Monkeys A and C were trained to perform a randomly interleaved gap pro-saccade and

anti-saccade paradigm. Each trial began with a colored central fixation point, either red or green,

which provided the pro-saccade or anti-saccade task instruction. The animals were required to

fixate on the fixation point within a 0.5° x 0.5° window for 700-900 ms at the beginning of each

trial. On half the trials, the colored fixation point remained visible throughout the trial (overlap

condition, Fig. 2.1A), while on the other half of trials, the colored fixation point was

extinguished 200 ms before stimulus presentation (gap condition, Fig. 2.1B). Subsequently, a

peripheral white visual stimulus (0.15°) was pseudorandomly presented with equal probability in

either the response field (RF) of an isolated SC neuron or at the mirror location. Monkeys were

required to generate a saccade toward the stimulus on pro-saccade trials and away from the
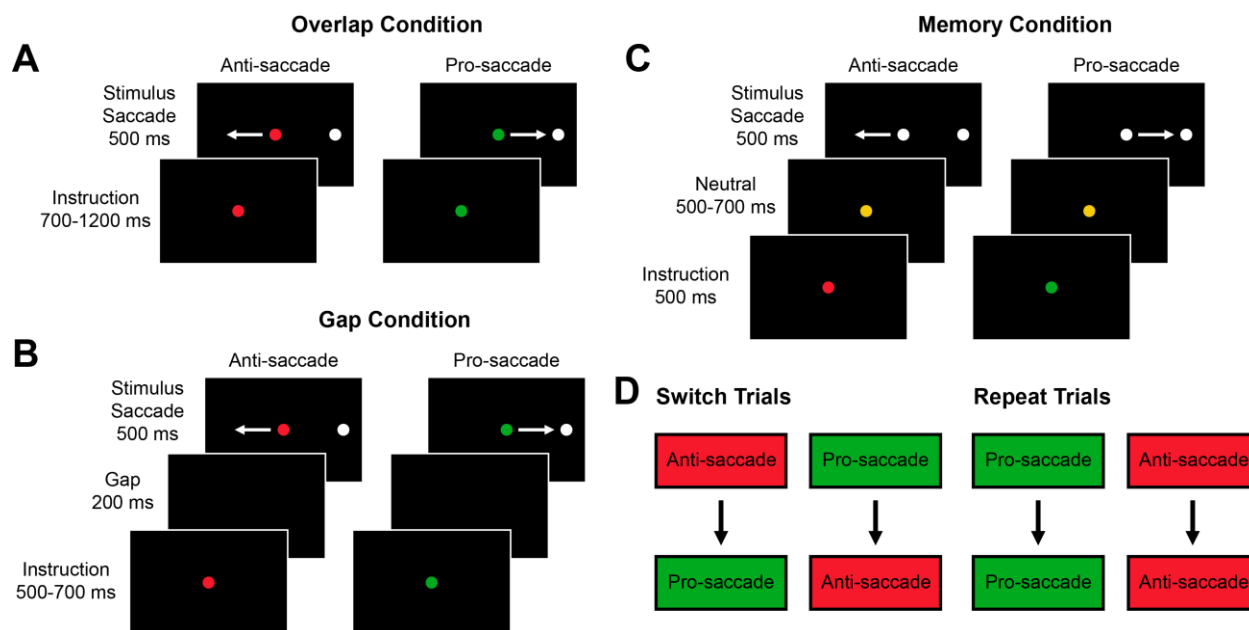
Figure 2.1. Task conditions. *A*, Overlap condition. Each trial began with a colored fixation point, which provided the task instruction to perform a pro-saccade or anti-saccade. A peripheral stimulus appeared either within the RF of the neuron or at the mirror opposite location. *B*, Gap condition. Same as *A*, but the fixation point was extinguished 200 ms before stimulus presentation. *C*, Memory condition. Same as *A*, but the fixation point changed to a neutral color 500-700 ms before stimulus presentation. *D*, A switch trial occurred if the task on the current trial was different from the previous trial, whereas a repeat trial occurred if the task on the current trial was the same as the previous trial.

stimulus on anti-saccade trials, and rewarded when saccade endpoints were within a 5° x 5° window. The intertrial interval was 1000 ms. Training progressed from performing correct overlap pro-saccades, to interleaved overlap pro-saccades and anti-saccades, and finally to the gap paradigm with interleaved overlap and gap pro- and anti-saccade trials.

2.2.3 Memory Paradigm

Monkeys A and B were trained to perform a randomly interleaved memory pro-saccade and anti-saccade paradigm. Each trial began with a colored central fixation point, either red or green, which provided the task instruction. Animals were required to fixate on the fixation point within a 0.5° x 0.5° window for 1000-1200 ms at the beginning of each trial. On half the trials, the colored fixation point remained visible throughout the trial (overlap condition, Fig. 2.1A), while on the other half of trials, the colored fixation point changed to yellow 500-700 ms before stimulus presentation (memory condition, Fig. 2.1C). Subsequently, a peripheral white visual stimulus (0.15°) was pseudorandomly presented with equal probability either within the RF of an isolated SC neuron or at the mirror location. Monkeys were required to generate a saccade toward the stimulus on pro-saccade trials and away from the stimulus on anti-saccade trials, and rewarded when saccade endpoints were within a 5° x 5° window. The intertrial interval was 1000 ms. During training, monkey B progressed from performing overlap pro-saccades, to interleaved overlap pro-saccades and anti-saccades, and finally to the memory paradigm with interleaved overlap and memory pro-saccades and anti-saccades. Monkey A was able to immediately perform the memory paradigm after training on the gap paradigm.

2.2.4 Recording Method

The activity of saccade-related neurons was recorded in the intermediate layers of the caudal SC (saccade amplitudes 5°-12°) using standard electrophysiological techniques (Johnston and Everling, 2006). To be considered a saccade-related neuron and included in the analysis, an isolated neuron had to discharge more than 100 spikes/s for pro-saccades into its RF in the interval from 10 ms before to 10 ms after saccade onset. Neural activity was amplified, filtered, and stored by a Plexon multichannel acquisition processor (MAP) system (Plexon Inc., Dallas, TX, USA). Eye movements were recorded at 500 Hz with high-speed infrared video eye tracking (Eyelink II, Kanata, ON, Canada).

2.2.5 Data Analysis

All analyses were performed using custom Matlab (The Mathworks Inc., Natick, MA) code. A switch trial occurred if the task on the current trial was different from the task on the previously performed trial (e.g. pro-saccade preceded by an anti-saccade), and a repeat trial occurred if the task on the current trial was the same as the task on the previously performed trial (e.g. pro-saccade preceded by a pro-saccade) (Fig. 2.1D). The previously performed trial did not differentiate between overlap and gap trials or overlap and memory trials. The effects of switches between the overlap and gap condition, overlap and memory condition, or left and right saccade responses on behavior and SC spiking activity were not examined due to small sample sizes after accounting for trial types.

For pro-saccades, trials were defined as correct if a saccade was made toward the location of the peripheral stimulus and defined as errors if a saccade was made to the opposite location. For anti-saccades, trials were defined as correct if a saccade was made to the location opposite to

the peripheral stimulus and defined as errors if a saccade was made toward the peripheral

stimulus. Saccadic reaction times (SRTs) were calculated for correct trials as the time from

stimulus onset to saccade onset. Trials with SRTs below 80 ms or above 500 ms were excluded

from further analysis as trials with anticipatory saccades or no responses, respectively. Switch

costs were calculated by subtracting error rates and SRTs for repeat trials from error rates and

SRTs for switch trials.

The effects of previous trial type (switch or repeat) and saccade task (pro-saccade or anti-

saccade) on error rates and SRTs were examined using two-way ANOVA analyses. Paired t-tests

were used for specific comparisons between switch and repeat trials and between pro-saccades

and anti-saccades, with p-values corrected for 4 comparisons using false discovery rate

estimation with the Benjamini-Hochberg step-up procedure (Benjamini and Hochberg, 1995). To

compare switch costs between the overlap condition and gap condition, and between the overlap

condition and memory condition, ANOVA analyses were performed with task condition and

saccade task (pro-saccade or anti-saccade) as factors. Paired t-tests were used for specific

comparisons between task conditions and between pro-saccades and anti-saccades, with p-values

corrected for 4 comparisons using false discovery rate estimation with the Benjamini-Hochberg

step-up procedure (Benjamini and Hochberg, 1995). Statistical significance was accepted at $P <$

0.05.

To evaluate neural activity in relation to stimulus onset and saccade onset, continuous

spike density functions were constructed. The activation waveform was obtained by convolving

each spike with an asymmetric function that resembled a postsynaptic potential (a combination

of growth and decay exponential functions with a 1 ms rise and 20 ms decay) (Hanes and Schall,

1996; Thompson et al., 1996). The advantage of this function over a standard Gaussian function (Richmond and Optican, 1987) is that a spike exerts an effect forward, but not backward in time.

Sliding receiver operating characteristic (ROC) analyses were conducted to determine the timecourse of task switching effects on the populations of SC neurons. For SC activity relative to stimulus onset, the ROC value was calculated for a 10 ms window (centred around the time point) starting 200 ms before stimulus onset and repeated in 1 ms increments up to 300 ms after stimulus onset. For SC activity relative to saccade onset, the analysis was conducted starting 350 ms before saccade onset up to when the saccade was initiated. Bootstrap analyses were used to test the significance of ROC values. The following procedure was repeated 10,000 times to create a distribution of ROC values: for each neuron, the 2 active conditions (switch and repeat) were randomly exchanged or unchanged with equal probability (50%), and a single average ROC timecourse was calculated. The 97.5th and 2.5th percentile values of the distribution of 10,000 average ROC values at each time point were used to indicate the 5% significance criterion. Significance was accepted when SC activity was significantly different for greater than 10 consecutive 1 millisecond bins (Cohen et al., 2009).

In addition, preparatory period activity was quantified in the period 400 to 200 ms before stimulus onset. Overlap trials and gap trials in the gap paradigm were combined because the instructions and stimulus conditions for these types of trials were identical. Prestimulus activity was quantified in the period 50 ms before to 50 ms after stimulus onset. Neural activity on switch trials was compared with neural activity on repeat trials using the Wilcoxon signed rank test.

We additionally conducted a Poisson spike-train analysis (Hanes et al., 1995) to investigate differences in the onset times of the saccade burst between switch and repeat trials.

This analysis was carried out using custom Matlab code developed by the Schall laboratory (http://www.psy.vanderbilt.edu/faculty/schall/scientific-tools/).

2.3 Results

In this study, we analyzed error rates, reaction times, and the neural activity of saccade-related neurons in the SC associated with switch and repeat trials. For the gap paradigm, 28 SC neurons (6 from monkey A and 22 from monkey C) were included in the analyses from a total of 49 experimental sessions. On average, the animals performed 85 overlap pro-saccade trials, 66 overlap anti-saccade trials, 77 gap pro-saccade trials, and 70 gap anti-saccade trials per session. For the memory paradigm, 35 SC neurons (15 from monkey A and 20 from monkey B) were included in the analyses from a total of 51 experimental sessions. On average, 67 overlap pro-saccade trials, 61 overlap anti-saccade trials, 65 memory pro-saccade trials, and 60 memory anti-saccade trials were performed per session. Behavioral differences between pro- and anti-saccade trials were consistent with those observed in previous studies (Munoz and Everling, 2004).

2.3.1 Switch Costs Present in the Gap and Memory Conditions

Table 2.1 shows gap condition error rates and SRTs on switch trials and repeat trials and the corresponding switch costs, whereas Table 2.2 shows results for the individual animals. The effects of previous trial type on error rates and SRTs for monkeys A and C were similar. All experimental sessions were combined for all analyses. For error rates, the main effect of previous trial type (switch versus repeat trials) was significant [$F(1,192) = 5.22$, $P = 0.024$, $\eta^2 = 0.009$]. This was primarily due to the fact that error rates on anti-saccade switch trials (35.1%) were

Table 2.1. Gap paradigm switch costs for error rate and SRT (means and standard errors). Asterisks indicate a significant difference between switch and repeat trials (i.e. a significant switch cost) ($P < 0.05$, paired t-test).

	Pro-saccades			Anti-saccades		
	Switch	Repeat	Cost	Switch	Repeat	Cost
Gap condition						
Error rate (%)	7.4 (0.9)	6.4 (0.8)	1.0 (0.7)	35.1 (1.9)	29.9 (1.5)	5.2 (1.4)*
SRT (ms)	224.6 (4.3)	216.1 (3.8)	8.5 (2.6)*	262.9 (5.3)	260.8 (5.1)	2.1 (3.5)
Overlap condition						
Error rate (%)	2.6 (0.5)	2.5 (0.6)	0.1 (0.5)	7.4 (0.9)	7.1 (0.7)	0.3 (0.9)
SRT (ms)	274.4 (3.6)	271.4 (3.8)	3.0 (2.4)	302.6 (4.3)	295.9 (3.8)	6.7 (2.8)*

Table 2.2. Gap condition error rate and SRT switch costs (means and standard errors) for monkeys A and C.

	Pro-saccades			Anti-saccades		
	Switch	**Repeat**	**Cost**	**Switch**	**Repeat**	**Cost**
Error rate (%)						
Monkey A	10.8 (4.1)	8.6 (2.7)	2.2 (2.9)	26.4 (5.2)	21.9 (5.8)	4.5 (2.8)
Monkey C	6.9 (0.9)	6.1 (0.9)	0.8 (0.8)	36.3 (2.0)	31.0 (1.5)	5.3 (1.6)
SRT (ms)						
Monkey A	173.4 (11.6)	169.2 (6.2)	4.2 (7.2)	195.2 (4.6)	194.0 (5.3)	1.2 (2.0)
Monkey C	231.3 (4.4)	222.6 (3.2)	9.2 (2.8)	272.3 (4.4)	270.1 (4.1)	2.2 (4.0)

significantly greater than on repeat trials (29.9%) (Fig. 2.2A, Table 2.1, $P < 0.001$, d = 0.44, paired t-test). Error rates on pro-saccade trials did not differ significantly between switch (7.4%) and repeat (6.4%) trials (Fig. 2.2A, Table 2.1, $P = 0.20$, paired t-test). No significant interaction between the effects of previous trial type and saccade task was observed [$F(1,192) = 2.49$, $P = 0.12$]. For SRTs, the main effect of previous trial type was not significant [$F(1,192) = 1.29$, $P = 0.26$]. Nonetheless, SRTs on correct pro-saccade switch trials (224.6 ms) were significantly longer than on repeat trials (216.1 ms) (Fig. 2.2B, Table 2.1, $P = 0.0025$, d = 0.30, paired t-test). SRTs did not differ significantly between correct anti-saccade switch (262.9 ms) and repeat trials (260.8 ms) (Fig. 2.2B, Table 2.1, $P = 0.56$, paired t-test). There was no significant interaction between the effects of previous trial type and saccade task [$F(1,192) = 0.48$, $P = 0.49$]. Overall, switch costs in the gap condition were reflected in increased error rates for anti-saccade trials and increased SRTs for pro-saccade trials.

Table 2.3 depicts error rates and SRTs on switch and repeat trials and the corresponding switch costs for the memory condition, pooled across monkeys A and B. Results for individual animals are shown in Table 2.4. The effects of previous trial type on error rates for monkeys A and B were similar. The following results are for experimental sessions combined. For error rates, the main effect of previous trial type was significant [$F(1,200) = 7.43$, $P = 0.007$, $\eta^2 = 0.036$]. Error rates on both pro-saccade and anti-saccade switch trials were significantly greater than on repeat trials (17.5% vs. 13.1% and 17.2% vs. 11.7% for pro- and anti-saccade trials respectively, Fig. 2.2C, Table 2.3, $P < 0.001$, d = 0.35 and d = 0.45 for each paired t-test respectively). There was no significant interaction between the effects of previous trial type and saccade task [$F(1,200) = 0.08$, $P = 0.77$]. For SRTs, the main effect of previous trial type was
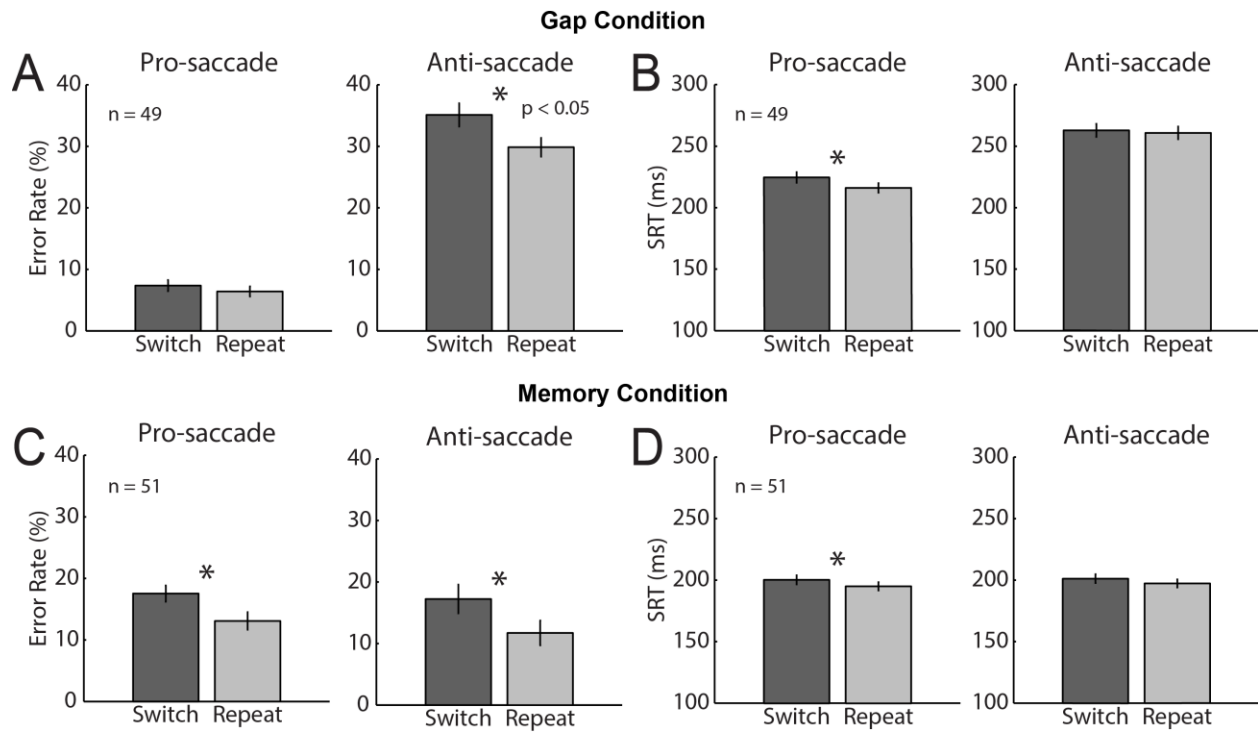
Figure 2.2. Behavior for gap and memory pro- and anti-saccade trials. *A*, Error rates for gap pro- and anti-saccades. *B*, SRTs for correct gap pro-and anti-saccades. *C*, *D*, Same as *A* and *B*, but for memory pro- and anti-saccades. Asterisks indicate a significant difference between switch trials and repeat trials ($P < 0.05$).

Table 2.3. Memory paradigm switch costs for error rate and SRT (means and standard errors). Asterisks indicate a significant difference between switch and repeat trials (i.e. a significant switch cost) ($P < 0.05$, paired t-test).

	Pro-saccades			Anti-saccades		
	Switch	Repeat	Cost	Switch	Repeat	Cost
Memory condition						
Error rate (%)	17.5 (1.3)	13.1 (1.4)	4.4 (1.1)*	17.2 (2.3)	11.7 (2.0)	5.5 (1.4)*
SRT (ms)	200.3 (3.7)	195.0 (3.4)	5.3 (2.4)*	201.2 (3.5)	197.3 (3.3)	3.9 (3.0)
Overlap condition						
Error rate (%)	2.2 (0.7)	1.3 (0.5)	0.9 (0.6)	4.9 (1.1)	3.5 (0.7)	1.4 (0.9)
SRT (ms)	176.4 (4.3)	174.0 (4.1)	2.4 (1.6)	204.9 (5.2)	204.4 (4.3)	0.5 (2.6)

Table 2.4. Memory condition error rate and SRT switch costs (means and standard errors) for monkeys A and B.

	Pro-saccades			Anti-saccades		
	Switch	**Repeat**	**Cost**	**Switch**	**Repeat**	**Cost**
Error rate (%)						
Monkey A	19.1 (1.9)	14.5 (2.1)	4.6 (1.5)	24.6 (3.6)	17.4 (3.3)	7.2 (2.3)
Monkey B	15.7 (1.8)	11.4 (1.9)	4.3 (1.6)	8.3 (1.2)	4.9 (1.0)	3.4 (1.2)
SRT (ms)						
Monkey A	213.1 (5.3)	204.1 (4.7)	9.0 (3.9)	207.0 (5.5)	199.0 (5.0)	8.0 (4.9)
Monkey B	184.6 (2.7)	183.9 (3.8)	0.5 (2.0)	194.1 (3.7)	195.4 (4.0)	-1.3 (2.7)

not significant [$F(1,200) = 1.71$, $P = 0.19$]. Nonetheless, SRTs on correct pro-saccade switch trials (200.3 ms) were significantly greater than on repeat (195.0 ms) trials (Fig. 2.2D, Table 2.3, $P < 0.032$, d = 0.24, paired t-test). No significant difference in SRTs was observed between correct anti-saccade switch (201.2 ms)and repeat (197.3 ms) trials (Fig. 2.2D, Table 2.3, $P = 0.20$, paired t-test). Based on individual data, the differences observed in SRTs are largely attributable to the fact that while monkey A showed switch costs, Monkey B showed little effect, and actually had shorter SRTs on anti-saccade trials (Table 2.4). There was no significant interaction between the effects of previous trial type and saccade task [$F(1,200) = 0.04$, $P = 0.84$]. Overall, pro-saccade and anti-saccade error rate and pro-saccade SRT switch costs were present in the memory condition. The magnitude of switch costs in the gap and memory conditions were comparable to those reported in previous human studies using pro- and anti-saccade tasks (Cherkasova et al., 2002; Weiler and Heath, 2012) and studies in rhesus monkeys using other tasks (Stoet and Snyder, 2003; Caselli and Chelazzi, 2011).

2.3.2 Minimal Switch Costs in the Overlap Condition

The overlap condition was interleaved with the gap condition in the gap paradigm and the memory condition in the memory paradigm. As such, behavior for the overlap condition was examined separately for each paradigm to account for differences in the second interleaved task. Overlap condition error rates and SRTs were similar for monkeys A and C that performed the gap paradigm and were combined for analyses. Similarly, data for monkeys A and B that performed the memory paradigm were combined. Error rates and SRTs are for the gap and memory paradigms are shown in Table 2.1 and Table 2.3 respectively. For the overlap condition in both the gap and memory paradigm, the main effect of previous trial type was not significant

for error rates [$F(1,192) = 0.08$, $P = 0.78$ and F(1,200) = 2.52, $P = 0.11$ respectively]. Error rates were not significantly different between switch and repeat trials for either pro- (2.6% vs. 2.5%) or anti-saccades (7.4% vs. 7.1%) (Table 2.1, Table 2.3, $P = 0.83$ for both, paired t-tests). There was no significant interaction between previous trial type and saccade task [$F(1,192) = 0.01$, $P = 0.90$ and F(1,200) = 0.17, $P = 0.68$ respectively]. For SRTs, the main effect of previous trial type was not significant [$F(1,192) = 1.59$, $P = 0.21$ and F(1,200) = 0.11, $P = 0.74$ respectively]. SRTs on correct anti-saccade switch trials (302.6 ms) were significantly greater than on repeat trials (295.9 ms) for the overlap condition in the gap paradigm (Table 2.1, $P = 0.027$, d = 0.18, paired t-test). Otherwise, SRTs did not differ between pro- and anti-saccade switch and repeat trials (Table 2.1, $P = 0.21$ for pro-saccades, Table 2.3, $P = 0.21$ and $P = 0.84$ for pro-saccades and anti-saccades respectively, paired t-tests). There was no significant interaction between previous trial type and saccade task [$F(1,192) = 0.22$, $P = 0.64$ and F(1,200) = 0.04, $P = 0.84$ respectively]. Overall, an anti-saccade SRT switch cost was observed for overlap trials that were randomly interleaved with gap trials.

Analysis of error rate switch costs between the overlap and gap conditions demonstrated that the effect of task condition was significant [F(1,192) = 9.18, $P = 0.0028$, $\eta^2 = 0.044$], with the anti-saccade switch cost being significantly greater in the gap condition (5.2% vs. 0.3%) (Table 2.1, $P = 0.0041$, d = 0.59, paired t-test). There was a significant interaction between task condition and saccade task [F(1,192) = 4.62, $P = 0.033$, $\eta^2 = 0.022$]. Similarly, task condition was significant between the overlap condition and memory condition [F(1,200) = 13.98, $P = 0.0002$], with the pro-saccade switch cost (4.4% vs. 0.9%) being significantly greater in the memory condition (Table 2.3, $P = 0.039$, d = 0.61, paired t-test). There was no significant interaction between task condition and saccade task [F(1,200) = 0.05, $P = 0.83$]. Analysis of SRT

switch costs demonstrated that the effect of task condition was not significant between the overlap condition and gap condition and between the overlap condition and memory condition [$F(1,192) = 0.02$, $P = 0.88$ and $F(1,200) = 1.58$, $P = 0.21$ respectively]. There was no significant interaction between task condition and saccade task [$F(1,192) = 3.11$, $P = 0.079$ and $F(1,200) = 0.01$, $P = 0.93$ respectively].

2.3.3 Neural Correlates of Switch Costs in Stimulus-Related SC Activity

SC spiking activity for monkeys A and C that performed the gap condition were similar and combined for analysis. Figure 2.3 shows SC spiking activity aligned to stimulus onset for the gap condition. On pro-saccade trials where the stimulus was presented within the neurons' response field, repeat trials showed a significantly greater response than switch trials, starting 79 ms after stimulus onset (Fig. 2.3A). In contrast, there was little response and no difference between switch and repeat trials for pro-saccades when the stimulus was presented at a location mirror opposite to the neurons' RF (Fig. 2.3B). On anti-saccade trials on which the stimulus was presented within the RF and the saccade was made opposite to the RF, responses were initially similar, but switch trials showed a significantly greater response than repeat trials, starting 142 ms after stimulus onset (Fig. 2.3C). Similar to pro-saccades into the RF, anti-saccade trials on which the stimulus was presented opposite to the RF and the saccade was made into the RF showed a significantly greater response for repeat trials compared to switch trials, starting 93 ms after stimulus onset (Fig. 2.3D). Notably, significant differences in neural activity occurred after 50 ms, the time at which SC neurons begin to have visual onset responses (Everling et al., 1999), and prior to saccade onset. When activity was instead plotted with respect to saccade initiation
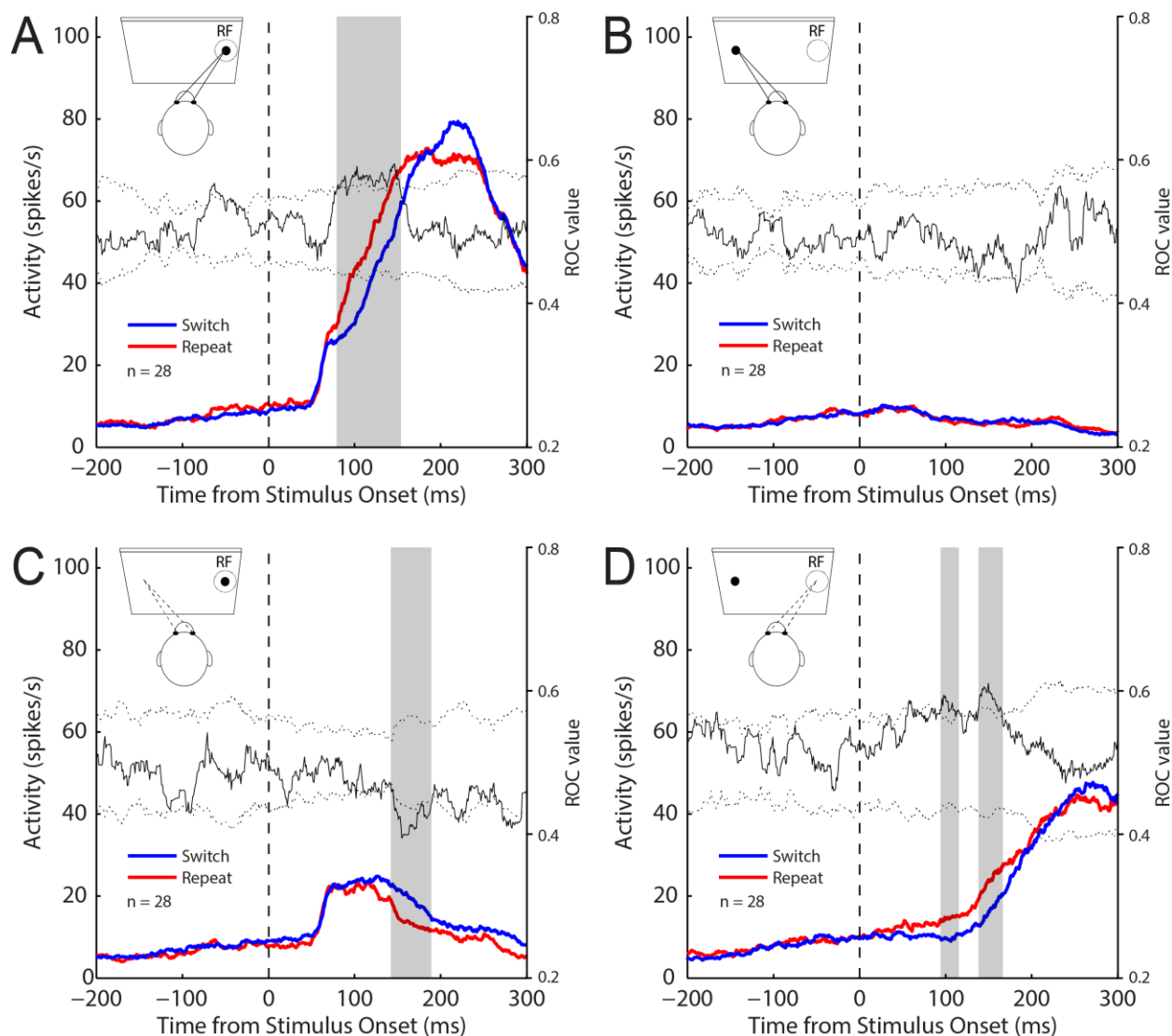
Figure 2.3. SC activity aligned to stimulus onset for the gap pro- and anti-saccade task. *A*, Mean spike density on switch (blue) and repeat (red) trials for correct pro-saccades in which the stimulus was presented into the RF of neurons. The timecourse of average population ROC values for the comparison of switch and repeat trials is overlaid (black), with dotted lines representing the 97.5th and 2.5th percentile values obtained from a bootstrap analysis. Periods in which the solid line lies above or below the dotted lines indicate periods with significant differences ($P < 0.05$). The shaded region indicates a period after stimulus onset when activity for switch and repeat trials was significantly different for greater than 10 consecutive milliseconds. *B*, Same as *A*, but for correct pro-saccades in which the stimulus was presented opposite to the RF. *C*, *D*, Same as *A* and *B*, but for correct anti-saccades.

Figure 2.4. SC activity aligned to saccade onset for the gap pro- and anti-saccade task. *A*, Mean spike density on switch (blue) and repeat (red) trials for correct pro-saccades in which the stimulus was presented into the RF of neurons. The timecourse of average population ROC values for the comparison of switch and repeat trials is overlaid (black), with dotted lines representing the 97.5th and 2.5th percentile values obtained from a bootstrap analysis. Periods in which the solid line lies above or below the dotted lines indicate periods with significant differences ($P < 0.05$). *B*, Same as *A*, but for correct pro-saccades in which the stimulus was presented opposite to the RF. *C*, *D*, Same as *A* and *B*, but for correct anti-saccades.

(Fig. 2.4), there were no significant differences between switch trials and repeat trials around the time of saccade onset for either pro- or anti-saccades. This was true whether the stimulus was presented within or at a location opposite the neurons' RF. In particular, there were no significant differences earlier than 8 ms before saccade onset, which is the latest time at which a neural signal from the SC can influence saccade initiation (Munoz & Wurtz, 1993; Miyashita and Hikosaka, 1996; Munoz et al., 1996). Overall, we observed differences in activity aligned to stimulus onset for gap switch and repeat trials. Activity was significantly greater on repeat than switch trials for pro-saccades into the RF of SC neurons. On anti-saccade trials, we observed a late elevation in activity when the visual stimulus was presented in the RF on switch trials, and greater activity on repeat trials on which saccades were directed toward the RF.

In contrast to the gap condition, for the memory condition there were no significant differences between switch and repeat trials on pro-saccade trials where the stimulus was presented either within the neurons' RF (Fig. 2.5A) or at a location opposite to it (Fig. 2.5B), or on anti-saccade trials where the stimulus was presented either within the neurons' RF (Fig. 2.5C) or at a location opposite to it (Fig. 2.5D). When activity was aligned to saccade onset, there were no significant differences between switch trials and repeat trials around the time of saccade onset on either pro-saccade or anti-saccade trials, whether the stimulus was presented within or at a location opposite the neurons' RF (Fig. 2.6). As described earlier, switch costs were primarily observed in monkey A, and accordingly, we separated neural data for these two animals to investigate any differences in neural activity between animals exhibiting and not exhibiting behavioral switch costs. Monkeys A and B did demonstrate differences in SC spiking activity on pro-saccade trials where the stimulus was presented within the neurons' RF that paralleled their differences in pro-saccade SRTs (Fig. 2.7, Table 2.4). For monkey A, activity on repeat trials

Figure 2.5. SC activity aligned to stimulus onset for the memory pro- and anti-saccade task. *A*, Mean spike density on switch (blue) and repeat (red) trials for correct pro-saccades in which the stimulus was presented into the RF of neurons. The timecourse of average population ROC values for the comparison of switch and repeat trials is overlaid (black), with dotted lines representing the 97.5th and 2.5th percentile values obtained from a bootstrap analysis. Periods in which the solid line lies above or below the dotted lines indicate periods with significant differences ($P < 0.05$). *B*, Same as *A*, but for correct pro-saccades in which the stimulus was presented opposite to the RF. *C*, *D*, Same as *A* and *B*, but for correct anti-saccades.

Figure 2.6. SC activity aligned to saccade onset for the memory pro- and anti-saccade task. *A*, Mean spike density on switch (blue) and repeat (red) trials for correct pro-saccades in which the stimulus was presented into the RF of neurons. The timecourse of average population ROC values for the comparison of switch and repeat trials is overlaid (black), with dotted lines representing the 97.5th and 2.5th percentile values obtained from a bootstrap analysis. Periods in which the solid line lies above or below the dotted lines indicate periods with significant differences ($P < 0.05$). *B*, Same as *A*, but for correct pro-saccades in which the stimulus was presented opposite to the RF. *C*, *D*, Same as *A* and *B*, but for correct anti-saccades.
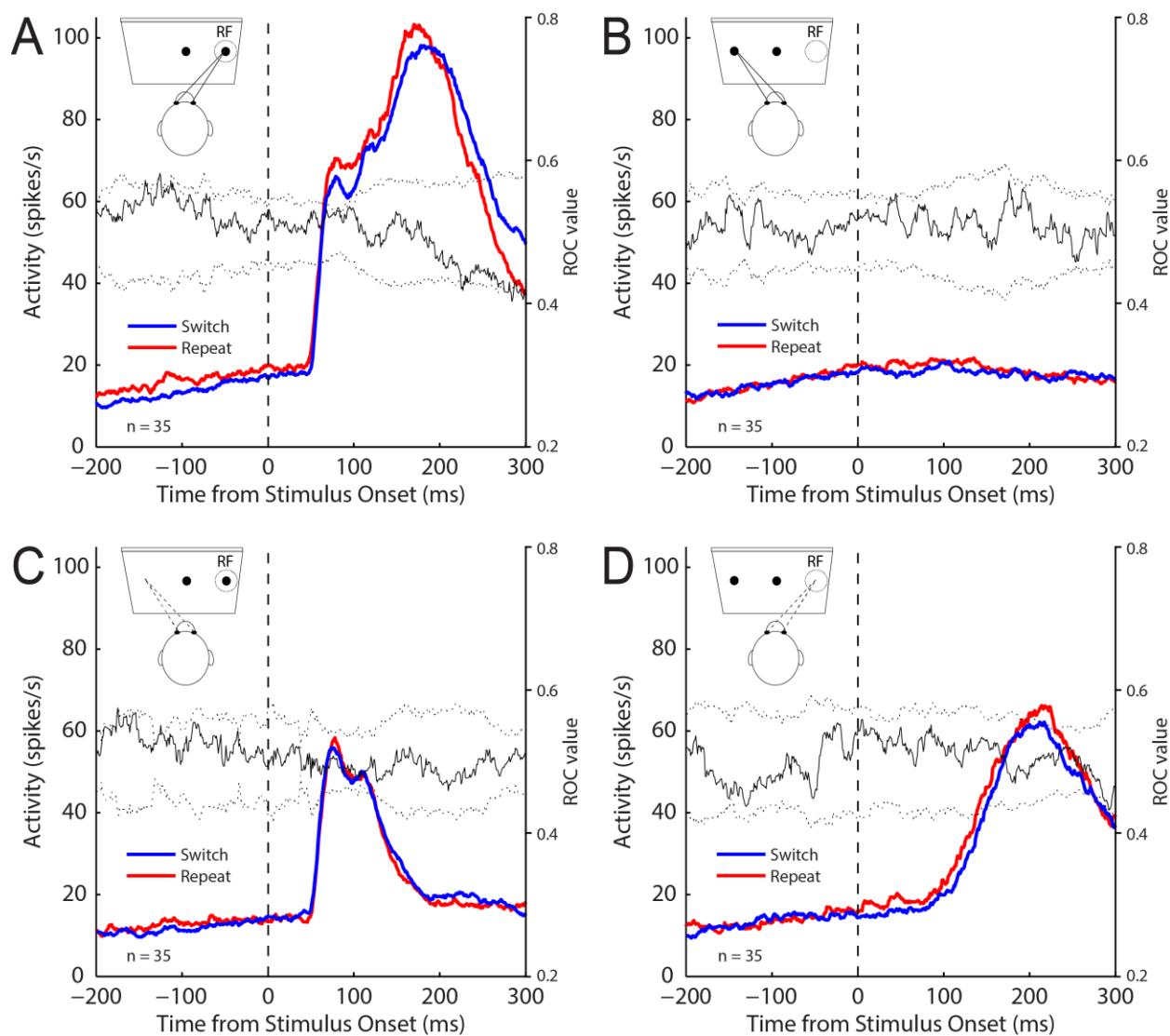
Figure 2.7. SC activity on correct memory pro-saccades in which the stimulus was presented into the RF of neurons for individual monkeys. *A*, Mean spike density aligned to stimulus onset on switch (blue) and repeat (red) trials for monkey A. The time course of average population ROC values for the comparison of switch and repeat trials is overlaid (black), with dotted lines representing the 97.5th and 2.5th percentile values obtained from a bootstrap analysis. Periods in which the solid line lies above or below the dotted lines indicate periods with significant differences ($P < 0.05$). The shaded region indicates a period after stimulus onset when activity for switch and repeat trials was significantly different for greater than 10 consecutive milliseconds. *B*, Same as *A*, but for monkey B.

was significantly greater than that on switch trials starting 87 ms after stimulus onset (Fig. 2.7A), whereas monkey B had a comparable response for switch trials and repeat trials (Fig. 2.7B).

Although the sample sizes of 28 neurons for the gap condition and 35 neurons for the memory condition could be considered low, they were comparable to other studies of SC neurons (Jantz et al., 2013; Shen and Paré, 2014) and were sufficient to achieve statistical significance as demonstrated by ROC analyses (Fig. 2.3-2.6). Furthermore, statistically significant effects from these samples of saccade-related neurons have been previously reported in Johnston et al. (2014) and Koval et al. (2011) for the gap condition and memory condition respectively.

2.3.4 Prestimulus and Preparatory Activity

In the memory condition, prestimulus activity on correct pro-saccade repeat trials did not differ significantly from that on switch trials (20.1 spikes/s compared to 17.9 spikes/s, $P = 0.067$, Wilcoxon signed rank test). In the gap condition, there were no significant differences in prestimulus activity between correct switch trials and repeat trials for pro-saccades and anti-saccades ($P > 0.47$ for all, Wilcoxon signed rank test). With regard to preparatory activity in the memory condition and gap condition, there were no significant differences between correct switch trials and repeat trials for pro-saccades and anti-saccades, ($P > 0.17$ for all, Wilcoxon signed rank test).

Of saccade-related neurons, buildup neurons have been shown to have task-specific changes in prestimulus and preparatory activity (Everling et al., 1999). To be classified as a buildup neuron, a neuron was required to exhibit prestimulus activity, 50 ms before and after stimulus onset, that was significantly greater than during the preparatory period, 300 to 200 ms

before stimulus onset (Dorris et al., 1997). Overall, 7/28 and 9/35 saccade-related neurons were classified as buildup neurons in the gap condition and memory condition, respectively. In the gap task, buildup neurons showed no significant differences in preparatory period activity between correct anti-saccade switch and repeat trials (13.1 spikes/s compared to 11.6 spikes/s, $P = 0.094$, Wilcoxon signed rank test). There were no significant differences in prestimulus activity between correct pro-saccade repeat trials and switch trials (24.8 spikes/s compared to 22.3 spikes/s, $P = 0.0781$, Wilcoxon signed rank test). The relatively small subset of buildup neurons may not have allowed for sufficient statistical power to detect significant differences between switch and repeat trials.

2.3.5 Onset of Motor Activity

An obvious correlate of an SRT switch cost would be changes in the onset of the motor burst in SC neurons. To investigate any such changes between switch and repeat trials, we carried out a Poisson spike train analysis (Hanes et al., 1995) on a subset of saccade-related neurons showing little or no stimulus-related activity, for pro- and anti-saccade trials on which a saccade was made into the response field. This subset of neurons was chosen to avoid any contamination of the motor burst by residual stimulus-related activity, which could lead to inaccurate estimation of onset times. After applying this restriction, a representative sample size remained only for the gap condition. Figure 2.8 depicts average spike density functions aligned on stimulus onset for pro- (Fig. 2.8A) and anti-saccades (Fig. 2.8B) on switch and repeat trials, for these neurons. Of this sample, 3 of 12 neurons showed significantly longer onset times for switch compared to repeat trials during the pro-saccade task ($P < 0.05$, Wilcoxon rank sum test).
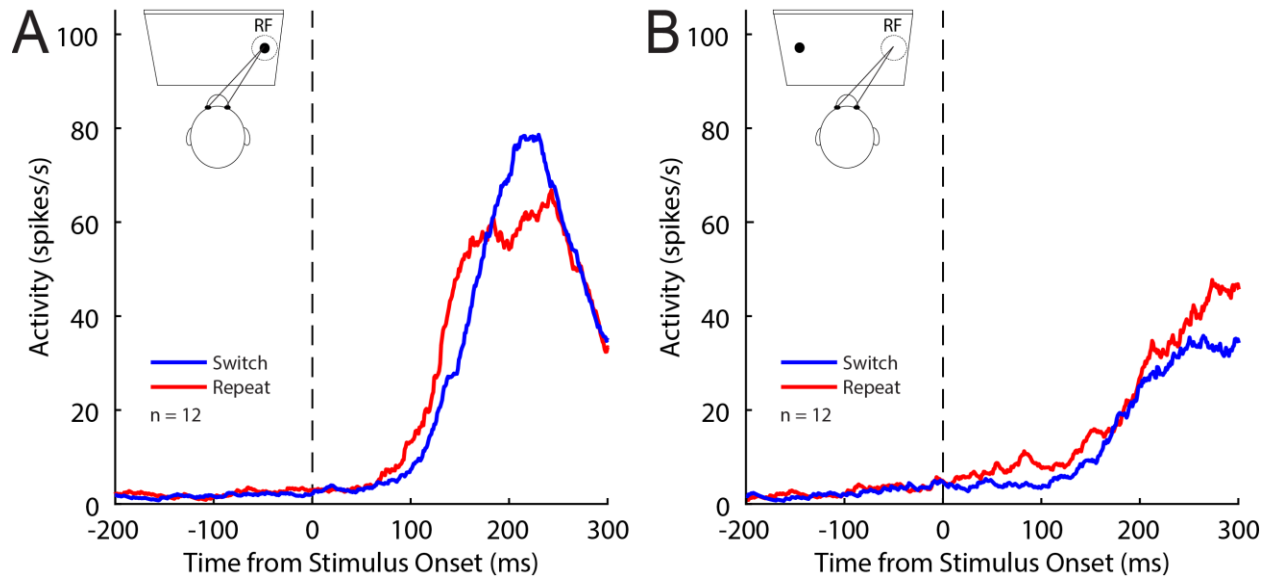
Figure 2.8. Timing of burst onset in SC neurons with little to no visual activity on switch and repeat trials. *A*, Mean spike density aligned to stimulus onset for correct pro-saccade switch (blue) and repeat (red) trials on which a saccade was made into the RF of neurons. Burst onset is earlier for repeat trials. *B*, Same as *A*, but for correct anti-saccade trials on which a saccade was made into the RF of neurons. No differences in burst onset were observed between switch and repeat trials.

Though this difference only approached statistical significance for the population (Fig. 2.8A, 185.7 ms and 171.6 ms for repeat and switch trials, respectively, $P = 0.064$, Wilcoxon signed rank test), the direction was consistent with the increase in SRTs between switch and repeat trials for the pro-saccade task in the gap condition. In addition, we did not observe any differences in onset times of the motor burst for switch and repeat anti-saccade trials in the gap condition (Fig. 2.8B, 229.9 ms and 226.8 ms for switch and repeat trials, respectively, $P = 0.70$, Wilcoxon signed rank test), consistent with the lack of SRT switch costs we observed for these trials.

2.3.6 Error Trials

Although switch-related differences are typically examined using correct trials, SRTs and SC activity were also analyzed for error trials. Unlike for correct trials, there were no significant differences in SRTs between switch trials and repeat trials for pro-saccades and anti-saccades in both the gap and memory conditions ($P > 0.18$ for all, two-sample t-tests). For SC activity, analyses were conducted using neurons with at least four erroneous switch and repeat trials for each specific comparison. Figure 2.9 shows SC spiking activity on gap anti-saccade error trials for 11 neurons where the stimulus was presented within the RF and 20 neurons where the stimulus was presented opposite to the RF. While there was no significant difference in activity aligned to stimulus onset between switch and repeat trials on anti-saccade trials where the stimulus was presented within the RF (Fig. 2.9A), switch trials showed a significantly greater response than repeat trials when aligned to saccade onset that is likely reflective of stimulus-related activity (Fig. 2.9B). Although activity appeared higher on switch than repeat trials when aligned to stimulus onset (Fig. 2.9A), this difference was not statistically significant as shown in the overlaid ROC value envelop. There were no significant differences between switch and
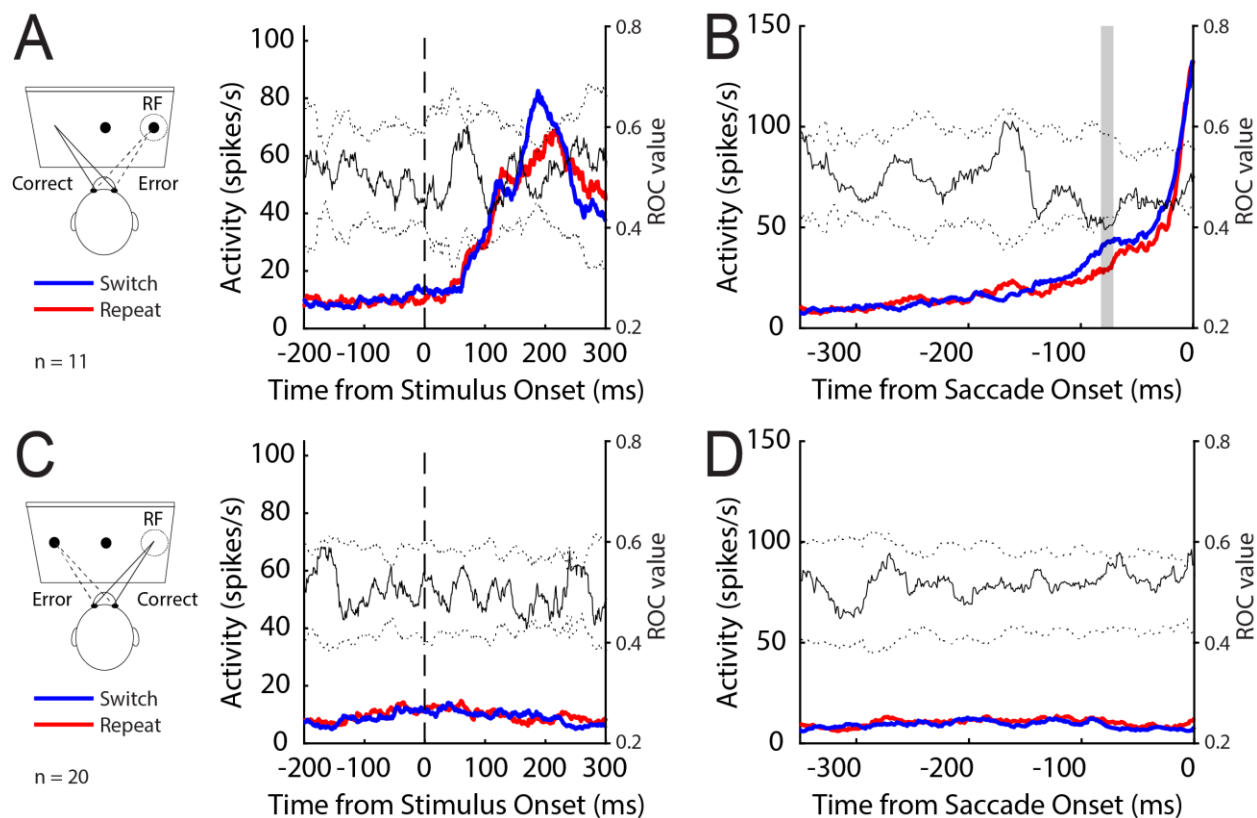
Figure 2.9. SC activity on gap anti-saccade error trials. *A*, Mean spike density aligned to stimulus onset on switch (blue) and repeat (red) trials for anti-saccades in which the stimulus was presented into the RF of neurons. The timecourse of average population ROC values for the comparison of switch and repeat trials is overlaid (black), with dotted lines representing the 97.5th and 2.5th percentile values obtained from a bootstrap analysis. Periods in which the solid line lies above or below the dotted lines indicate periods with significant differences ($P < 0.05$). *B*, Same as *A*, but for mean spike density aligned to saccade onset. The shaded region indicates a period when activity for switch and repeat trials was significantly different for greater than 10 consecutive milliseconds. *C*, *D*, Same as *A* and *B*, but for anti-saccades in which the stimulus was presented opposite to the RF.

repeat trials for anti-saccade error trials where the stimulus was presented opposite to the RF (Fig. 2.9CD). Gap pro-saccade error trials and memory pro-saccade and anti-saccade error trials all had 5 or less neurons with at least four erroneous switch and repeat trials and were not analyzed.

2.4 Discussion

In this study, we investigated behavioral switch costs and the role of the SC in task switching in macaque monkeys performing randomly interleaved pro- and anti-saccade tasks. We predicted that SC activity would differ between switch and repeat trials, such that activity for the previous task rule would persist and contaminate the current trial. Specifically, we predicted that activity on pro-saccade switch trials would be lower than that on repeat trials, and that activity on anti-saccade switch trials would exceed that observed on repeat trials. SC activity following stimulus onset matched these predictions for gap pro- and anti-saccade trials when a visual stimulus was presented in the response field. This pattern was reversed for anti-saccades made toward the response field, with activity being greater on repeat than switch trials. A similar pattern was also observed in the memory condition, although these effects failed to reach significance.

The link between SC activity and pro- and anti-saccade performance has been conceptualized as an accumulator model in which SC activity accumulates toward a fixed threshold, at which a saccade is triggered (Munoz and Everling, 2004). We observed an elevation of activity on repeat pro-saccades into the response field which, according to this model, would drive activity closer to threshold, thereby facilitating the correct pro-saccade. We further found that the onset time of the saccade burst was earlier for repeat than switch trials. These activity

differences are consistent with the SRT advantage for pro-saccade repeat trials we observed here. For correct anti-saccade performance, the accumulator model stipulates that activity must be maintained below threshold to avoid reflexive saccades toward the visual stimulus. On anti-saccade trials in which the visual stimulus was presented within the response field of SC neurons, we observed the predicted increase in activity following stimulus onset on switch as compared to repeat trials. Such an increase would result in activity being closer to saccade threshold and an increased likelihood of erroneous saccades. This is consistent with the error rate switch cost we observed for anti-saccade switch trials. We additionally found that activity was greater for repeat than switch anti-saccade trials on which a saccade was generated into the response field. Although not matching our initial prediction, such activity would facilitate performance of the correct anti-saccade away from the visual stimulus and could be considered a signature of a fully configured task-set. We did not, however, observe any changes in the onset times of the saccade burst for these trials, nor changes in SRTs consistent with such a facilitation, so the correspondence of this finding with behavioral switch costs remains speculative.

Compared to the gap condition, differences in stimulus-related SC activity in the memory condition were less clear. Monkey A demonstrated the predicted decrease in stimulus-related activity on switch as opposed to repeat trials for pro-saccades into the RF consistent with the observed pro-saccade SRT switch cost in this animal. In contrast, there were no significant differences for monkey B, which was consistent with the absent SRT switch cost. There were no other significant differences in stimulus-related SC activity, although error rate switch costs were found. Altogether, for the memory condition, we found partial support for our initial predictions. Switch costs in the memory condition may arise from an increased demand on working memory, whereas switch costs and switch-related differences in SC activity in the gap condition may be a

result of the gap directly modulating the activity of saccade-related neurons in the SC (Munoz and Everling, 2004). Thus, for the memory condition, higher level brain areas that maintain task instruction in working memory, such as the DLPFC (Koval et al., 2011), may better reflect the completion of task-set reconfiguration than the SC.

Our initial predictions with respect to changes in SC activity on switch versus repeat trials were based on the concept of task-set inertia, or the persistence of the previous task-set on the current trial (Allport et al., 1994; Allport and Wylie, 2000). While we did observe some changes consistent with this in the stimulus-related activity of SC neurons for both pro- and anti-saccades, our findings with respect to prestimulus SC activity were inconsistent with such a conceptualization. If activity from the previous trial were to interfere with activity during the current trial, this should be observed particularly in the earliest activity on the current trial. In this case, this would correspond to prestimulus activity, which has previously been shown to be greater for pro- than anti-saccade trials in buildup neurons (Everling et al., 1998; Everling et al., 1999), and to be modulated by previous repeated and non-repeated saccades in saccade neurons (Dorris et al., 2000). Here, we found no switch-related differences in prestimulus activity for saccade-related neurons in the memory condition or in prestimulus and preparatory period activity for build-up neurons in the gap condition. Alternatively, our findings may indicate a cortical locus of task-set inertia, which only later influences SC activity. Recent human studies support a role for interference from task-set inertia in generating the unidirectional pro-saccade SRT switch cost (Weiler and Heath, 2014; Yeung et al., 2014). Neural correlates of task-set inertia may be found in brain areas with preparatory task-related differences in activity between pro- and anti-saccades, including the DLPFC (Everling and DeSouza, 2005; Johnston et al.,

2007), FEF (Everling and Munoz, 2000), SEF (Schlag-Rey et al., 1997), and ACC (Johnston et al., 2007).

Theoretical accounts other than task-set inertia have been proposed to account for switch costs (Monsell, 2003; Kiesel et al., 2010). These may generally and collectively be described as "two-process" models. According to such models, switch costs are a result of "endogenous" executive control processes required to reconfigure cognitive systems in preparation for the upcoming task following a switch, and "exogenous" processes driven by the appearance of task stimuli. For example, according to the "retrieval hypothesis" as proposed by Rubinstein et al. (2001), the endogenous executive processes taking place in advance of task switches entail retrieval of the task set for the to-be-performed task from long-term memory, and loading of this set into working memory. This is followed by a "task implementation" stage that is triggered by the onset of task stimuli. Such conceptualizations are not inconsistent with the results we have observed here. Although speculative, it seems plausible that the lack of pre-stimulus differences in SC activity between switch and repeat trials we observed here are not necessarily a result of *task-set-inertia* taking place in higher cortical areas such as DLPFC, but may instead be attributable to cortical areas being involved in the *first-stage executive reconfiguration processes* taking place during the instruction period of our tasks during switch trials, preceding onset of the visual stimuli. The SC could then be involved in the task-implementation stage, with differences in activity occurring only after stimulus onset. Indeed, this is consistent with the timing of activity differences between switch and repeat trials we observed here, which could be interpreted as incomplete instantiation of a task-implementation stage. Our findings may also be compatible with the model of De Jong (2000), which proposes that task-sets are reconfigured in an all-or-none, probabilistic fashion. According to this account, if advance reconfiguration fails,

task-set reconfiguration must take place entirely following stimulus onset. It may be that in our tasks, the lack of activity differences for switch and repeat trials in advance of stimulus onset were a neural correlate of complete failures of advance reconfiguration, which subsequently took place following stimulus onset as evidenced by the observed post-stimulus changes in neural activity. A complete investigation of these possibilities would require systematic variations in the duration of the pro- and anti-saccade instruction cues we employed here, as a means of varying the time allowed for first-stage processes to take place, combined with further recordings, and thus await further study.

The DLPFC, ACC, and PPC are thought to be critical brain areas for task switching (Sohn et al., 2000; Braver et al., 2003; Forstmann et al., 2005; Liston et al., 2006; Chiu and Yantis, 2009; Jamadar et al., 2010; Ruge et al., 2010;). In the DLPFC, task rules are represented in single neuron activity (White and Wise, 1999; Asaad et al., 2000; Everling and DeSouza, 2005) and local field potential activity (Buschman et al., 2012), and the ACC and PPC have been implicated in signaling a task switch and selecting the appropriate task (Johnston et al., 2007; Kamigaki et al., 2009). The ability to select, establish, and maintain task rules makes these areas susceptible to interference from task-set inertia and implicates them in the unidirectional pro-saccade switch cost. Reduced blood oxygen level-dependent (BOLD) activity in the FEF and SEF was found for pro-saccade trials preceded by an anti-saccade trial and may contribute to the unidirectional pro-saccade switch cost (Manoach et al., 2007). However, single unit recordings have not yet investigated whether switch-related activity exists in cortical areas and further studies are required to elucidate the neural mechanisms of task switching. Overall, both error rate and unilateral reaction time switch costs are likely due to switch-related processing in a broad neural network.

While humans consistently demonstrate error rate and reaction time switch costs while performing cued switch tasks, it has thus far been less clear whether macque monkeys display switch costs (Stoet and Snyder, 2003; Caselli and Chelazzi, 2011; Avdagic et al., 2014). Here, switches to gap pro-saccade trials had longer SRTs than repeat trials, and switches to gap anti-saccade trials had higher error rates than repeat trials. Similar switch costs were found in the memory condition, with the addition of higher error rates on switches to pro-saccade trials compared to repeat trials. Notably, SRT switch costs were present for pro-saccades, but not anti-saccades, in both the gap and memory conditions. Unidirectional reaction time switch costs are commonly observed for switches between dominant tasks (e.g. the pro-saccade task) and non-dominant tasks (e.g. the anti-saccade task), and can be attributed to increased cognitive control for the non-dominant task interfering with the preparation of the dominant task-set (Allport et al., 1994; Monsell, 2003). Overall, these results are consistent with switch costs found in human experiments using randomly interleaved pro- and anti-saccade tasks, which have demonstrated a unidirectional pro-saccade SRT switch cost and error rate switch costs for pro- and anti-saccades (Cherkasova et al., 2002; Barton et al., 2006; Manoach et al., 2007; Chan and DeSouza, 2013). The absence of significant switch costs in the overlap condition compared to the gap and memory conditions may be due to differences in task difficulty or cognitive demand.

Anti-saccades are more difficult to perform in the gap condition than the overlap condition. The gap period, in which the fixation stimulus is extinguished has been associated with decreased fixation-related neuron activity and increased saccade-related neuron activity in both the SC and FEF (Dorris et al., 1997; Everling and Munoz, 2000; Munoz and Everling, 2004). This neural correlate of released fixation accounts for increased error rates and decreased SRTs for anti-saccades (Everling et al., 1999; Munoz and Everling, 2004), and increased

inhibitory control is thought to be required for correct anti-saccade performance (Curtis et al., 2001). Consequently, the pro-saccade SRT switch cost may reflect increased inhibition of saccade-related neurons due to the previous anti-saccade interfering with pro-saccade generation, while the anti-saccade error rate switch cost may reflect direction errors resulting from the combined effects of increased excitability from the previous pro-saccade and the release of fixation. In the memory condition, increased cognitive control is required to maintain the task instruction in working memory for both pro-saccades and anti-saccades (Koval et al., 2011). Increased cognitive demand through the presence of an attentional load has been shown to increase switch costs for pro-saccades and anti-saccades in humans (Chan and DeSouza, 2013) and similarly, an increased demand on working memory may interfere with task-set representation and result in error rate switch costs for both tasks. In the gap and memory conditions, instruction cue switching may also have contributed to switch costs (Schneider and Logan, 2011). However, the lack of switch costs in the overlap condition, which used the same instruction cues as the gap and memory conditions, suggest task switching comprised the majority of the cost. Taken together, both macaque monkeys and humans demonstrate similar error rate and reaction time switch costs when performing cued and randomly interleaved pro-saccades and anti-saccades.

These results also provide support for switch costs in macaques performing cued switch tasks and are consistent with switch costs observed by Caselli and Chelazzi (2011). Several other studies, however, have found inconsistent switch costs (Avdagic et al., 2014; Stoet and Synder, 2003). In particular, Stoet and Synder (2003) proposed that residual switch costs, or costs that persist despite long preparation or intertrial intervals, are absent in macaque monkeys and that they can complete task-set reconfiguration before the onset of task stimuli. In this study, switch

costs were present despite intertrial intervals of 1000 ms. However, it is possible that these were not true residual switch costs. The presence of a gap and a requirement to maintain task instruction in working memory immediately before stimulus onset may have eliminated the benefit of advanced task preparation. Similarly, the switch costs found by Caselli and Chelazzi (2011) may be due to increased cognitive demands immediately before task stimuli were presented. Caselli and Chelazzi (2011) and Stoet and Snyder (2003) both trained macaques to switch between two discrimination tasks, but the former study used a longer delay before stimulus presentation where the task instruction was held in working memory. Thus, although macaque monkeys may be able to complete task-set reconfiguration before stimuli onset, increased cognitive demands immediately before stimuli onset may disrupt reconfiguration and introduce switch costs.

In summary, we found switch costs in macaque monkeys performing randomly interleaved gap and memory pro-saccade and anti-saccade tasks that were comparable to humans and add to the extant literature on switch costs in macaque monkeys. Switch-related differences in SC activity in the gap condition may have contributed to switch costs and demonstrated a neural correlate for task switching. SC activity is likely modulated by task switching processes from other brain areas and may reflect the completion of task-set reconfiguration.

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CHAPTER 3

Dorsolateral prefrontal cortex deactivation in monkeys reduces preparatory

beta and gamma power in the superior colliculus

3.1 Introduction

As our environment changes, certain behaviours become more appropriate than others. Our ability to flexibly engage in goal-directed behaviour depends on cognitive control. A critical component of this control is the ability to select and maintain task-relevant stimulus-response associations, or rules. In particular, the dorsolateral prefrontal cortex (DLPFC) is thought to encode representations of rules and goals, and bias other brain areas to achieve the desired outcome (Miller and Cohen, 2001).

The anti-saccade task, where subjects suppress a saccade toward a peripheral stimulus (pro-saccade) and generate a saccade in the opposite direction (Hallett, 1978; Munoz and Everling, 2004), is a useful paradigm for investigating the neural basis of cognitive control. Pro-saccades and anti-saccades are realized by distinct stimulus-response associations, and the DLPFC has been implicated in their performance. Patients with DLPFC lesions have been found to have longer reaction times and produce more errors for anti-saccades (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991, 2003; Ploner et al., 2005) and functional imaging studies in humans suggest DLPFC involvement in anti-saccade preparation (Sweeney et al., 1996; Desouza et al., 2003; Ford et al., 2005; Brown et al., 2007). In particular, single-unit recordings in

monkeys have found task-selective activity for pro-saccades and anti-saccades in DLPFC neurons (Funahashi et al., 1993; Everling and DeSouza, 2005; Johnston and Everling, 2006b; Johnston et al., 2007). The DLPFC also contains neurons that project directly to and send task-selective signals to the superior colliculus (SC) (Goldman and Nauta, 1976; Leichnetz et al., 1981; Johnston and Everling, 2006b), a critical component of the oculomotor system that is strongly modulated by the anti-saccade task (Everling et al., 1999; Munoz and Everling, 2004).

Deactivation of the DLPFC with cooling has been shown to affect single neuron activity in the SC. First, unilateral DLPFC deactivation increases preparatory activity in the contralateral SC on pro-saccade and anti-saccade trials, and increases stimulus-related activity in the contralateral SC on anti-saccade trials (Johnston et al., 2014). Second, bilateral deactivation decreases preparatory activity on pro-saccade and anti-saccade trials, and increases stimulus-related activity and decreases saccade-related activity on anti-saccade trials (Koval et al., 2011). Both studies linked DLPFC-induced changes in SC activity to behaviour and, together with other studies that manipulated DLPFC activity (Condy et al., 2007; Wegener et al., 2008), suggest that the DLPFC exerts an excitatory influence on the SC (for review see Everling and Johnston, 2013). However, the mechanisms by which the DLPFC biases the SC and other brain areas remain unclear.

A complementary approach to examining spiking activity is to examine local field potentials (LFPs), which reflect the average synaptic activity of a group of neurons (Buzaski et al., 2012). LFPs and neuronal oscillations have been implicated in neuronal communication and top-down control (Varela et al., 2001; Fries, 2005; Siegel et al., 2012), and may help elucidate how the DLPFC communicates task-relevant signals to target areas. Here, we report the effects

of bilateral DLPFC deactivation on LFP activity in the SC. LFP activity was collected together with the spiking activity previously reported by Koval et al. (2011).

3.2 Materials and Methods

All procedures were conducted in accordance with 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. Details of the surgical procedures, behavioural task, and reversible cryogenic deactivation have been previously described by Koval et al. (2011) and are summarized below.

3.2.1 Surgical Procedures

Two adult male macaque monkeys (*Macaca mulatta*) weighing 11 and 16 kg were prepared for LFP and single-neuron recordings in the SC using previously described techniques (Johnston and Everling, 2006b). Stainless steel cryoloops were implanted bilaterally into the posterior principal sulci (Fig. 3.1A) for reversible deactivations of parts of the DLPFC (posterior parts of area 46 and portions of 9/46d, 9/46v). The technical details of the cryoloop surgery and deactivation method have been previously described (Lomber et al., 1999).

3.2.2 Behavioural Task

During the experiment, monkeys performed a randomly interleaved pro-saccade and anti-saccade task (Fig. 3.1B). Each trial began with the presentation of a coloured central fixation
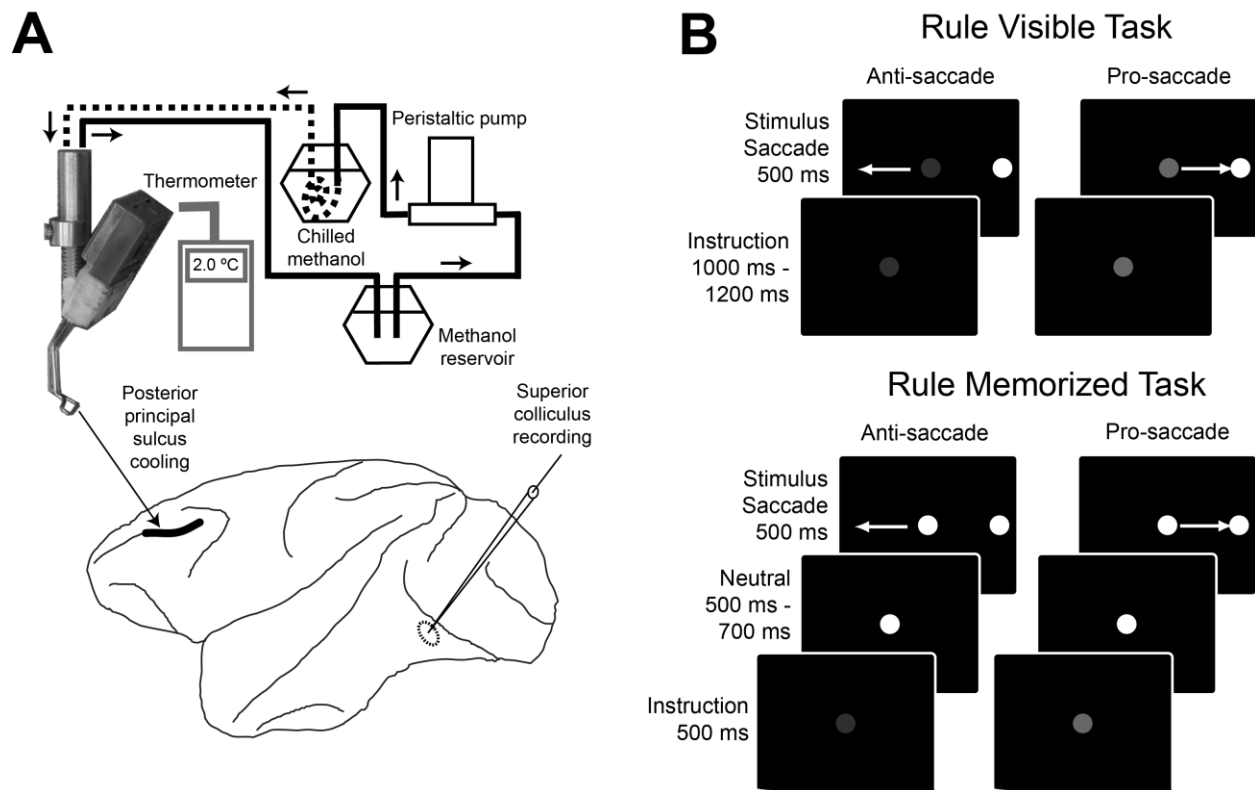
Figure 3.1. Experimental setup and experimental paradigm. *A*, The DLPFC was deactivated bilaterally by pumping chilled methanol through cryoloops. LFP and single-neuron activity were recorded in the SC. *B*, Each trial began with a fixation point that signalled, by its colour, a pro-saccade or anti-saccade trial. A stimulus subsequently appeared in the RF of the recording site or opposite to the RF on the other side. In the rule memorized task, the colour of the fixation point changed to a task neutral colour 500-700 ms before stimulus presentation.

point. For one monkey, a green fixation point signalled a pro-saccade trial and a red fixation point signalled an anti-saccade trial. For the other monkey, the colour instructions were reversed. Monkeys were required to fixate on the fixation point within a 0.5° x 0.5° window for 1000-1200 ms at the beginning of each trial. On half the trials, the colour cue remained visible throughout the trial (rule visible/overlap task), while on the other half of trials, the colour cue changed to yellow 500-700ms before stimulus presentation (rule memorized task). Subsequently, a peripheral white visual stimulus (0.15°) was pseudorandomly presented with equal probability in either the response field (RF) of an isolated SC neuron or at the mirror location. Monkeys were required to generate a saccade toward the stimulus on pro-saccade trials and away from the stimulus on anti-saccade trials, and rewarded when saccade endpoints were within a 5° x 5° window.

3.2.3 Reversible Cryogenic Deactivation

To deactivate the posterior principal sulcus, methanol was chilled using an ice bath containing dry ice and passed through a cryoloop to deactivate adjacent cortical tissue (Fig. 3.1A). Evoked neural activity is absent when cortical tissue is cooled below 20°C (Adey 1974). Given that the effective spread of cooling is restricted to ~2 mm on either side of the cryoloop (Payne and Lomber, 1999) and that each cryoloop measured 6 x 3 x 2 mm, the volume of cortex deactivated can be approximated by the volume of a box with dimensions of 10 x 7 x 4 mm, or 280 mm³. Accordingly, cooling of the cryoloops affected the posterior half of the principal sulci, corresponding mainly to parts of area 46 and area 9/46 (Petrides and Pandya, 1999).

Each experimental session began with a precool period where the pumps were turned off. The pumps were subsequently turned on to start the cool period. The first 4 minutes after the

pumps were turned on were excluded from all data analysis to ensure that the cortical tissue adjacent to the cryoloops was cooled below 20°C and that neurons were deactivated. At the end of the cool period, the pumps were turned off. The first 3 minutes after the pumps were turned off were excluded from all data analysis to ensure that the cortical tissue adjacent to the cryoloops returned to normal body temperature.

3.2.4 Recording Method

The activity of saccade-related neurons and the accompanying LFP activity were recorded in the intermediate layers of the caudal SC (saccade amplitudes 5-12°) using standard electrophysiological techniques (Johnston and Everling, 2006b). To be considered a saccade-related neuron, an isolated cell had to discharge over 100 spikes/s for pro-saccades into its RF, 10 ms before to 10 ms after saccade onset. Neural activity was amplified, filtered, and stored by a Plexon multichannel acquisition processor (MAP) system using a headstage with unit gain (Plexon Inc., Dallas, TX, USA). The LFP was extracted with a passband filter (0.7-170 Hz), and further amplified and digitized at 1 kHz. We only included those LFP sites in our analysis where a saccade-related neuron was recorded at the same time. The powerline artifact was removed from 10 s long data segments using a discrete Fourier transform filter that has been previously described (Womelsdorf et al., 2006). Eye movements were recorded at 500 Hz with high-speed infrared video eye tracking (Eyelink II, Kanata, ON, Canada).

3.2.5 Data Analysis

Custom Matlab (The MathWorks Inc., Natick, MA) code using the FieldTrip toolbox (Oostenveld et al., 2011) was used for data analysis. Only recording sessions and neurons that did not show any significant differences in neuronal firing in the 500 ms period before stimulus onset between precool and postcool trials (*t*-test, $p > 0.05$) were analyzed to ensure that stability of the recording did not change during the experimental session.

LFP activity related to the generation of correct and erroneous pro-saccades and anti-saccades was examined using data from the precool period to eliminate the potential for deactivation effects. To examine the effects of DLPFC deactivation on LFP activity, the precool and postcool data when the DLPFC was active (noncool) was compared with the cooling data when the DLPFC was deactivated (cool). This comparison included both correct and error trials.

To evaluate the event-related LFP, the LFP signal was zero-phase filtered using a 3rd order, low-pass Butterworth filter with a cutoff frequency of 30 Hz. Only the LFP signal before saccade initiation was used to avoid ocular artifacts, and a 100 ms baseline window that started 600 ms before stimulus onset was subtracted from the LFP. The event-related LFPs of pro-saccade and anti-saccade trials were averaged separately, and aligned to stimulus and saccade onset.

To compare event-related LFPs to spiking activity, continuous spike density functions were constructed. The activation waveform was obtained by convolving each spike with an asymmetric function that resembled a postsynaptic potential (Hanes and Schall, 1996; Thompson et al., 1996). The advantage of this function over a standard Gaussian function (Richmond and Optican, 1987) is that a spike exerts an effect forward in time, but not backward.

Sliding receiver operating characteristic (ROC) analyses were conducted to highlight differences in event-related LFPs and spiking activity over time. The pro-saccade and anti-saccade task, and the noncool and cool conditions were compared. The ROC value was calculated for a 10 ms window (centered around the time point) starting 200 ms before stimulus onset and repeated in 1 ms increments up to 150 ms after stimulus onset. Bootstrap analyses were used to test the significance of the ROC values. The following procedure was repeated 10000 times: for each recording site or neuron, the 2 active conditions (pro-saccade and anti-saccade, or noncool and cool) were randomly exchanged or unchanged with equal probability (50%), and a single average ROC timecourse was calculated. The 97.5th and 2.5th percentile values of the distribution of 10000 average ROC values at each time point were used to indicate the 5% significance criterion.

Fourier transformations in 334 ms time windows calculated every 50 ms with Slepian sequences as tapers and 4.5 Hz frequency smoothing were used to calculate LFP power from 3 to 60 Hz. LFP power from 60 to 150 Hz was calculated with 24 Hz frequency smoothing. Analyses were conducted on periods of -800 to 200 ms from stimulus onset and -300 to 800 ms from fixation cue onset. For stimulus onset analyses, LFP power was normalized by subtracting the mean power in a 200 ms baseline window that started 1000 ms before stimulus onset and dividing by the standard deviation. For fixation cue onset analyses, LFP power was normalized by subtracting the mean power in a 200 ms baseline window that started 500 ms before fixation cue onset and dividing by the standard deviation.

To test whether power differed significantly between two task conditions, cluster-based nonparametric permutation tests were conducted (Maris and Oostenveld, 2007). T-values were calculated for each time-frequency sample as the test statistic. T-values above a threshold of

alpha = 0.05 were then clustered based on temporal and spectral adjacency and summed for each cluster. The significance of each cluster was determined using a permutation test with 10000 repetitions. To determine whether LFP power could predict the outcome (correct or error) of a trial, ROC analyses were conducted. ROC values were calculated for each time point using mean power in the theta (5-8 Hz), alpha (8-13 Hz), low beta (13-20 Hz), high beta (20-30 Hz), low gamma (30-60 Hz), and high gamma (60-150 Hz) frequency bands. The significance of the ROC values was tested using the same method used for event-related LFPs and spiking activity.

To determine whether there was a relationship between preparatory LFP power and preparatory spiking activity, a period of -800 to -200 ms from stimulus onset was examined. This time period was chosen because it maximized the length of time in the preparatory period while excluding activity from the poststimulus period. For each neuron, the mean power in the theta (5-8 Hz), alpha (8-13 Hz), low beta (13-20 Hz), high beta (20-30 Hz), low gamma (30-60 Hz), and high gamma (60-150 Hz) frequency bands was computed and compared to the average spike rate in the same -800 to -200 ms window. Mean power at each frequency band was correlated with spike rate for each neuron using the Spearman correlation coefficient.

To determine whether there was a relationship between LFP power and saccadic reaction time (SRT), a period of -50 to 50 ms from stimulus onset was examined. This period was the same as the prestimulus period previously used for single neuron activity (Koval et al., 2011) and can detect oscillations in the high beta, low gamma, and high gamma frequency bands. Lower frequency bands were not examined due to the lack of sensitivity of this time period to detect low frequency oscillations. For each trial, the mean power in the high beta, low gamma, and high gamma frequency bands was computed for the prestimulus period. Trials and the associated SRTs were divided into five equal sized bins based on the magnitude of mean power. A one-way

ANOVA was used to test whether SRTs were significantly different between the power bins (Haegens et al., 2011). This analysis was also conducted for preparatory LFP power using the period -800 to -200 ms from stimulus onset.

3.3 Results

Over a total of 52 experimental sessions, LFPs from 26 LFP sites and 35 SC neurons were included in the analyses (15 LFP sites and 20 neurons from the first monkey, and 11 LFP sites and 15 neurons from the second monkey). The effects of bilateral DLPFC deactivation on error rates and reaction times have previously been reported in detail by Koval et al. (2011). Briefly, DLPFC deactivation increased error rates on anti-saccade trials, and increased SRTs on anti-saccade and pro-saccade trials (Table 3.1). In this study, we present LFP activity and spiking activity related to the LFP.

3.3.1 Event-related LFPs Respond to Stimulus Presentation

Figure 3.2 shows event-related LFPs aligned to stimulus onset for the rule visible task. On trials where the stimulus was presented into the response field (RF) of LFP sites, pro-saccade trials showed a significantly greater stimulus-related response than anti-saccade trials, starting 58 ms after stimulus onset (Fig. 3.2A, Fig. 3.3A, red line). In contrast, on trials where the stimulus was presented opposite to the RF, anti-saccade trials showed a significantly greater response than pro-saccade trials, starting 92 ms after stimulus onset (Fig. 3.2B, Fig. 3.3B, red line). There were no significant differences between pro-saccade and anti-saccade trials before stimulus onset.

Table 3.1. Behavioural effects of DLPFC deactivation.

	Prosaccades				Antisaccades			
	Rule visible		Rule memorized		Rule visible		Rule memorized	
	Noncool	Cool	Noncool	Cool	Noncool	Cool	Noncool	Cool
Monkey 1								
Error (%)	3.4	0.5	18.6	7.7	6.9	22.2	20.7	42.5
SRT (ms)	187.8	199.4	206.9	205.5	209.7	254.3	200.5	241.2
Monkey 2								
Error (%)	0.1	0.1	14.0	15.8	1.0	2.0	8.6	13.1
SRT (%)	154.6	174.7	184.4	236.5	188.9	215.7	194.1	232.7
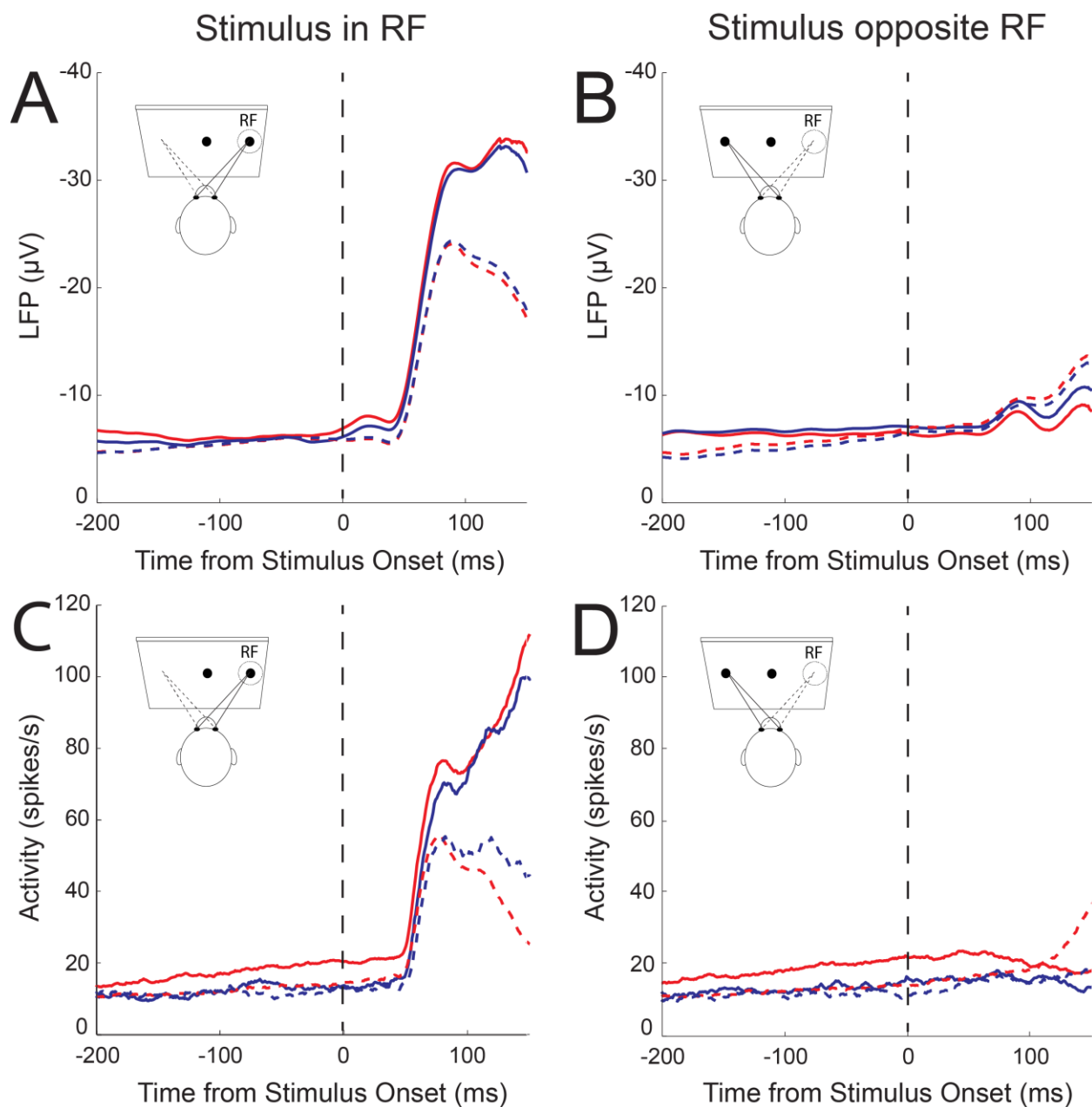
Figure 3.2. Event-related LFPs and spike density aligned to stimulus onset. *A*, Mean LFP on noncool (red lines) and cool trials (blue lines) for pro-saccade (solid lines) and anti-saccade trials (dashed lines) in which the stimulus was presented into the RF of recording sites (correct and error trials combined). *B*, Same as *A*, but for pro-saccade and anti-saccade trials in which the stimulus was presented opposite to the RF of recording sites. *C*, *D*, Same as *A* and *B*, but for mean spike density.
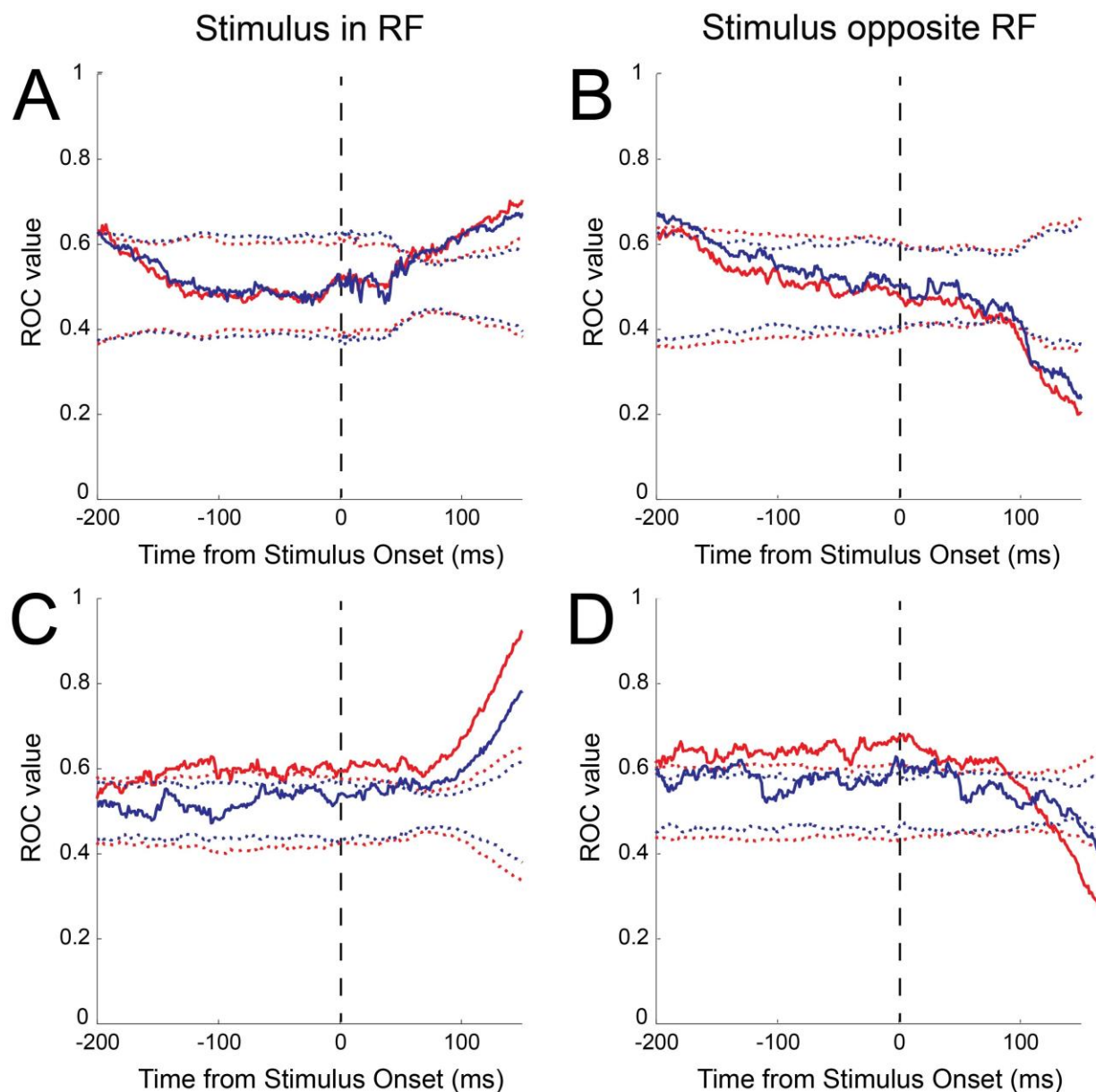
Figure 3.3. ROC time course for event-related LFPs and spike density aligned to stimulus onset. *A*, Time course of average population ROC values for the comparison of anti-saccade trials with pro-saccade trials in which the stimulus was presented into the RF of LFP sites. Dotted lines represent percentile values obtained from a bootstrap analysis. Periods in which the solid lines (red for noncool, blue for cool) lay above or below the dotted lines indicate periods with significant differences ($p < 0.05$). *B*, Same as *A*, but for pro-saccade and anti-saccade trials in which the stimulus was presented opposite to the RF of recording sites. *C*, *D*, Same as *A* and *B*, but for mean spike density.

There were no significant differences between DLPFC cooling (blue lines) and noncooling trials (red lines).

Similar to the event-related LFPs, pro-saccade trials showed significantly greater stimulus-related spiking activity than anti-saccade trials when the stimulus was presented into the RF (Fig. 3.2C). Unlike the event-related LFPs, this difference was significant as early as 165 ms before stimulus onset (Fig. 3.3C, red line). For trials where the stimulus was presented opposite to the RF, anti-saccade trials showed a significantly greater response than pro-saccade trials, starting 118 ms after stimulus onset (Fig. 3.2D, Fig. 3.3D, red line). Koval et al. (2011) found that DLPFC deactivation significantly decreased prestimulus activity for both pro-saccades and anti-saccades. While DLPFC deactivation did not affect activity after stimulus onset on pro-saccade trials, neurons remained active longer on anti-saccade trials (Koval et al., 2011). Aligning event-related LFPs to saccade onset demonstrated that the event-related LFPs were dominated by stimulus presentation. The LFP decreased prior to saccade onset for both pro-saccade and anti-saccade trials regardless of stimulus location, whereas spiking activity showed a prominent saccade-related motor burst (Fig. 3.4)

3.3.2 LFP Power and Task Performance

The rule memorized task required that the task instruction be held briefly in working memory and had a greater cognitive demand than the rule visible task, where the task instruction was visible throughout the task. Here, we examined whether or not this increased cognitive demand is reflected in SC LFP activity. LFP power before cooling was not significantly different between the rule visible task and rule memorized task, for pro-saccades and anti-saccades into and opposite to the RF of LFP sites ($p > 0.05$). In addition, power was not significantly different

Figure 3.4. Event-related LFPs and spike density aligned to saccade onset. *A*, Mean LFP on noncool (red lines) and cool trials (blue lines) for pro-saccade (solid lines) and anti-saccade trials (dashed lines) in which the stimulus was presented into the RF of recording sites (correct and error trials combined). *B*, Same as *A*, but for pro-saccade and anti-saccade trials in which the stimulus was presented opposite to the RF of recording sites. *C*, *D*, Same as *A* and *B*, but for mean spike density.
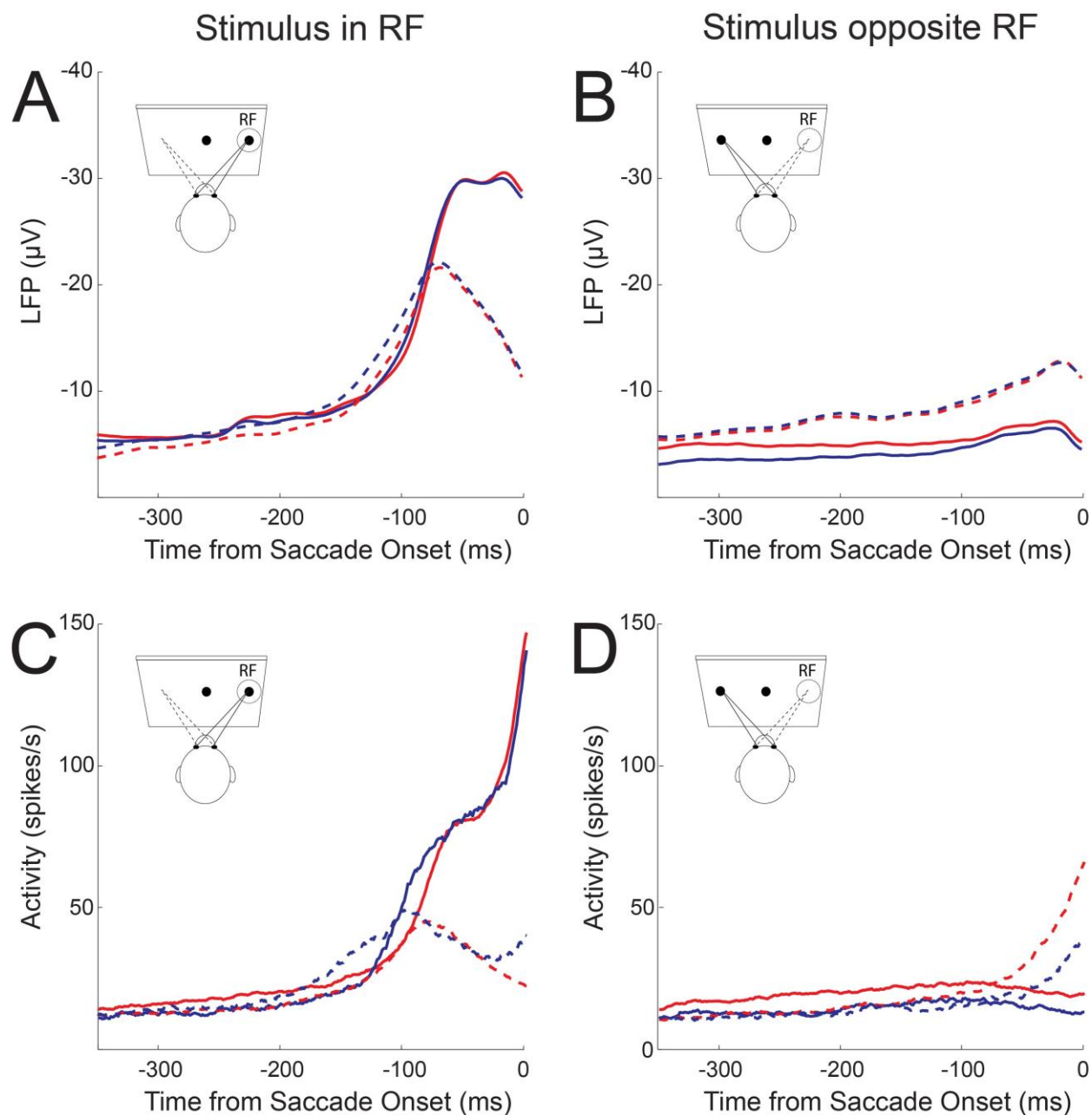
between pro-saccades and anti-saccades or for saccade direction, for both the rule visible and rule memorized tasks ($p > 0.05$).

Figure 3.5 shows the average evolution of LFP power for correct and error trials in the pro-saccade and anti-saccade conditions during the precool period in the rule memorized task. The evolution of LFP power for high gamma (60-150 Hz) is shown in Figure 3.6. LFP activity was prominent after stimulus onset for correct pro-saccades and anti-saccades into and opposite to the RF of LFP sites, in the theta (5-8 Hz), alpha (8-13 Hz), low beta (13-20 Hz), high beta (20-30 Hz), low gamma (30-60 Hz), and high gamma (60-150 Hz) frequency bands. This activity was diminished for erroneous pro-saccades and anti-saccades. Contrasts of these time-frequency plots were performed to examine LFP power related to correct and erroneous pro-saccade and anti-saccade generation.

Overall, correct saccades were associated with higher power at the time of stimulus onset than erroneous saccades. Specifically, correct pro-saccades into the RF of LFP sites had significantly higher power in the theta, alpha, low beta, high beta, and low gamma frequency bands around the time of stimulus onset ($p < 0.05$) (Fig. 3.5A). Correct pro-saccades opposite to the RF had significantly higher power in the low beta and high beta frequency bands after stimulus onset (Fig. 3.5B), and in the high gamma frequency band around the time of stimulus onset (Fig. 3.6B) ($p < 0.05$). Correct anti-saccades into the RF had significantly higher power in the theta, alpha, and low beta frequency bands after stimulus onset ($p < 0.05$) (Fig. 3.5C). Correct anti-saccades opposite to the RF had significantly higher power in the alpha and low beta frequency bands from 350 ms to 150 ms before stimulus onset (Fig. 3.5D), and in the high gamma frequency band around the time of stimulus onset (Fig. 3.6D) ($p < 0.05$). These
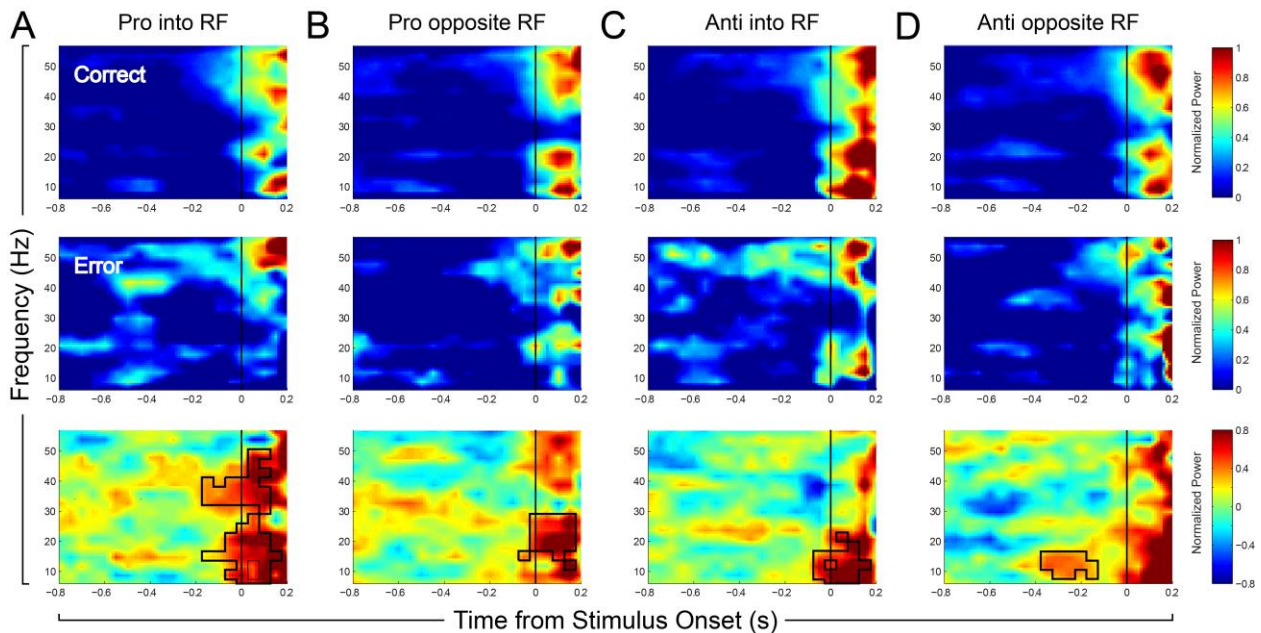
Figure 3.5. LFP power spectrograms for correct and error trials. *A*, Average time-frequency evolution of normalized LFP power aligned to stimulus onset for correct (top) and error (middle) pro-saccade trials into the RF of LFP sites during the precool period in the rule memorized task. Difference in normalized power for correct trials minus error trials is shown (bottom) with black lines outlining areas of significance ($p < 0.05$). *B*, *C*, *D*, Same as *A*, but for pro-saccade trials opposite the RF, anti-saccade trials into the RF, and anti-saccade trials opposite the RF respectively.
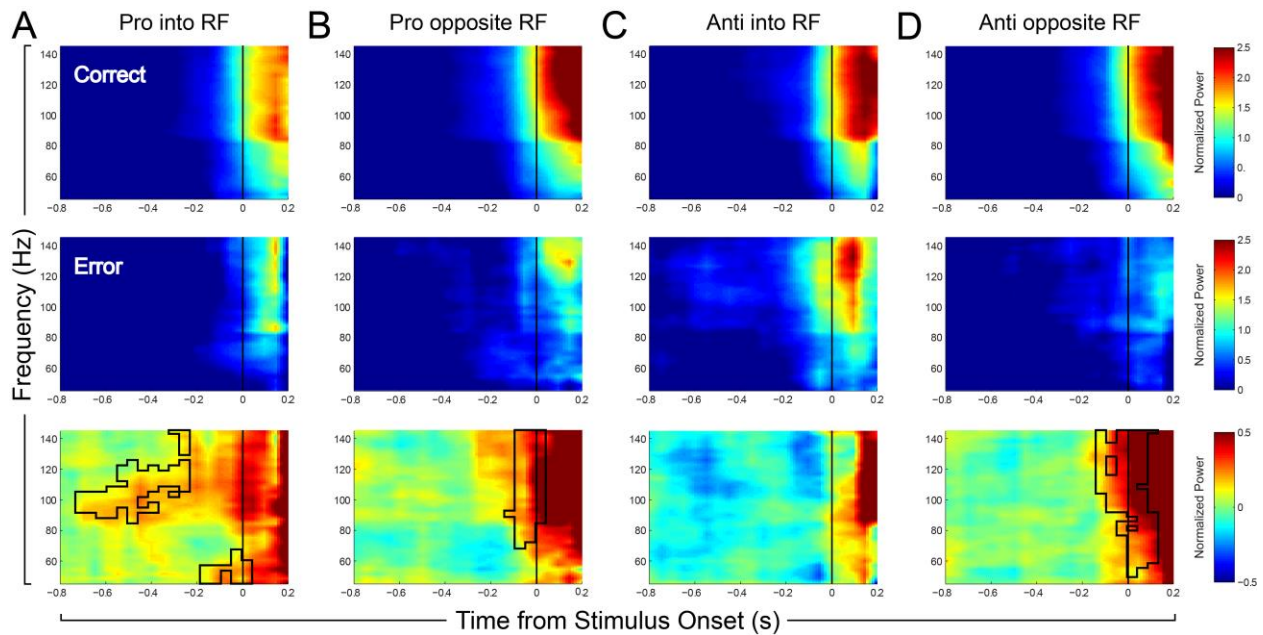
Figure 3.6. LFP power spectrograms for correct and error trials for frequencies in high gamma. *A*, Average time-frequency evolution of normalized LFP power aligned to stimulus onset for correct (top) and error (middle) pro-saccade trials into the RF of recording sites during the precool period in the rule memorized task. Difference in normalized power for correct trials minus error trials is shown (bottom) with black lines outlining areas of significance ($p < 0.05$). *B*, *C*, *D*, Same as *A*, but for pro-saccade trials opposite the RF, anti-saccade trials into the RF, and anti-saccade trials opposite the RF respectively.

differences between correct and erroneous pro-saccades and anti-saccades were not observed

during the cooling period in the lower frequency bands ($p > 0.05$) (Figure 3.7). ROC analyses

showed that the outcome of a trial can be predicted by LFP power in the same frequency bands

and time periods that showed significant differences based on cluster-based nonparametric

permutation tests (Figure 3.8).

3.3.3 DLPFC Deactivation Reduces Beta and Gamma Power

Figure 3.9 shows the average evolution of LFP power aligned to stimulus onset for pro-

and anti-saccade trials during the noncool and cool periods in the rule visible and rule

memorized tasks. The evolution of LFP power for high gamma (60-150 Hz) is shown in Figure

3.10. LFP activity was prominent after stimulus onset for pro-saccades and anti-saccades during

the noncool and cool periods, in the theta, alpha, low beta, high beta, low gamma, and high

gamma frequency bands. To examine LFP power related to DLPFC deactivation, LFP power

during the noncool period was contrasted with LFP power during the cool period. DLPFC

activity may be particularly important for maintaining task rules in working memory in the rule

memorized task. Contrasts using only trials during the precool period were very similar to

contrasts using only trials during the postcool period (Fig. 3.11); therefore, trials during the

precool and postcool periods were combined (noncool). Similarly, contrasts using only trials into

the RF were very similar to contrasts using only trials opposite to the RF, and trials into and

opposite to the RF were combined.

Pro-saccade and anti-saccade trials showed differences before stimulus onset (Fig. 3.9,

Fig. 3.10, bottom). In particular, pro-saccades and anti-saccades during the cool period in both

Figure 3.7. LFP power spectrograms for correct and error trials during the cool period. *A*, Average time-frequency evolution of normalized LFP power aligned to stimulus onset for correct (top) and error (middle) pro-saccade trials into the RF of LFP sites during the cool period in the rule memorized task. Difference in normalized power for correct trials minus error trials is shown (bottom) with black lines outlining areas of significance ($p < 0.05$). *B*, *C*, *D*, Same as *A*, but for pro-saccade trials opposite the RF, anti-saccade trials into the RF, and anti-saccade trials opposite the RF respectively.
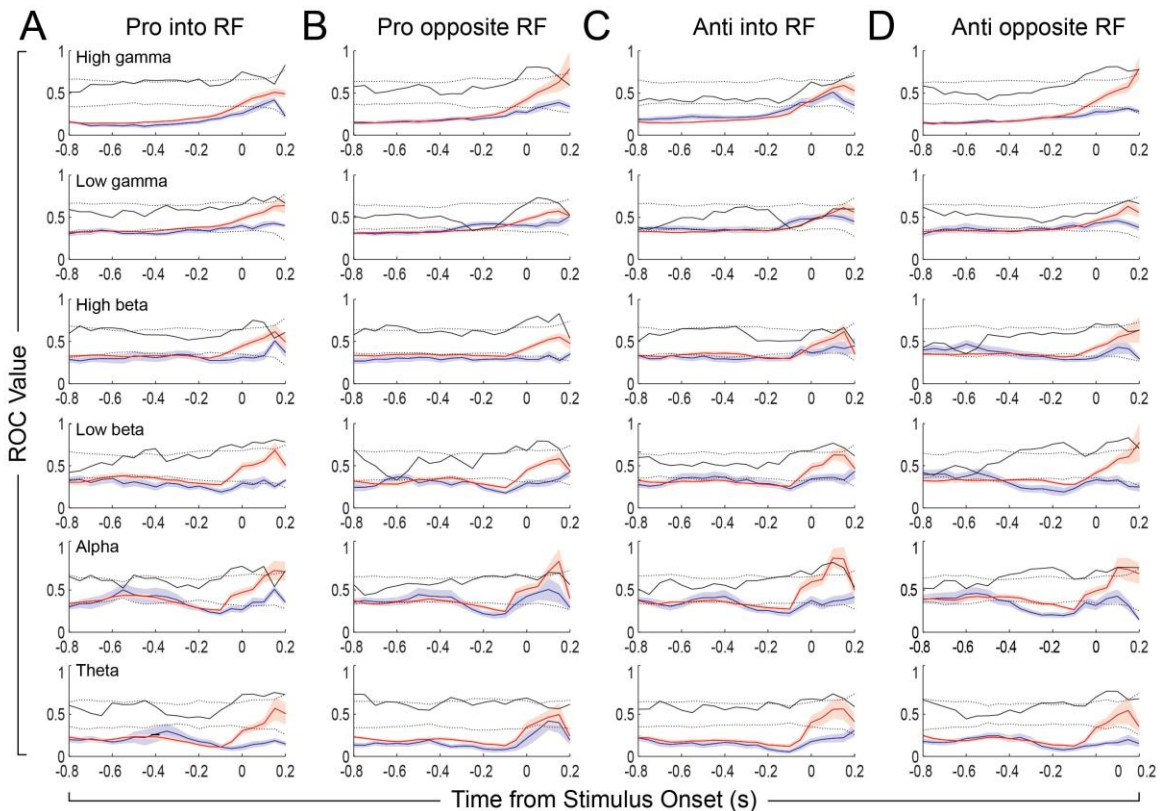
Figure 3.8. ROC time course for normalized LFP power in frequency bands. *A*, Time course of average population ROC values for the comparison of correct trials with error trials, for pro-saccade trials into the RF of LFP sites during the precool period in the rule memorized task (black line). Dotted lines represent percentile values obtained from a bootstrap analysis. Periods in which the black lines lay above or below the dotted lines indicate periods with significant differences (*p* < 0.05). Time courses of mean normalized power for correct trials (red line) and erroneous trials (blue line) are overlayed, with shaded areas indicating standard error of the mean. *B*, *C*, *D*, Same as *A*, but for pro-saccade trials opposite the RF, anti-saccade trials into the RF, and anti-saccade trials opposite the RF respectively.
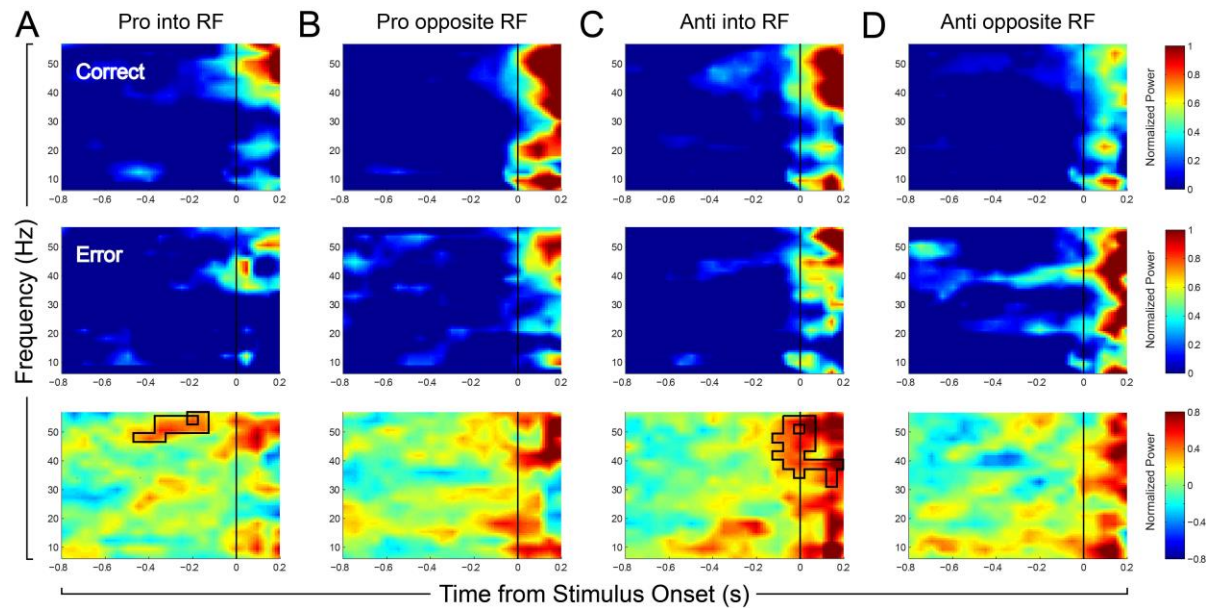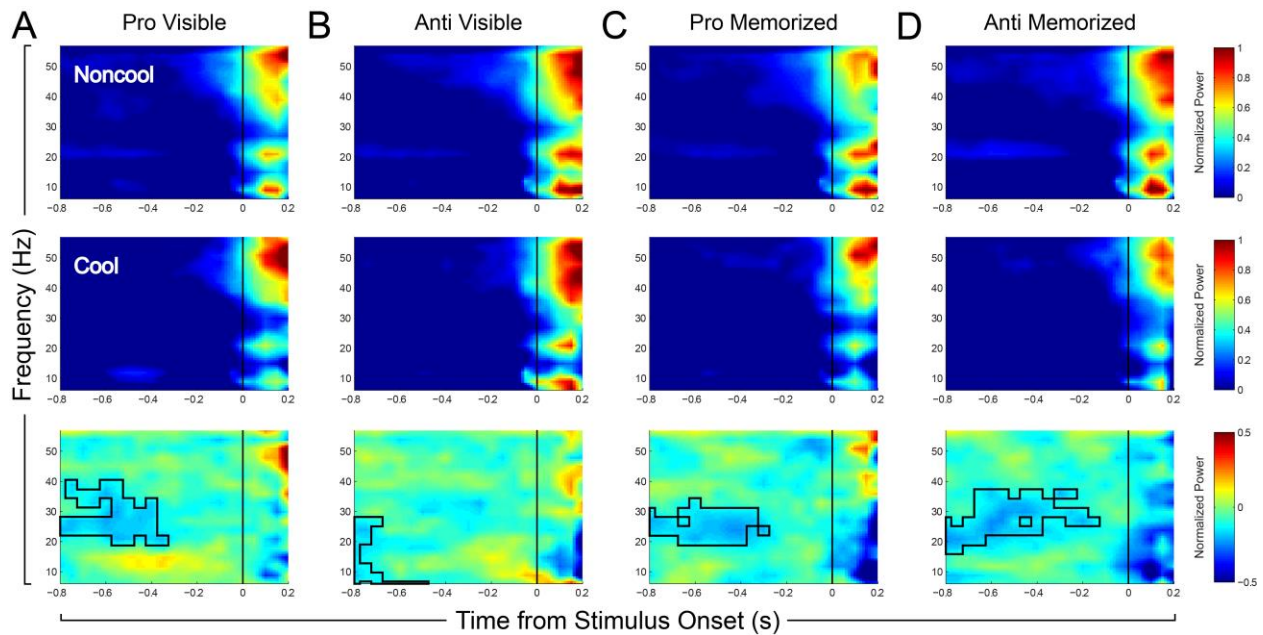
Figure 3.9. LFP power spectrograms for noncool and cool trials aligned to stimulus onset. *A*, Average time-frequency evolution of normalized LFP power aligned to stimulus onset for pro-saccade trials during the noncool (top) and cool (middle) periods in the rule visible task (correct and error trials combined, saccades into and opposite to the RF of LFP sites combined). Difference in normalized power for cool trials minus noncool trials is shown (bottom) with black lines outlining areas of significance ($p < 0.05$). *B*, *C*, *D*, Same as *A*, but for anti-saccade trials in the rule visible task, pro-saccade trials in the rule memorized task, and anti-saccade trials in the rule memorized task respectively.
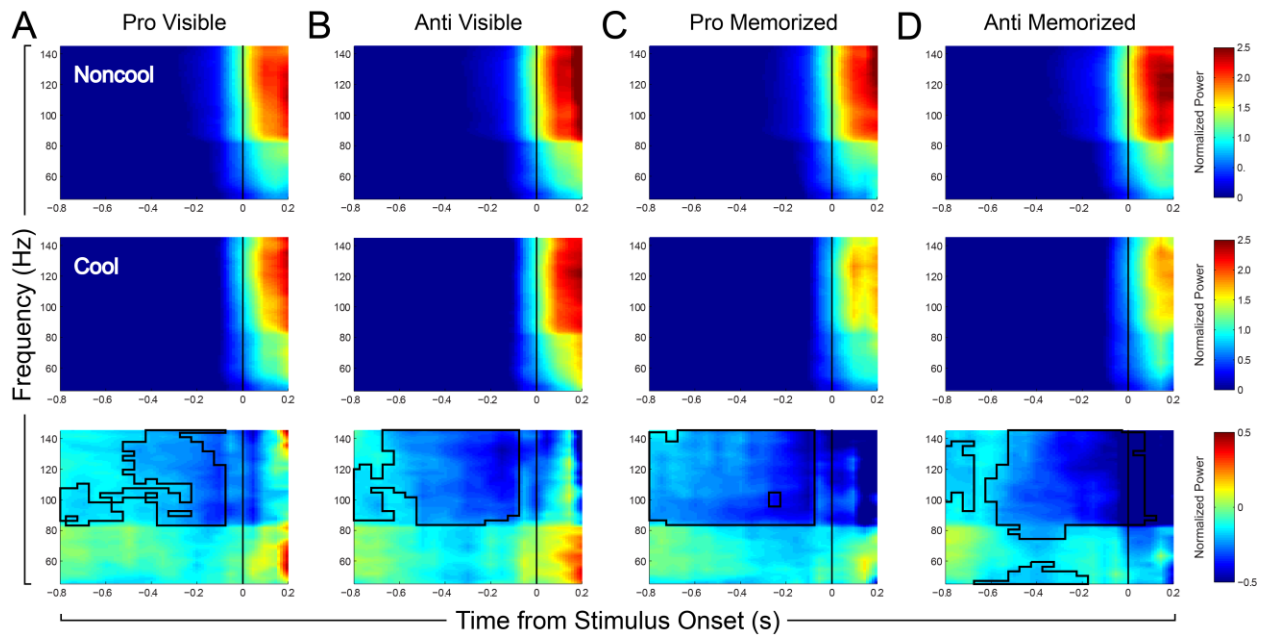
Figure 3.10. LFP power spectrograms for noncool and cool trials aligned to stimulus onset for frequencies in high gamma. *A*, Average time-frequency evolution of normalized LFP power aligned to stimulus onset for pro-saccade trials during the noncool (top) and cool (middle) periods in the rule visible task (correct and error trials combined, saccades into and opposite to the RF of LFP sites combined). Difference in normalized power for cool trials minus noncool trials is shown (bottom) with black lines outlining areas of significance ($p < 0.05$). *B*, *C*, *D*, Same as *A*, but for anti-saccade trials in the rule visible task, pro-saccade trials in the rule memorized task, and anti-saccade trials in the rule memorized task respectively.
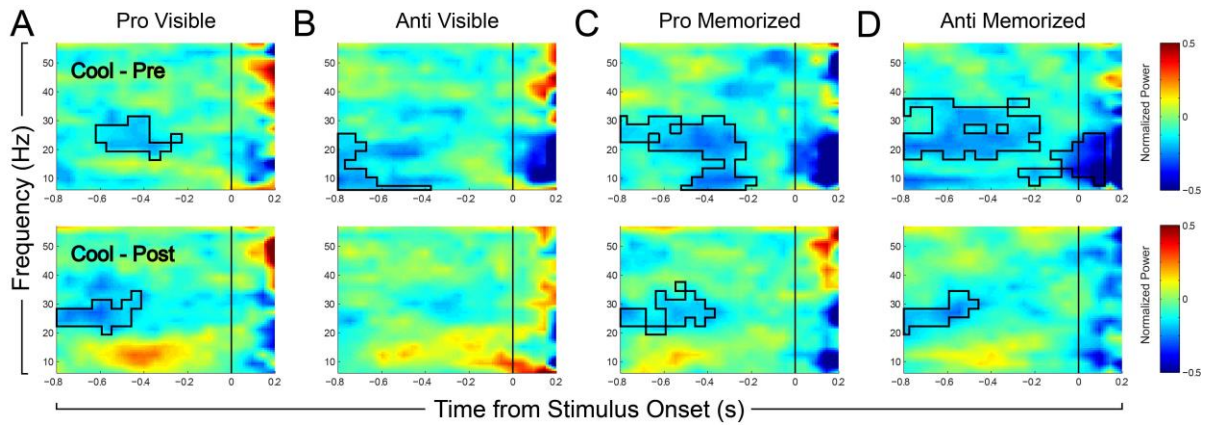
Figure 3.11. Differences in normalized power for cool trials minus precool trials and cool trials minus postcool trials. *A*, Difference for pro-saccade trials in the rule visible task, with black lines outlining areas of significance ($p < 0.05$). *B*, *C*, *D*, Same as *A*, but for anti-saccade trials in the rule visible task, pro-saccade trials in the rule memorized task, and anti-saccade trials in the rule memorized task respectively.

the rule visible and rule memorized tasks had significantly lower power in the high beta frequency band starting from 800 ms before stimulus onset ($p < 0.05$). Power was also lower in the high gamma frequency band starting from 800 ms before stimulus onset ($p < 0.05$). There were no significant differences in the rule visible and rule memorized tasks between the noncool and cool periods after stimulus onset in any frequency band ($p > 0.05$). Cooling affected LFP power in the rule visible task and rule memorized task similarly.

To determine whether the decrease in high beta power was dependent or independent of task preparation, LFP power was aligned to the onset of the coloured fixation point which conveyed the task rule for the upcoming trial. Figure 3.12 shows the average evolution of LFP power aligned to fixation cue onset for pro-saccade and anti-saccade trials during the noncool and cool periods in the rule visible and rule memorized tasks. LFP activity was prominent after cue onset for pro-saccades and anti-saccades during the noncool period, in the theta, alpha, low beta, high beta, and low gamma frequency bands. Activity in the low beta and high beta frequency bands was diminished for pro-saccades and anti-saccades with DLPFC deactivation. As with stimulus onset, LFP power related to DLPFC deactivation was examined by contrasting LFP power during the noncool period with LFP power during the cool period, with trials into and opposite to the RF combined.

Pro-saccade and anti-saccade trials during the cool period in the rule visible and rule memorized tasks showed significantly lower power in the low beta and high beta frequency bands in the 300 ms period after fixation cue onset ($p < 0.05$) (Fig. 3.12, bottom). This coincided with the prominent LFP activity seen in Figure 3.12 (top). For pro-saccades in the rule memorized task and anti-saccades in the rule visible and rule memorized task, the significant
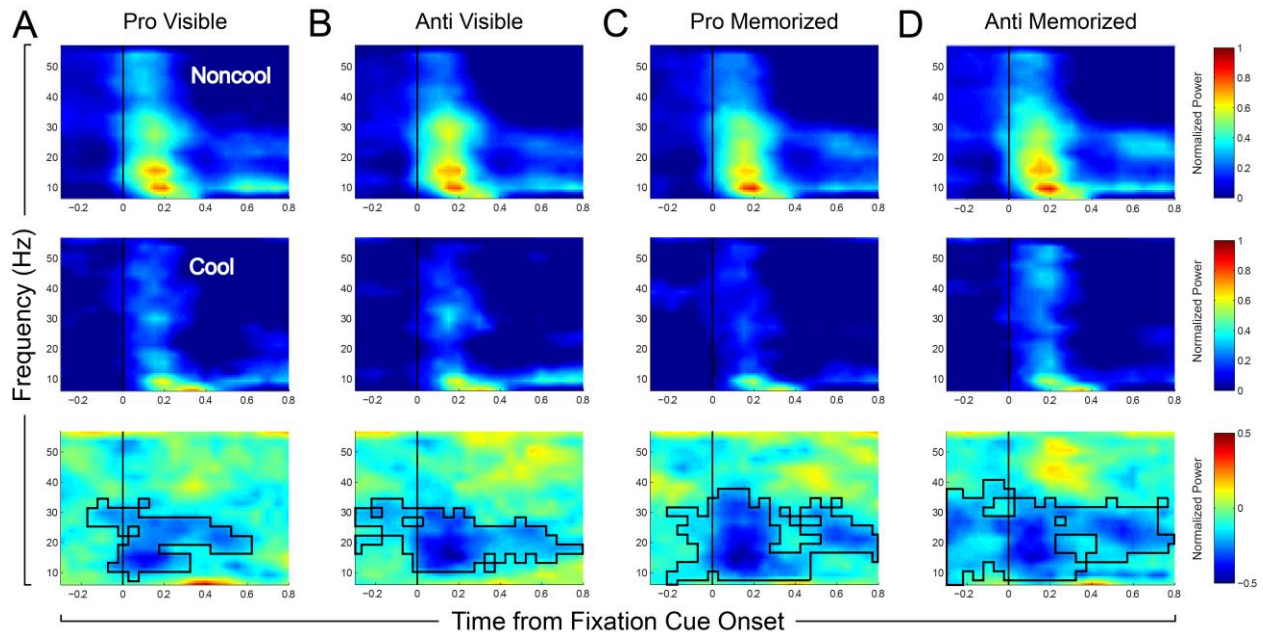
Figure 3.12. LFP power spectrograms for noncool and cool trials aligned to fixation cue onset. *A*, Average time-frequency evolution of normalized LFP power aligned to fixation cue onset for pro-saccade trials during the noncool (top) and cool (middle) periods in the rule visible task (correct and error trials combined, saccades into and opposite to the RF of LFP sites combined). Difference in normalized power for cool trials minus noncool trials is shown (bottom) with black lines outlining areas of significance ($p < 0.05$). *B*, *C*, *D*, Same as *A*, but for anti-saccade trials in the rule visible task, pro-saccade trials in the rule memorized task, and anti-saccade trials in the rule memorized task respectively.

decrease in beta power persisted beyond 300 ms after fixation onset ($p < 0.05$). The contrasts also show that high beta power was significantly decreased during the cool period already before fixation cue onset for pro- and anti-saccades. This finding indicates that high beta power was decreased during DLPFC cooling before the task instruction was presented.

3.3.4 DLPFC Deactivation Reduces Correlations Between Spiking Activity and Gamma Power

LFP activity may reflect neuronal processes that influence the spike rate of neurons. Figure 3.13 shows the proportion of SC neurons with spike rates that were significantly positively or negatively correlated with LFP power during the preparatory period (800 to 200 ms before stimulus onset, see Methods). During the noncool and cool periods, more neurons were significantly positively correlated than negatively correlated with spike rate at the low gamma and high gamma frequency bands ($\chi^2_{(1)} > 4.3$ and $p < 0.05$ for all comparisons). DLPFC deactivation significantly decreased the proportion of positively correlated neurons at these frequency bands ($\chi^2_{(1)} > 4.2$ and $p < 0.05$ for all comparisons). Significant differences between proportions of neurons with positive correlations and negative correlations were not observed for the theta, alpha, low beta, and high beta frequency bands. Overall, 77.1% of the neurons recorded (27/35) had spike rates that were significantly correlated with LFP power.

3.3.5 LFP Power and SRT

Previous studies (Dorris et al., 1997; Everling et al., 1999) have examined the relationship between single neuron activity and SRT for pro- and anti-saccades, but not the
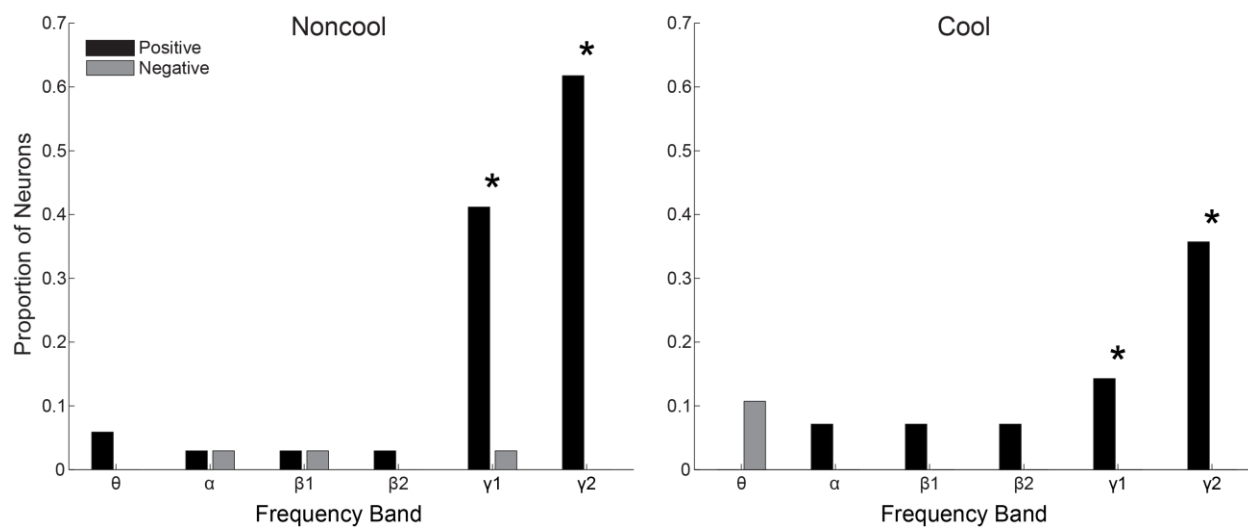
Figure 3.13. Proportion of neurons with spike rates that were significantly positively or negatively correlated with LFP power during the preparatory period in the theta (5-8 Hz), alpha (8-13 Hz), low beta (13-20 Hz), high beta (20-30 Hz), low gamma (30-60 Hz), and high gamma (60-150 Hz) frequency bands, for noncool and cool trials. Asterisks indicate a significant difference between proportions of neurons with positive correlations and negative correlations in a frequency band.
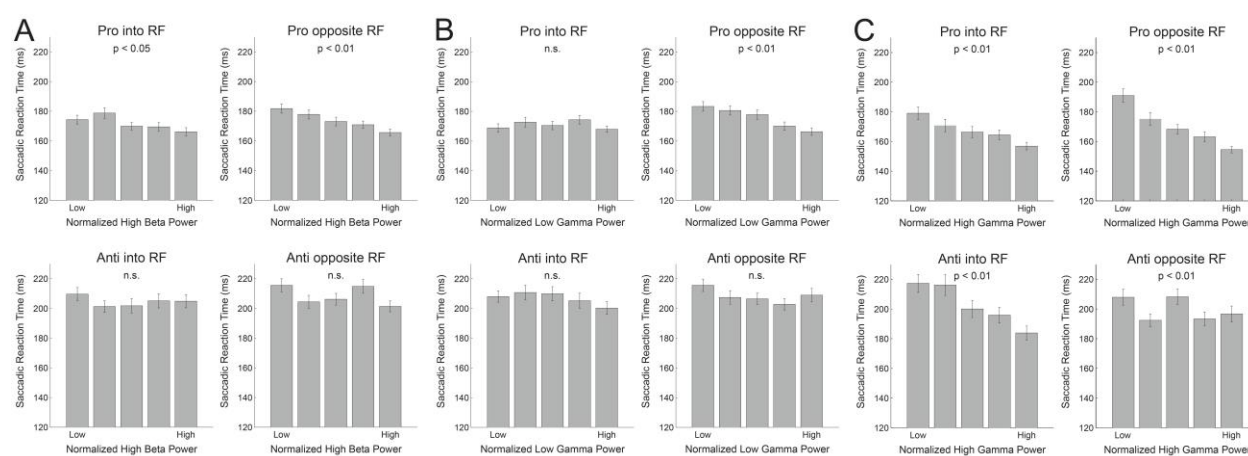
Figure 3.14. Relationship between LFP power and SRT. *A*, Mean SRTs for five equal sized high beta power bins for pro-saccades and anti-saccades into and opposite to the RF of LFP sites. *B*,*C*, Same as *A*, but for low gamma and high gamma power respectively.

relationship between LFP power and SRTs. Figure 3.14 shows the relationship between LFP power -50 to 50 ms from stimulus onset and SRTs. For high beta, SRTs decreased as power increased for pro-saccades into the RF ($p < 0.05$) and opposite to the RF ($p < 0.01$) (Fig. 3.14A). For low gamma, SRTs decreased as power increased for pro-saccades opposite to the RF ($p < 0.01$) (Fig. 3.14B). For high gamma, SRTs decreased as power increased for pro-saccades and anti-saccades into the RF and opposite to the RF ($p < 0.01$) (Fig. 3.14C). During the cool period, only SRTs for anti-saccades opposite to the response field decreased as high gamma power increased ($p < 0.05$). While increases in power at short SRTs may be explained by the infringement of saccade-evoked potentials -50 to 50 ms from stimulus onset, this is unlikely as significant relationships between power and SRT were found for saccades opposite to the RF. During the preparatory period, SRTs for pro-saccades into the RF decreased as high beta power increased and SRTs for pro-saccades opposite to the RF decreased as high gamma power increased ($p < 0.01$).

3.4 Discussion

The DLPFC has been implicated to be involved in encoding rules and biasing other brain areas to execute the appropriate task (Miller and Cohen, 2001). While the DLPFC has been shown to send task-selective signals to the SC (Johnston and Everling, 2006b) and modulate SC neural activity (Koval et al., 2011; Johnston et al., 2014), how it does so is poorly understood. In this study, we characterized LFP activity in the SC during an interleaved pro- and anti-saccade task, and investigated the effects of bilateral DLPFC deactivation on LFP activity. We found that event-related LFPs showed stimulus-related differences between pro-saccades and anti-saccades, and LFP power distinguished between correct and erroneous saccades. While event-related LFPs

were not affected by DLPFC deactivation, DLPFC deactivation reduced beta and high gamma power during the preparatory period. In addition, the positive correlation between gamma power and spike rate during the preparatory period was attenuated by DLPFC deactivation. Overall, these results demonstrate that neuronal oscillations may mediate communication between the DLPFC and SC.

In contrast to spiking single neuron activity associated with saccade generation (Wurtz and Goldberg, 1972; Sparks et al., 1976; Munoz and Wurtz, 1995), almost nothing is know about LFPs in the SC. Whereas spiking activity represents the output of a single neuron, LFP activity reflects the synchronized synaptic activity of a group of neurons (Buzaki et al., 2012). LFP activity consequently provides different and complementary information about neuronal processing. Accordingly, we found that although event-related LFPs like single neuron activity showed a greater stimulus-related response for pro-saccades compared to anti-saccades (Everling et al., 1999), event-related LFPs were dominated by the stimulus-related response. This finding indicates that event-related LFPs in the SC primarily reflect the incoming visual signal, rather than the motor signal for the saccade.

While LFP power did not differentiate between pro- and anti-saccades, higher power was observed around stimulus onset for correct compared to error trials. Correct pro-saccades into the RF had greater power in the theta, alpha, low beta, high beta, and low gamma frequency bands. This is consistent with a report of LFPs in the human SC while subjects fixated on a central fixation point or made horizontal saccades (Liu et al., 2009). Although Liu et al. (2009) did not use a task that produced errors, they found that theta and alpha power increased during saccade generation. Beta activity has been implicated in processing for motor control (Engel and Fries, 2010) and low gamma activity may represent local neuronal processing (Kopell et al., 2000;

Fries, 2005). Taken together, LFP activity may facilitate the processing of incoming information to the SC. In particular, neuronal oscillations may enable fixation-related and saccade-related neurons throughout the SC to receive the appropriate temporal and spatial information required for saccade generation. This coordination of information may be critical for determining which neurons increase spiking output, how much spiking is generated, and when changes in spiking occur. Thus, LFP activity may reflect the modulation of single neuron activity to correctly generate a saccade toward a visual stimulus.

Compared to pro-saccades, anti-saccades emphasize greater cognitive control. They require the suppression of a prepotent saccade toward a stimulus and the generation of a voluntary saccade in the opposite direction (Everling and Fischer, 1998; Munoz and Everling, 2004). Here, higher power for correct compared to erroneous anti-saccades was limited to the lower frequency bands: theta, alpha, and low beta for anti-saccades into the RF, and alpha and low beta for anti-saccades opposite to the RF. Indeed, alpha activity has been proposed to be involved in inhibition (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Haegens et al., 2011) whereas beta activity may be involved in motor set maintenance (Engel and Fries, 2010). In particular, Swann et al. (2009) found that in a stop-signal task alpha and beta power decreased in motor cortex for both successful and unsuccessful stop trials, but the effect was less pronounced for successful trials. This relative increase in power was proposed to be related to increased GABA inhibition. Thus, the power increases observed for correct anti-saccades could be related to inhibitory processes in the SC. Given the role of alpha activity in inhibition and beta activity in motor set maintenance, increased power may also reflect saccade generation under a general state of increased cognitive control.

The DLPFC is implicated in the cognitive control of pro-saccades and anti-saccades and has been shown to send task-selective signals that bias neural activity in the SC (Johnston and Everling, 2006a, 2006b; Koval et al., 2011; Johnston et al., 2014). While bilateral DLPFC deactivation affected post-stimulus spiking activity in the SC (Koval et al., 2011), effects were not observed for LFP activity, thereby highlighting further differences between spiking and LFP activity. Nonetheless, deactivation decreased both spiking and beta activity during the preparatory period for pro-saccades and anti-saccades. This coincided with increased reaction times for both tasks and supports our recent proposal that the DLPFC does not inhibit but excite the SC (for review see Everling and Johnston, 2013). The LFP results are consistent with studies that suggest a role for the DLPFC in task preparation (Desouza et al., 2003; Ford et al., 2005; Brown et al., 2007), and studies by Condy et al. (2007), Wegener et al. (2008), and Johnston et al. (2014) that manipulated the DLPFC unilaterally using pharmacological deactivation, microstimulation, and cryogenic deactivation respectively. Taken together, these findings indicate that DLPFC deactivation impairs the ability to establish and maintain the appropriate task rule.

In the DLPFC, task rules are represented in the spiking activity of single neurons (White and Wise, 1999; Asaad et al., 2000; Wallis et al., 2001; Everling and DeSouza, 2005), the activity of neural populations (Stokes et al., 2013), and LFP activity (Buschman et al., 2012). In particular, Buschman et al. (2012) showed that task-specific neural ensembles were formed by increases in synchrony in the high beta frequency band. The role of beta activity in task representation is supported by findings that prefrontal beta oscillations are involved in working memory (Siegel et al., 2009; Salazar et al., 2012; Spitzer et al., 2013) and the maintenance of cognitive sets (Engel and Fries, 2010). Here we found that beta power was already reduced

before the onset of the fixation stimulus, which conveyed the specific task instruction. Therefore, DLPFC deactivation seems to reduce high beta power in the SC independent of a specific task preparation.

Beta activity is increased in top-down control (Buschman and Miller, 2007; Siegel et al., 2013) and is thought to mediate communication between distant brain areas through synchrony (Kopell et al., 2000; Fries, 2005). While synchrony between the DLPFC and SC was not investigated in this study, cortical-subcortical coupling in the beta frequency band has been shown for the subthalamic nucleus (Lalo et al., 2008). Thus, persistent communication between the DLPFC and the SC may be mediated by beta oscillations.

Changes in neuronal oscillations may reflect processes that influence neural activity. Accordingly, LFP power has been correlated with neuronal spiking (Pesaran et al., 2002; Rasch et al., 2008; Manning et al., 2009). While spiking was correlated with low gamma power during the preparatory period, differences in power in this frequency band were not observed. Low gamma oscillations may represent local neuronal processing (Kopell et al., 2000; Fries, 2005) in the SC, regardless of the task being performed or the input received from the DLPFC. On the other hand, spiking was correlated with high gamma power, and DLPFC deactivation decreased preparatory period power in this frequency band. Changes in high gamma power are thought to reflect changes in spiking activity (Ray et al., 2008). The decrease in prestimulus SC spiking activity for pro- and anti-saccades and the decrease in the proportion of neurons correlated with high gamma power with DLPFC deactivation are consistent with this idea. In this study, only the spiking activity of saccade-related neurons was examined. Thus, it is possible that the spiking activity of other types of neurons contributed to the changes observed for high gamma power.

Overall, given that DLPFC deactivation also decreased high beta power, SC neural activity may be modulated by DLPFC-associated beta activity.

Although the DLPFC sends direct projections to the SC (Goldman and Nauta, 1976; Leichnetz et al., 1981), SC LFP activity may also be influenced indirectly. DLPFC deactivation has been shown to affect activity in the thalamus (Alexander and Fuster, 1973). Based on its wide connectivity with other brain areas, the thalamus may actively regulate neural synchrony, particularly using low frequency oscillations (Saalmann and Kastner, 2011). DLPFC deactivation may also affect the frontal eye field (FEF), supplementary eye field, and basal ganglia, which send task-related signals to the SC (Schlag-Rey et al., 1997; Everling and Munoz, 2000; Watanabe and Munoz, 2009). For example, the FEF, shows comparable spiking activity to the SC for pro-saccades and anti-saccades (Everling and Munoz, 2000), and likely receives excitatory input from the DLPFC, given that the majority of corticocortical connections are between excitatory neurons (Bunce and Barbas, 2011). Consequently, the FEF may also show a decrease in beta power with DLPFC deactivation. Overall, the changes observed in SC LFP activity may be due to LFP changes in a broader neural network.

In summary, our results suggest a mechanism by which the DLPFC exerts control on the SC. Decreased beta power during bilateral DLPFC deactivation suggest beta oscillations may play a critical role in mediating communication between the DLPFC and the SC.

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Effects of bilateral dorsal anterior cingulate cortex deactivation on cognitively demanding task performance in macaque monkeys

4.1 Introduction

Cognitive control is required to select goals and guide behaviour to achieve the desired outcomes. This is particularly evident when behaviour is flexibly adapted to swift changes in the external environment and internal goals. The dorsal anterior cingulate cortex (dACC) is thought to be critical to this control. Lesion, functional imaging, and neurophysiological studies have implicated the dACC in a broad range of cognitive functions, including task conflict, action selection, working memory, episodic memory, decision making, problem solving, emotion, and motivation (Duncan and Owen, 2000; Shenhav et al., 2013). Different interpretations of these data have led to several models of dACC function.

One hypothesis proposes that the dACC is involved in conflict monitoring, such that it detects conflict when two or more competing processes are co-activated by a single stimulus (MacDonald et al., 2000; Botvinick et al., 2001; Kerns et al., 2004). Notably, conflict-related signals have not been found with single-neuron recordings in monkeys. Rather, dACC neurons have been shown to respond to correct and erroneous responses or to rewarded and unrewarded responses, and support a role of the dACC in performance monitoring (Shima and Tanji, 1998; Ito et al., 2003; Nakamura et al., 2005). Similarly, the dACC is thought to associate reward and value with actions (Kennerley et al., 2006; Quilodran et al., 2008). Another hypothesis proposes

that the dACC signals error-likelihood and increased cognitive demands (Brown and Braver, 2005; Johnston et al., 2007; Sheth et al., 2012). Taken together, the dACC may integrate reward and cost information to determine how cognitive control is allocated to perform the appropriate task (Shenhav et al., 2013).

The appropriate allocation of cognitive control is particularly important when an individual switches from one task to another. Consequently, task switching has been extensively used to investigate cognitive processing (Allport et al., 1994; Monsell, 2003). Functional neuroimaging studies have consistently shown increased activation of the dACC on trials where the task is switched (Liston et al., 2006; Woodward et al., 2006). Consistent with a role in task switching, task-selective activity in the dACC is strongest after a task switch and declined following repetitions of the same task (Johnston et al., 2007). In addition, lesions to the dACC in monkeys have resulted in impairments in task switching (Rushworth et al., 2003; Kennerley et al., 2006). These lesion studies suggest that impairments in task switching are due to the inability to monitor the outcome of responses and associate value with responses. To further investigate the role of the dACC in task switching, we trained monkeys to perform pro-saccades and anti-saccades.

Pro-saccades, where subjects generate a saccade towards a peripheral stimulus, and anti-saccades, where subjects generate a saccade away from the peripheral stimulus to the mirror opposite location, have been well characterized anatomically and functionally, and extensively used to investigate cognitive control (Hallett, 1978; Munoz and Everling, 2004). With regard to the dACC, task-selective spiking activity and local field potential activity have been found for pro-saccades and anti-saccades, with task selectivity being especially pronounced following an erroneous trial (Johnston et al., 2007; Womelsdorf et al., 2010). In addition, dACC lesions in

humans impair anti-saccade performance (Gaymard et al., 1998), while dACC microstimulation in monkeys facilitates performance by decreasing saccadic reaction times (Phillips et al., 2011). Accordingly, the dACC may facilitate the performance of anti-saccades, which require increased cognitive control to suppress pre-potent pro-saccade behaviour.

In this study, the direct contribution of the dACC to cognitive control and task switching was investigated by reversibly deactivating the dACC bilaterally using chronically implanted cryoloops in the cingulate sulcus. Monkeys performed an uncued switch task, where they acquired the current task rule based on reward feedback after each trial. Monkeys also performed a cued switch task, which eliminated the need to use reward feedback to acquire the current task rule and working memory to maintain it. Here, we report the effects of bilateral dACC deactivation on task switching behaviour, in the context of pro-saccade and anti-saccade performance.

4.2 Materials and Methods

All procedures were conducted in accordance with 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.

4.2.1 Surgical Procedures

Three adult male macaque monkeys (2 *Macaca mulatta* and 1 *Macaca fascicularis*) weighing 6.5-9.5 kg were prepared for chronic deactivation experiments using previously described aseptic surgical procedures (DeSouza and Everling, 2004). For all procedures, animals

received analgesics and antibiotics postoperatively and were closely monitored by a university veterinarian. In the first surgery, a plastic head restraint was implanted using dental acrylic. After the monkeys were trained to perform uncued and cued pro-saccade and anti-saccade switch tasks, they underwent a second surgery in which stainless steel cryoloops (8-10 x 3 mm) were implanted bilaterally into the anterior cingulate sulci. The posterior ends of the cryoloops were placed at the same position on the anterior-posterior axis as the posterior ends of the principal sulci. The dACC (area 24c) was targeted for reversible deactivation. Neurons with task-selective activity for pro-saccades and anti-saccades have been found in this area of the dACC (Johnston et al., 2007). The technical details of the cryoloop surgery and deactivation method have been previously described (Lomber et al., 1999).

4.2.2 Behavioural Task

During the experiment, monkeys performed an uncued pro-saccade and anti-saccade switch task (Fig. 4.1A). Each trial began with the presentation of white central fixation point. Monkeys were required to fixate on the fixation point within a 0.5° x 0.5° window for 1100-1400 ms at the beginning of each trial. Subsequently, the fixation point was extinguished and a peripheral white stimulus (0.15°) was pseudorandomly presented with equal probability 8° to the left or 8° to the right of centre. To receive a liquid reward, monkeys were required to generate a saccade within 500 ms toward the stimulus on pro-saccade trials and away from the stimulus on anti-saccade trials, within a 5° x 5° window. After 15-25 correct trials, the task switched (e.g. from pro-saccades to anti-saccades and vice versa) without any explicit signal to the monkeys. Consequently, monkeys acquired the current task rule by trial and error based on the presence or absence of reward after each trial, and a task switch was required once the previous task was no
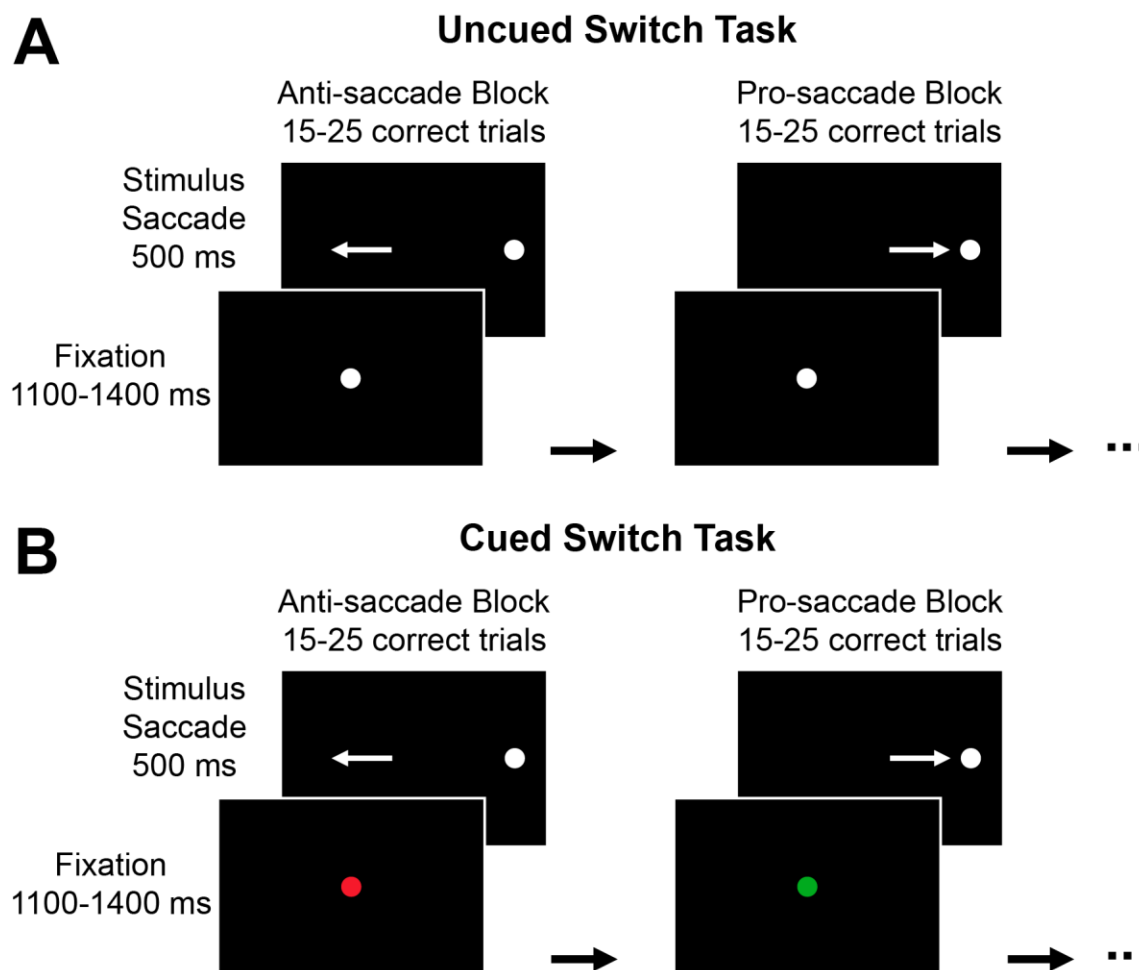
Figure 4.1. Uncued and cued switch tasks. *A*, In the uncued switch task, each trial began with a fixation point that was followed by a peripheral stimulus to the left or right. No explicit instruction was provided to signal the performance of a pro-saccade or anti-saccade and the task switched after 15-25 correct trials were performed. *B*, In the cued switch task, the fixation point signalled a pro-saccade or anti-saccade trial by its colour.

longer rewarded. Monkeys C and T also performed a cued pro-saccade and anti-saccade switch task, where a red or green central fixation point provided instruction for the current task rule in alternating blocks of pro-saccades and anti-saccades (Fig. 4.1B). In contrast to the uncued switch task, monkeys were not required to acquire the current task rule by reward-based feedback or maintain the rule in working memory.

4.2.3 Reversible Cryogenic Deactivation

To deactivate the dACC, methanol was pumped through a cryoloop with Teflon tubing, which passed through a methanol ice bath that was reduced to subzero temperatures by the addition of dry ice. Methanol that passed through the cryoloop was returned to the same reservoir from which it came. Evoked neural activity is absent when cortical tissue is cooled below 20°C. Cryoloop temperature was monitored by an attached thermocouple and maintained at 1-3°C to deactivate as large an area of cortical tissue as possible, while avoiding potentially damaging subzero temperatures at the cortical surface (Lomber et al., 1999). Monkey T was more sensitive to cryogenic deactivation and cryoloop temperature was maintained at 14-15°C. Given that the effective spread of cooling is restricted to about 2 mm on either side of the cryoloop (Payne and Lomber, 1999) and that each cryoloop measured 8-10 x 3 x 2 mm, the volume of deactivated cortex can be approximated by the volume of a box with dimensions 12-14 x 7 x 4 mm, or 336-392 mm³. Thus, cooling of the cryoloops affected the dorsal and ventral banks of the anterior cingulate sulci, corresponding to the rostral cingulate motor area (CMAr) or area 24c.

For monkey M, each cooling session consisted of precool, cool, and postcool periods that were 20 min in duration. A cooling session started with a precool period where the pumps were turned off. The pumps were turned on to start the cool period. The first 4 min after the pumps

were turned on were excluded from all data analysis to ensure that the cortical tissue adjacent to the cryoloops was cooled below 20°C and that neurons were deactivated. At the end of the cool period, the pumps were turned off to start the postcool period. The first 3 min after the pumps were turned off were excluded from all data analysis to ensure that the cortical tissue adjacent to the cryoloops returned to normal body temperature. For monkeys C and T, each cooling session consisted of precool and cool periods that were 30 min in duration to increase the number of trials performed during cooling. A cooling session started with a precool period where the pumps were turned off. The pumps were turned on to start the cool period. The first 4 min after the pumps were turned on were excluded from all data analysis. At the end of the cooling session, the pumps were turned off. In addition, monkeys C and T performed control sessions that consisted of precool and control periods that were 30 min in duration to control for the effects of time and fatigue over the course of a session. During the control period, the pumps were turned on, but methanol was not pumped through the cryoloops and cortical tissue was not deactivated. Each monkey performed an equal number of cooling and control sessions.

4.2.4 Data Analysis

All analyses were performed using custom Matlab (The Mathworks Inc., Natick, MA) code. Pro-saccade trials were defined as correct if a saccade was made toward the location of the peripheral stimulus and as erroneous if a saccade was made to the mirror opposite location. Anti-saccade trials were defined as correct if a saccade was made to the location mirror opposite to the peripheral stimulus and as erroneous if a saccade was made toward the stimulus. Saccade onset was identified as the time at which saccade velocity exceeded 30°/s and saccade offset was identified as the time at which saccade velocity fell below 30°/s. SRT was defined as the time

from stimulus onset to saccade onset. Trials with SRTs below 80 ms or above 500 ms were excluded from further analysis as anticipatory saccades and no response trials respectively.

Time courses for pro-saccade and anti-saccade performance and SRTs before and after a task switch were calculated for each experimental session and averaged for each monkey. In addition, pro-saccade performance and SRTs on the trial immediately following a correct or erroneous pro-saccade trial, and anti-saccade performance and SRTs on the trial immediately following a correct or erroneous anti-saccade trial were calculated. The percentage of skipped, broken fixation, and no response trials was calculated for pro-saccades and anti-saccades as percentages of the total number of correct, erroneous, skipped, broken fixation, and no response trials combined. On skipped trials, the monkey did not initiate fixation of the central fixation point within 2000 ms of its appearance. On broken fixation trials, the monkey initiated fixation, but looked away from the fixation point prior to the onset of the peripheral stimulus. On no response trials, the monkey initiated and maintained fixation, but did not respond within 500 ms of peripheral stimulus onset.

To statistically examine the effects of dACC deactivation on behaviour, the precool and postcool data when the dACC was active (noncool) was compared with the cooling data when the dACC was deactivated (cool) using paired t-tests for monkey M. For monkeys C and T, the precool period in the first 30 min of an experimental session (noncool) was compared to the cool and control periods using two-sample t-tests with p-values corrected for multiple comparisons using false discovery rate estimation. The effects of previous trial reward (correct or error) and dACC condition (noncool or cool) on error rates and SRTs were examined using two-way ANOVA analyses. Paired t-tests for monkey M and two-sample t-tests for monkeys C and T

were used for specific comparisons within previous trial reward and dACC condition, with p-values corrected for multiple comparisons using false discovery rate estimation.

4.3 Results

For the uncued switch task, data were collected over 10 experimental sessions for monkey M, 34 experimental sessions for monkey C (17 cooling sessions and 17 control sessions), and 30 experimental sessions for monkey T (15 cooling sessions and 15 control sessions). Here, the effects of bilateral dACC deactivation on switch task behaviour are presented individually to highlight the commonalities and differences between each individual monkey.

4.3.1 dACC Deactivation Impairs Anti-saccade Performance

Figure 4.2A, 4.2C, and 4.2E show performance for monkeys M, C, and T respectively, before and after a task switch to uncued pro-saccades and anti-saccades during the noncool (red line) and cool (blue line) periods. In general, monkeys displayed stable performance for pro-saccades and anti-saccades before a task switch. Performance dropped when the task was switched and recovered quickly to preswitch levels within five trials. This pattern of behaviour is consistent with previous studies using the uncued switch task (Everling and DeSouza, 2005; Johnston et al., 2007; Hussein et al., 2014).

The effect of bilateral dACC deactivation on task performance was investigated using mean error rates for the 10 trials immediately before a task switch, when performance was stable. While error rates for pro-saccades were not significantly different between the noncool and cool
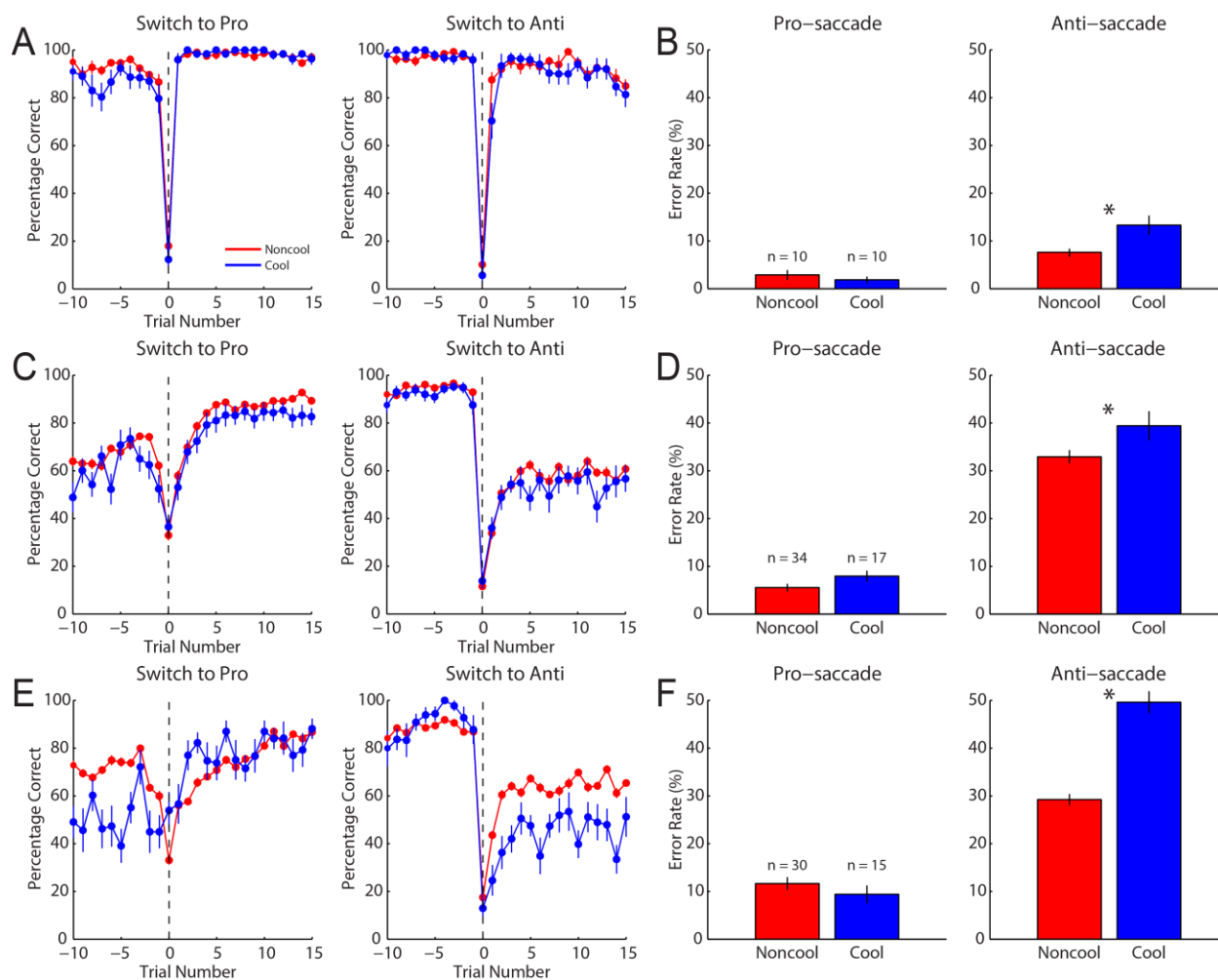
Figure 4.2. Effects of bilateral dACC deactivation on uncued switch task performance. *A*, Performance before and after a task switch to pro-saccades and anti-saccades during the noncool and cool periods for monkey M. Data are averaged across all experimental sessions. Trial zero is the first trial following a task switch. *B*, Mean error rates on the 10 trials immediately before a task switch for pro-saccades and anti-saccades during the noncool and cool periods for monkey M. Asterisks indicate a significant difference between the noncool and cool periods. *C*, *D*, and *E*, *F*, Same as *A* and *B*, but for monkeys C and T respectively.

periods ($P > 0.05$ for all), error rates for anti-saccades during the cool period were significantly greater than during the noncool period for all monkeys ($P < 0.05$ for all) (Fig. 4.2*B,D,F*) . In addition, for monkeys C and T, error rates for anti-saccades were not significantly different between the noncool and control periods ($P > 0.05$ for both) and were significantly greater during the cool period than the control period ($P < 0.05$ and $P < 0.01$ respectively).

To determine whether impaired anti-saccade performance during dACC deactivation was associated with working memory, monkeys C and T performed a cued switch task (7 and 6 experimental sessions respectively), where the task instruction was provided during each trial by the colour of the fixation point. Figures 4.3A and 4.3C show the performance of monkeys C and T respectively, before and after a task switch to cued pro-saccades and anti-saccades during the noncool (red line) and cool (blue line) periods. For monkey C, although the direction of the effect of cooling was the same as the uncued switch task, error rates for anti-saccades were not significantly different between the noncool and cool periods ($P > 0.05$) (Fig. 4.3B). For monkey T, error rates for anti-saccades were significantly greater during the cool period compared to the noncool period ($P < 0.05$) (Fig. 4.3D).

The effect of deactivation on the recovery of performance following a task switch was examined using error rates on the trial following an error on the switch trial. For all monkeys, pro-saccade error rates on the trial after an erroneous switch trial were not significantly different between the noncool and cool periods ($P > 0.05$ for all). In contrast, the effect of deactivation on anti-saccade error rates on the trial after an erroneous switch trial was variable. For monkey T, error rates were significantly greater during the cool period than the noncool period ($P < 0.05$). In addition, error rates were not significantly different between the noncool and control periods ($P > 0.05$) and there was a trend for error rates to be greater during the cool period than control
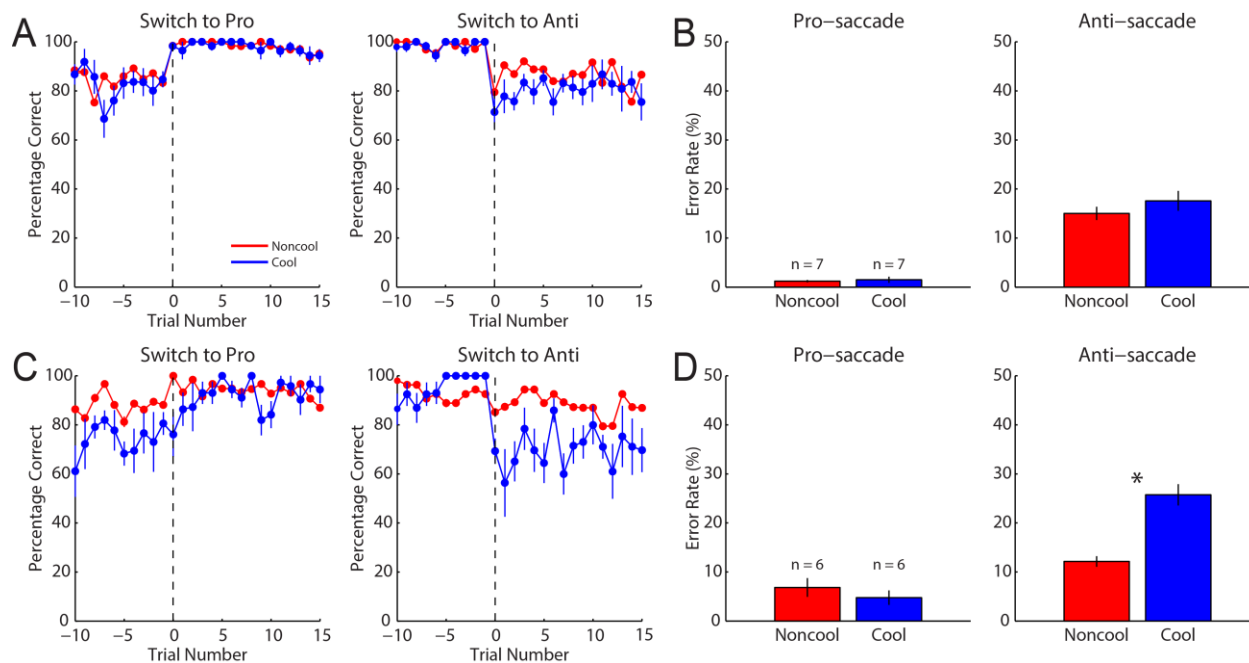
Figure 4.3. Effects of bilateral dACC deactivation on cued switch task performance. *A*, Performance before and after a task switch to pro-saccades and anti-saccades during the noncool and cool periods for monkey C. Data are averaged across all experimental sessions. Trial zero is the first trial following a task switch. *B*, Mean error rates on the 10 trials immediately before a task switch for pro-saccades and anti-saccades during the noncool and cool periods for monkey C. Asterisks indicate a significant difference between the noncool and cool periods. *C*, *D*, Same as *A* and *B*, but for monkey T.

period ($P = 0.06$). For monkey M, there was a trend for anti-saccade error rates on the trial after an erroneous switch trial to be greater during the cool period than noncool period ($P = 0.087$). Monkey C showed no significant difference between the noncool and cool periods ($P > 0.05$).

4.3.2 Performance Following Correct and Erroneous Trials

To further characterize uncued pro-saccade and anti-saccade performance, error rates on pro-saccade trials preceded by a correct or erroneous pro-saccade trial and error rates on anti-saccade trials preceded by a correct or erroneous anti-saccade trial were examined. Figure 4.4 shows error rates on trials preceded by correct or erroneous responses during the noncool and cool periods.

For pro-saccade error rates, the main effect of previous trial reward (correct or error) was significant for monkey M [$F(1,36) = 9.41$, $P < 0.01$], monkey C [$F(1,64) = 451.63$, $P < 0.01$], and monkey T [$F(1,56) = 52.69$, $P < 0.01$]. Specifically, error rates on trials preceded by an erroneous response were significantly greater than trials preceded by a correct response during the noncool ($P < 0.01$), cool ($P < 0.01$), and control ($P < 0.01$) periods for monkey C, and during the noncool ($P < 0.01$) and control periods ($P < 0.01$) for monkey T. There was a trend for error rates to be greater during the noncool period for monkey M ($P = 0.057$) and during the cool period for monkey T ($P = 0.053$). Bilateral dACC deactivation significantly increased error rates on pro-saccade trials preceded by a correct response for monkey C ($P < 0.01$) (Fig. 4.4B). In addition, error rates were not significantly different between the noncool and control periods ($P > 0.05$) and there was a trend for error rates to be greater during the cool period than control period ($P = 0.077$). There was no significant interaction between previous trial reward and dACC
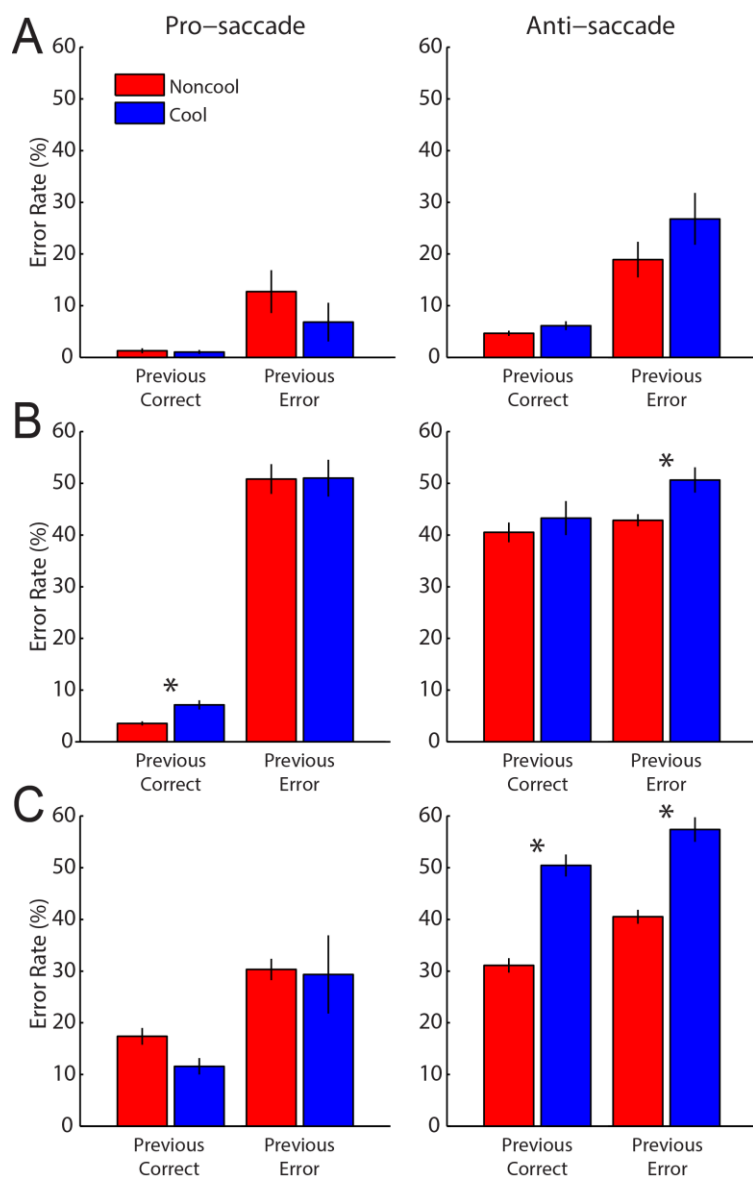
Figure 4.4. Error rates on pro-saccade and anti-saccade trials preceded immediately by a correct or erroneous response during the noncool and cool periods. *A*, Mean error rates for monkey M. *B*, Mean error rates for monkey C. *C*, Mean error rates for monkey T. Asterisks indicate a significant difference between the noncool and cool periods.

deactivation for monkey M [$F(1,36) = 1.02$, $P > 0.05$], monkey C [$F(1,64) = 1.83$, $P > 0.05$], and monkey T [$F(1,56) = 2.43$, $P > 0.05$].

For anti-saccades, the main effect of previous trial reward was significant for monkey M [$F(1,36) = 32.2$, $P < 0.01$], monkey C [$F(1,64) = 6.44$, $P < 0.05$], and monkey T [$F(1,56) = 30.75$, $P < 0.01$]. Specifically, error rates on trials preceded by an erroneous response were significantly greater than trials preceded by a correct response during the noncool ($P < 0.01$) and cool ($P < 0.01$) periods for monkey M, and during the noncool ($P < 0.01$), cool ($P < 0.05$), and control periods ($P < 0.01$) for monkey T. Bilateral dACC deactivation significantly increased error rates on anti-saccade trials preceded by an erroneous response for monkey C ($P < 0.05$) (Fig. 4.4B). In addition, error rates were not significantly different between the noncool and control periods ($P > 0.05$) and there was a trend for error rates to be greater during the cool period than control period ($P = 0.091$). For monkey T, dACC deactivation significantly increased error rates on anti-saccade trials preceded by a correct response and preceded by an erroneous response ($P < 0.01$ for both) (Fig. 4.4C). In addition, error rates were not significantly different between the noncool and control periods ($P > 0.05$ for both) and were significantly greater during the cool period than control period ($P < 0.01$ for both). There was no significant interaction between previous trial reward and dACC deactivation for monkey M [$F(1,36) = 1.09$, $P > 0.05$], monkey C [$F(1,64) = 0.74$, $P > 0.05$], and monkey T [$F(1,56) = 0.25$, $P > 0.05$].

4.3.3 dACC Deactivation Increases Pro-saccade and Anti-saccade SRTs

Figure 4.5A, 4.5C, and 4.5E show SRTs for monkeys M, C, and T respectively, before and after a task switch to uncued pro-saccades and anti-saccades during the noncool (red line) and cool (blue line) periods. In general, there was no effect of the task switch on the SRTs for
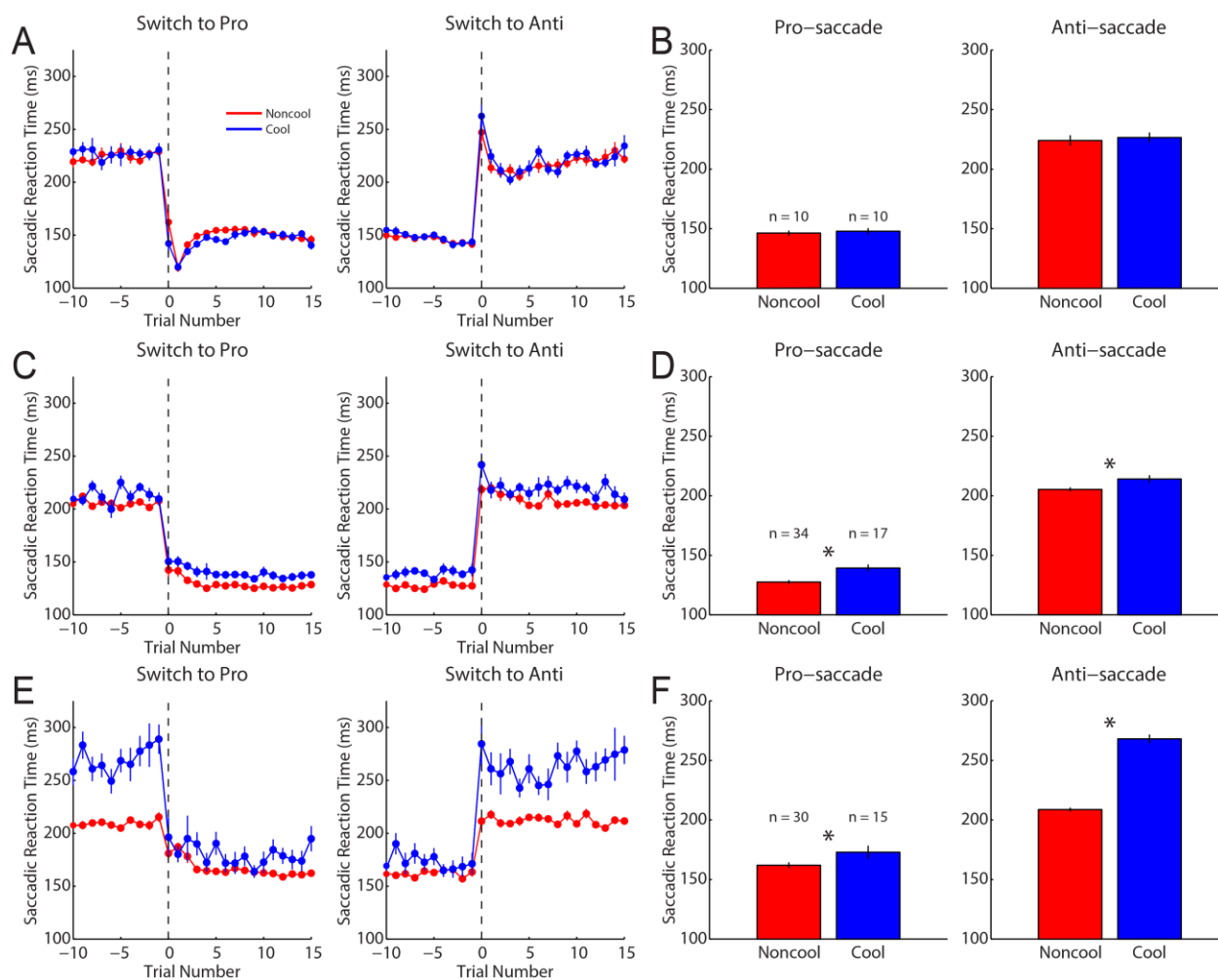
Figure 4.5. Effects of bilateral dACC deactivation on uncued switch task SRTs. *A*, SRTs before and after a task switch to pro-saccades and anti-saccades during the noncool and cool periods for monkey M. Data are averaged across all experimental sessions. Trial zero is the first trial following a task switch. *B*, Mean SRTs on the 10 trials immediately before a task switch for pro-saccades and anti-saccades during the noncool and cool periods for monkey M. Asterisks indicate a significant difference between the noncool and cool periods. *C*, *D*, and *E*, *F*, Same as *A* and *B*, but for monkeys C and T respectively.

pro-saccades and anti-saccades, with the exception of the first trial following a switch, which was associated with longer SRTs. This pattern of behaviour is consistent with previous studies using the uncued switch task (Johnston et al., 2007; Hussein et al., 2014).

As with task performance, the effects of bilateral dACC deactivation on SRTs were investigated using mean SRTs for the 10 trials immediately before a task switch, when performance was stable. For monkey M, SRTs for pro-saccades and anti-saccades were not significantly different between the noncool and cool periods ($P > 0.05$ for both) (Fig. 4.5B). However, for monkey C, SRTs for pro-saccades and anti-saccades were significantly greater during the cool period compared to the noncool period ($P < 0.01$ and $P < 0.05$ respectively) (Fig. 4.5D). In addition, although there was a trend for pro-saccade SRTs to be greater during the control period than noncool period ($P = 0.085$), there was also a trend for SRTs to be greater during the cool period than control period ($P = 0.085$). Anti-saccade SRTs were not significantly different between the noncool and control periods ($P > 0.05$) and were significantly greater during the cool period compared to the control period ($P < 0.01$). Similarly, for monkey T, SRTs for pro-saccades and anti-saccades were significantly greater during the cool period compared to the noncool period ($P < 0.05$ and $P < 0.01$ respectively) (Fig. 4.5F). Pro-saccade SRTs were not significantly different between the noncool and control periods ($P > 0.05$) or between the cool and control periods ($P > 0.05$). Although anti-saccade SRTs were significantly greater during the control period compared to the noncool period ($P < 0.05$), SRTs were also significantly greater during the cool period compared to the control period ($P < 0.01$).

To determine whether increased pro-saccade and anti-saccade SRTs during dACC deactivation was associated with working memory, monkeys C and T performed a cued switch task. Figures 4.6A and 4.6C show SRTs for monkeys C and T respectively, before and after a
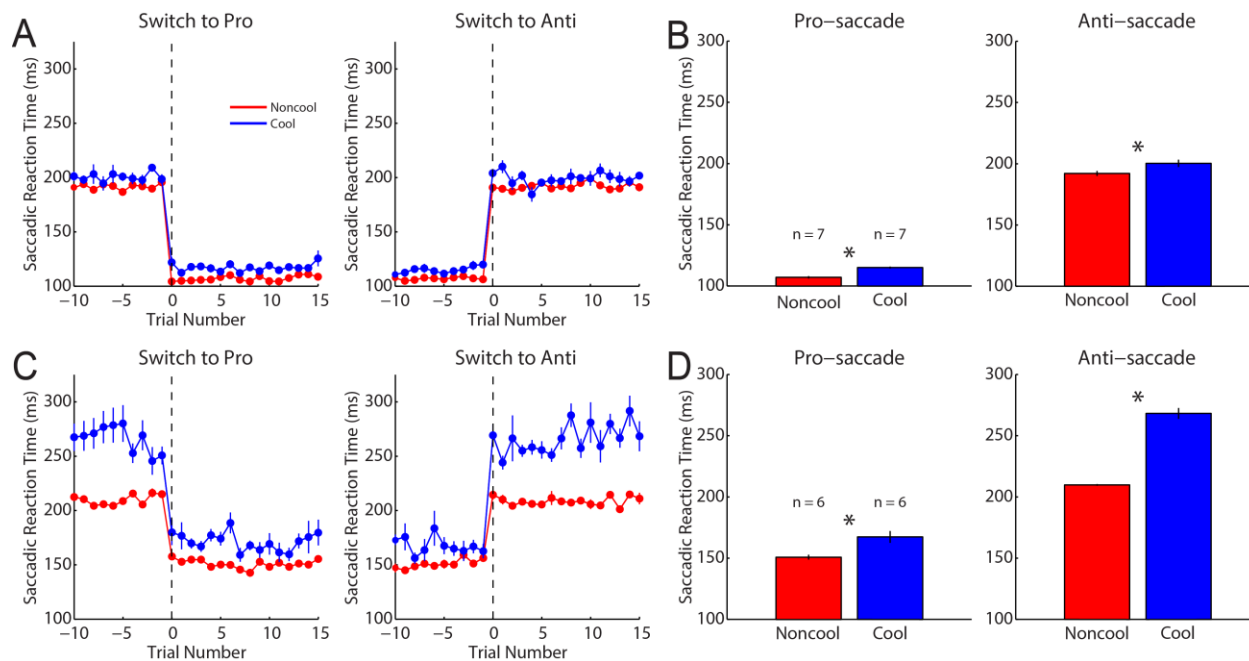
Figure 4.6. Effects of bilateral dACC deactivation on cued switch task SRTs. *A*, SRTs before and after a task switch to pro-saccades and anti-saccades during the noncool and cool periods for monkey C. Data are averaged across all experimental sessions. Trial zero is the first trial following a task switch. *B*, Mean SRTs on the 10 trials immediately before a task switch for pro-saccades and anti-saccades during the noncool and cool periods for monkey C. Asterisks indicate a significant difference between the noncool and cool periods. *C*, *D*, Same as *A* and *B*, but for monkey T.

task switch to cued pro-saccades and anti-saccades during the noncool (red line) and cool (blue line) periods. For monkeys C and T, SRTs for pro-saccades and anti-saccades were significantly greater during the cool period compared to the noncool period ($P < 0.05$ for all) (Fig. 4.6B, D).

4.3.4 SRTs Following Correct and Erroneous Trials

To further characterize uncued pro-saccade and anti-saccade SRTs, SRTs on pro-saccade trials preceded by a correct or erroneous pro-saccade trial and SRTs on anti-saccade trials preceded by a correct or erroneous anti-saccade trial were examined. Figure 4.7 shows SRTs on trials preceded by correct or erroneous responses during the noncool and cool periods.

For pro-saccades SRTs, the main effect of previous trial reward was significant for monkey M [$F(1,36) = 59.46$, $P < 0.01$], monkey C [$F(1,64) = 37.74$, $P < 0.01$], and monkey T [$F(1,56) = 15.52$, $P < 0.01$]. For monkey M, SRTs were significantly lower on trials preceded by an erroneous response than by a correct response during the noncool ($P < 0.01$) and cool ($P < 0.01$) periods. In contrast, SRTs were significantly greater on trials preceded by an erroneous response than by a correct response during the noncool ($P < 0.01$), cool ($P < 0.05$), and control periods ($P < 0.01$) for monkey C, and during the noncool ($P < 0.01$) and control ($P < 0.01$) periods for monkey T. Bilateral dACC deactivation significantly increased SRTs on pro-saccade trials preceded by a correct response for monkeys C and T ($P < 0.01$ and $P < 0.05$ respectively) (Fig. 4.7B, C). SRTs were not significantly different between the noncool and control periods ($P > 0.05$ for both) and between the cool and control periods ($P > 0.05$ for both). There was a significant interaction between previous trial reward and dACC deactivation for monkey T [$F(1,56) = 5.59$, $P < 0.01$], but no significant interaction for monkey M [$F(1,36) = 0.89$, $P > 0.05$] and monkey C [$F(1,64) = 0.85$, $P > 0.05$].
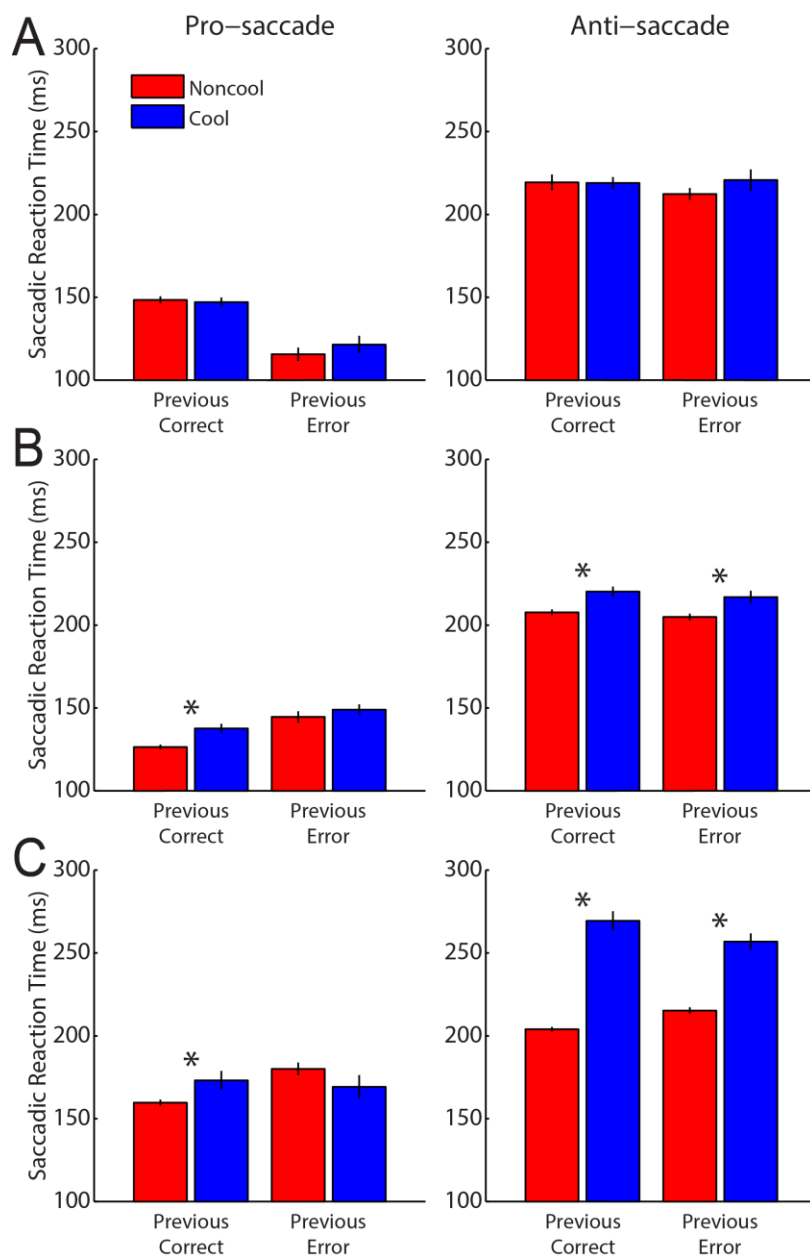
Figure 4.7. SRTs on pro-saccade and anti-saccade trials preceded immediately by a correct or erroneous response during the noncool and cool periods. *A*, Mean SRTs for monkey M. *B*, Mean SRTs for monkey C. *C*, Mean SRTs for monkey T. Asterisks indicate a significant difference between the noncool and cool periods.

For anti-saccades, the main effect of previous trial reward was not significant for monkey M [$F(1,36) = 0.30$, $P > 0.05$], monkey C [$F(1,64) = 0.87$, $P > 0.05$], and monkey T [$F(1,56) = 0.58$, $P > 0.05$]. Bilateral dACC deactivation significantly increased SRTs on anti-saccade trials preceded by a correct response and preceded by an erroneous response for monkey C ($P < 0.05$ for both) (Fig. 4.7B). SRTs on trials preceded by a correct response were not significantly different between the noncool and control periods ($P > 0.05$) and between the cool and control periods ($P > 0.05$). SRTs on trials preceded by an erroneous response were significantly greater during the control period than noncool period ($P < 0.05$) and not significantly different between the cool and control periods ($P > 0.05$). Deactivation also significantly increased SRTs on trials preceded by a correct response and preceded by an erroneous response for monkey T ($P < 0.01$ for both) (Fig. 4.7C). Although SRTs on trials preceded by a correct response were significantly greater during the control period than noncool period ($P < 0.01$), SRTs were also significantly greater during the cool period than control period ($P < 0.01$). SRTs on trials preceded by an erroneous response were not significantly different between the noncool and control periods ($P > 0.05$) and were significantly greater during the cool period than control period ($P < 0.01$). There was a significant interaction between previous trial reward and dACC deactivation for monkey T [$F(1,56) = 8.77$, $P < 0.01$], but no significant interaction for monkey M [$F(1,36) = 0.84$, $P > 0.05$] and monkey C [$F(1,64) = 0.21$, $P > 0.05$].

4.3.5 dACC Deactivation and Dropped Trials

Table 4.1 shows the percentage of skipped, broken fixation, and no response trials for pro-saccades and anti-saccades during the noncool and cool periods. For monkeys M and C, there were no significant differences between the noncool and cool periods for skipped, broken

Table 4.1. Effects of bilateral dACC deactivation on the percentage of skipped, broken fixation, and no response trials. Asterisks indicate a significant difference between the noncool and cool periods ($P < 0.01$).

	Pro-saccades		Anti-saccades	
	Noncool	Cool	Noncool	Cool
Monkey M				
Skipped trials (%)	0.2	0	0.52	0
Broken fixation (%)	4.1	2.9	4.1	3.6
No response (%)	0	0	0.5	0.4
Monkey C				
Skipped trials (%)	0.4	0.2	1.5	0.9
Broken fixation (%)	8.9	8.3	13.2	14.0
No response (%)	0	0	0.2	0.1
Monkey T				
Skipped trials (%)	0.5	8.2*	0.6	9.2*
Broken fixation (%)	11.0	32.6*	12.2	41.2*
No response (%)	0.2	0.9*	0.3	1.1*

fixation, and no response trials for both pro-saccades and anti-saccades ($P > 0.05$ for all). For monkey T, percentages of skipped, broken fixation, and no response trials for pro-saccades and anti-saccades were greater during the cool period than noncool period ($P < 0.01$ for all). In addition, although percentages of skipped and broken fixation trials were significantly greater during the control period than noncool period ($P < 0.05$ for all), percentages were also significantly greater during the cool period than control period ($P < 0.01$ for all). Percentages of no response trials for pro-saccades were not significantly different between the noncool and control periods ($P > 0.05$) and were significantly greater during the cool period than control period ($P < 0.01$). Percentages of no response trials for anti-saccades were significantly greater during the control period than noncool period ($P < 0.05$) and were not significantly different between the cool and control periods ($P > 0.05$).

4.4 Discussion

The dACC has been implicated in integrating reward and cost information to appropriately allocate cognitive control (Shenhav et al., 2013). While the dACC has been shown to encode task-selective signals and the outcome of responses, its causal role in driving voluntary behaviour is poorly understood. In this study, we investigated the behavioural effects of bilateral dACC deactivation in monkeys performing pro-saccade and anti-saccade task switching paradigms. We found that dACC deactivation consistently increased error rates for anti-saccades in all subjects. Two of the three subjects demonstrated increased SRTs for pro-saccades and anti-saccades with dACC deactivation. Error rate and SRT effects were present in both the uncued and cued switch task. In addition, in these same two subjects, dACC deactivation significantly increased error rates on anti-saccade trials preceded by an erroneous response, and increased

SRTs on pro-saccade trials preceded by a correct response and on anti-saccade trials preceded by correct and erroneous responses. Overall, these findings suggest that the dACC plays a direct role in facilitating the performance of cognitively demanding tasks by associating feedback with actions.

Compared to the pro-saccade task, the anti-saccade task requires greater cognitive control because it requires subjects to inhibit a habitual response to look at a peripheral stimulus (pro-saccade) and generate a voluntary saccade in the opposite direction. Previous studies suggest that the dACC facilitates anti-saccade performance. Human patients with unilateral ACC lesions have been found to make more anti-saccade errors than healthy controls (Gaymard et al., 1998). In addition, dACC microstimulation has been shown to decrease saccadic reaction times for anti-saccades while increasing reaction times for contralateral pro-saccades (Phillips et al., 2011). Accordingly, we found that bilateral dACC deactivation increases error rates for anti-saccades but not pro-saccades. Unlike other brain areas involved in oculomotor control, the dACC is unlikely to be directly involved in the generation of saccades. Given the dACC's extensive involvement with cognitive functions (Duncan and Owen, 2000; Shenhav et al., 2013), its role in facilitating anti-saccade performance is likely associated with the allocation of cognitive control. The dACC's specific role in cognitive control can be investigated with task switching.

In this study, bilateral dACC deactivation variably affected the ability to switch between tasks. One of three animals (Monkey T) showed a significant increase in anti-saccade error rates on the trial following a task switch, whereas the second (Monkey M) showed a trend and the third (Monkey C) showed no difference. However, all animals demonstrated impaired anti-saccade performance throughout the task block, which suggests that the dACC may be more involved in maintaining a task than switching the task being performed. This result is consistent

with a previous study that found that monkeys with bilateral dACC lesions were unable to sustain rewarded lifting or turning movements after switching their response (Kennerley et al., 2007). Whereas Kennerley et al. (2007) demonstrated impairment on both tasks in their switch paradigm, we found an asymmetric impairment for anti-saccades. Consequently, the role of the dACC in task maintenance may be related to the cognitive demands of the task.

Indeed, the dACC is thought to signal error likelihood and increase its activity when greater cognitive control is required due to increased task demands or difficulty (Brown and Braver, 2005). Human patients with ACC lesions in areas 32 and 24a-c have been shown to have an impaired ability to modulate performance based on the demands of the previous trial when performing a variant of the Simon task (di Pellegrino et al., 2007). In addition, several studies have found that the dACC encodes the task being performed and task difficulty (Johnston et al., 2007; Sheth et al., 2013; Wisniewski et al., 2015), making it well positioned to implement cognitive control for task maintenance based on cognitive demand.

Our laboratory previously used uninstructed alternating blocks of pro-saccades and anti-saccades to demonstrate that neurons in the dACC respond to an increase in task demand after a task switch by increasing task selectivity and that this task selectivity declines throughout task blocks (Johnston et al., 2007). Unlike the DLPFC, which is consistently implicated in working memory and shows constant task selectivity despite repetition of the same task (Miller and Cohen, 2001; Johnston et al., 2007), the dACC is unlikely to be directly responsible for maintaining tasks in working memory. Accordingly, impairment in anti-saccade performance with dACC deactivation persisted when subjects performed the cued switch task. Thus, although the dACC may facilitate the representation of task rules in the DLPFC, the dACC likely maintains the performance of cognitively demanding tasks through an alternative mechanism.

Lesion studies in monkeys and humans have implicated the dACC in maintaining rewarded behaviour. Kennerley et al. (2006) demonstrated that, in addition to being unable to sustain behaviour after a task switch, monkeys with bilateral dACC lesions made more errors on trials immediately following a rewarded trial. Similarly, human patients with dACC lesions had increased errors on trials immediately following trials with positive feedback in an action-value learning task (Camille et al., 2011). Although increased error rates were not observed after correct trials with bilateral dACC deactivation, we found that SRTs were increased on pro-saccade and anti-saccade trials following a rewarded trial. Increased SRTs may reflect impairment in processing reward information and is consistent with the idea that the dACC assesses the value of actions to guide and maintain behaviour.

In addition to signalling correct and rewarded behaviour, dACC neurons are known to signal errors, decreases in reward, and absent rewards (Shima and Tanji, 1998; Ito et al., 2003; Quilodran et al., 2008). Here, dACC deactivation was associated with increased error rates and SRTs on anti-saccade trials following an erroneous trial. The ability of the dACC to monitor both positive and negative feedback to maintain task performance may be impaired with dACC deactivation. Impairment on anti-saccade trials after an error, but not pro-saccade trials, may reflect its particular importance for cognitively demanding tasks. Given that dACC neurons enhance task selectivity following an error (Johnston et al., 2007), dACC deactivation may also interfere with its ability to implement cognitive control and specify the task to be performed to other brain areas. The dACC's role in integrating feedback and actions is supported by findings that individual dACC neurons can be tuned for both reward size and saccade direction (Hayden and Platt, 2010). Taken together, our results suggest that the dACC may associate feedback with

actions to facilitate task performance and this role may be related to the cognitive demands of a task.

Studies of cognitive function in animals often involve the delivery or omission of liquid reward as feedback. The dACC is thought to process this feedback for behavioural control in the facial/eye field of the CMAr in monkeys, which is situated in the cingulate sulcus anterior to the arcuate sulcus (Amiez and Petrides, 2014; Procyk et al., 2014). Consequently, cryoloops were placed with the posterior ends at the same position as the posterior ends of the principal sulci to target the CMAr. Nonetheless, the exact position of the cryoloops relative to CMAr may have varied between subjects, and different degrees of CMAr deactivation may have accounted for inter-subject variability in performance. Although dACC deactivation consistently increased anti-saccade error rates in all subjects, two of the three subjects demonstrated increased pro-saccade and anti-saccade SRTs and previous trial effects. Monkey T was particularly affected by dACC deactivation and demonstrated a significant increase in skipped, broken fixation, and no response trials. Deactivation may have been the most complete in this subject and supports the dACC's role in feedback-action association and motivation.

Inter-subject variability with dACC deactivation may also be related to a subject's perception of task difficulty. Notably, Monkey M had the lowest anti-saccade error rates with normal dACC function and was least affected by deactivation. Since the dACC encodes task difficulty and is thought to implement cognitive control accordingly (Shenhav et al., 2013; Sheth et al., 2013; Wisniewski et al., 2015), the dACC may be less involved in task performance when task difficulty and cognitive demand are low. Under these circumstances, dACC deactivation may minimally impair task performance. Conversely, subjects with high baseline anti-saccade

errors may rely more on the dACC for task performance and were more impaired by dACC deactivation.

In summary, we found that bilateral dACC deactivation was associated with increased anti-saccade error rates and impairment with integrating feedback from the previous trial. These results suggest that the dACC plays a direct role in associating feedback with actions to implement cognitive control and maintain task performance, particularly in cognitively demanding task situations.

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CHAPTER 5

Discussion

5.1 Summary of Main Findings

The ability to flexibly engage in goal-directed behaviour is a key feature of cognitive control. Successful task switching requires cognitive control and a network of brain areas to select, maintain, implement, and execute the appropriate task-set. In this thesis, the neural basis of task switching was investigated using the oculomotor system of the macaque monkey. The oculomotor system is well characterized anatomically and functionally, and provides a valuable framework for understanding the neural mechanisms of cognitive control and task processing. Specifically, pro-saccade and anti-saccade tasks were used to explore the contributions of oculomotor and cognitive brain areas to different stages of task processing, from task selection to execution. In Chapter 2, monkeys demonstrated switch costs in error rates and reaction times that were associated with a neural correlate for task switching in the SC. In Chapter 3, bilateral DLPFC deactivation demonstrated that communication between the DLPFC and SC may be mediated by neuronal oscillations and these oscillations may modulate SC neural activity for task preparation. In Chapter 4, bilateral dACC deactivation demonstrated that the dACC may be involved in associating feedback with actions to implement cognitive control and maintain task performance. Taken together, these results suggest that the dACC monitors feedback to select the appropriate task and implement cognitive control, the DLPFC maintains the current task-set and modulates the activity of other brain areas such as the SC, and the SC is modulated by task switching processes and contributes to the production of switch costs.

5.1.1 Monkeys demonstrate switch costs and switch-related differences in superior colliculus activity

Although switch costs have been consistently demonstrated in humans (Allport et al., 1994; Monsell, 2003), it is less clear whether monkeys demonstrate switch costs (Stoet and Snyder, 2003; Caselli and Chelazzi, 2011). Pro-saccade and anti-saccade tasks are particularly useful for clarifying switch costs in monkeys because these tasks consistently produce behavioural results that are comparable between both species (Munoz and Everling, 2004). In humans, randomly interleaved pro-saccade and anti-saccade tasks reliably produce switch costs, especially unidirectional pro-saccade reaction time switch costs (Cherkasova et al., 2002; Barton et al., 2006; Weiler and Heath, 2012; Chan and DeSouza, 2013). Accordingly, monkeys performing interleaved gap and memory pro-saccade and anti-saccade tasks demonstrated error rate and unidirectional pro-saccade reaction time switch costs. The absence of switch costs with overlap pro-saccade and anti-saccade trials suggests that the presence of switch costs may be associated with task difficulty or cognitive demand. These results clarify that monkeys demonstrate switch costs that are comparable to humans. Switch costs can arise from the inability to complete task-set reconfiguration prior to stimulus onset or task-set inertia (Allport et al., 1994; Monsell, 2003), and the macaque monkey provides a useful animal model for investigating the neural basis of task switching.

For the first time, we found a neural correlate for task switching in the form of switch-related differences in neural activity in the SC in monkeys. Stimulus-related activity of saccade-related neurons reflected the previous performed task, with lower activity on switch trials compared to repeat trials for pro-saccades and anti-saccades into the response field, and higher activity on switch trials compared to repeat trials for anti-saccades opposite to the response field.

These switch-related differences were resolved by the time a saccade was generated and may be influenced by excitatory or inhibitory processes within the SC or from other brain areas. SC activity may reflect the completion of task-set reconfiguration or may directly contribute to switch costs.

Based on our LFP recordings in the SC, neuronal oscillations may facilitate information integration to ensure that a task-appropriate response is executed. Correct pro-saccades and anti-saccades were associated with higher LFP power in a range of frequency bands after stimulus onset than erroneous responses. Beta activity in particular may mediate communication between the SC and higher-level brain areas through neural synchrony and coordinate incoming temporal and spatial information, while gamma activity may reflect neuronal processing for saccade generation (Kopell et al., 2000; Fries, 2005). Thus, neuronal oscillations may support the completion of task-set reconfiguration in the SC in response to task stimuli.

The existence of switch-related differences in SC activity suggests that neural correlates of task switching can be found in other brain areas with task-selective activity. The FEF, DLPFC, dACC, and SEF all contain neurons with task-selective activity (Schlag-Rey et al., 1997; Everling and Munoz, 2000; Everling and DeSouza, 2005; Johnston et al., 2007) and project to the SC (Goldman and Nauta, 1976; Leichnetz et al., 1981). Although single-unit recording studies have not yet identified switch-related differences in these areas, the time at which switch-related differences occur may be informative of each area's role in task processing and task switching. For example, like the SC, the FEF participates in saccade generation (Schall, 2002) and may exhibit switch-related differences in stimulus-related activity and contribute to switch costs. In addition, the presence of preparatory signals in the FEF (Everling and Munoz, 2000; Sommer and Wurtz, 2000) suggest that it may exhibit preparatory switch-related

differences and be influenced by interference from task-set inertia. This would be consistent with

reduced BOLD activation in the FEF for pro-saccade trials preceded by an anti-saccade trial

(Manoach et al., 2007). Another brain area that may exhibit preparatory switch-related

differences and be responsible for resolving interference from task-set inertia is the DLPFC. The

DLPFC is thought to be particularly important for maintaining task-sets and modulating other

brain areas, like the SC, to execute the appropriate task (Miller and Cohen, 2001).

5.1.2 Bilateral DLPFC deactivation reduces preparatory beta and gamma power in the SC

The DLPFC encodes task rules in the spiking activity of neurons (Asaad et al., 2000;

Wallis et al., 2001; Everling and DeSouza, 2005), activity of neural populations (Stokes et al.,

2013), and LFP activity (Buschman et al., 2012). How it implements these rules and modulates

other brain areas is a critical question in cognitive neuroscience. Here, we demonstrated that

bilateral DLPFC deactivation reduced preparatory beta and high gamma activity in the SC in

monkeys performing interleaved pro-saccade and anti-saccade tasks. This coincided with

decreased spiking activity during task preparation and increased reaction times for both tasks

(Koval et al., 2011), and provides further support that the DLPFC provides excitatory input to the

SC (Everling and Johnston, 2013). While the DLPFC has been shown to send task-selective

signals that bias SC activity (Johnston and Everling, 2006; Koval et al., 2011; Johnston et al.,

2014), these results provide a mechanism by which the DLPFC represents task rules,

communicates with other brain areas, and modulates neural activity.

In the DLPFC, task-specific neural ensembles are formed by increases in synchrony in

the beta frequency band (Buschman et al., 2012). The role of beta activity in task representation

is supported by evidence that prefrontal beta oscillations are involved in working memory and the maintenance of cognitive sets (Siegel et al., 2009; Engel and Fries, 2010; Salazar et al., 2012). More generally, beta activity is implicated in mediating communication between distant brain areas through neural synchrony (Kopell et al., 2000; Fries, 2005) and top-down control (Siegel et al., 2012). Thus, beta oscillations may facilitate the delivery of task-specific information from the DLPFC to SC.

Decreases in preparatory gamma power in the SC with bilateral DLPFC deactivation may reflect a decrease in local neuronal processing due to a lack of input from the DLPFC. This would be consistent with the coinciding decrease in spiking activity (Koval et al., 2011) and indeed, gamma power is thought to reflect changes in spiking activity (Ray et al., 2008). Notably, DLPFC deactivation also decreased the proportion of neurons in the SC that were correlated with gamma power. Given the concurrent decrease in SC beta power, beta oscillations between the DLFPC and SC may facilitate the modulation of neural activity in the SC.

Although the DLPFC is thought to be a critical brain area for cognitive control, task switching relies on a network of brain areas working together. Consequently, these results have implications for how these brain areas interact with each other. While DLPFC deactivation suggests that beta oscillations enable the DLPFC to exert control on the SC, beta oscillations likely facilitate communication between various other brain areas (Kopell et al., 2000; Fries, 2005). For example, like the SC, the FEF receives input from the DLPFC (Selemon and Goldman-Rakic, 1988) and this relationship may be mediated by beta activity. Beyond beta oscillations, this study highlights the importance of oscillations in neuronal communication and cognitive control. In particular, the DLPFC and dACC are strongly associated with each other (Bates and Goldman-Rakic, 1993; Duncan and Owen, 2000) and their function in cognitive

control may be influenced by neuronal oscillations. Whereas beta oscillations reflect task

representations in the DLPFC, task representations are encoded by theta activity in the dACC

(Womelsdorf et al., 2010). Successful shifts in attention have been shown to be associated with

theta-gamma phase-amplitude correlation between the dACC and DLPFC (Voloh et al., 2015).

Furthermore, theta and beta synchrony may coordinate communication between the dACC and

FEF and are predictive of correct task performance (Babapoor-Farrokhran et al., 2017). Thus,

LFP activity, in addition to spiking activity, can help elucidate the mechanisms underlying task

switching and cognitive control.

5.1.3 Bilateral dACC deactivation impairs feedback integration and cognitively demanding task performance

Although the dACC projects to brain areas involved in motor control, microstimulation

does not strongly evoke movements, including saccades (Luppino et al., 1991; Picard and Strick,

1996). Instead, numerous lesion, functional imaging, and neurophysiological studies have

implicated the dACC with the DLPFC in cognitive control (Duncan and Owen, 2000; Shenhav et

al., 2013). However, the role of the dACC in cognitive control is poorly understood. Difficulty in

determining a specific function has led to the development of multiple theories of dACC

function, including a role in conflict monitoring, performance monitoring, and error likelihood

prediction (Botvinick et al., 2001; Ito et al., 2003; Brown and Braver, 2005). Recently, the dACC

was proposed to integrate reward and cost information to specify where and how much cognitive

control to allocate (Shenhav et al., 2013). Here, we clarified the contributions of the dACC to

cognitive control using reversible bilateral dACC deactivation.

On alternating blocks of pro-saccades and anti-saccades, bilateral dACC deactivation impaired the monkeys' ability to perform anti-saccades and increased reaction times for both tasks. In addition, pro-saccade and anti-saccade reaction times were increased following rewarded trials and anti-saccade reaction times and error rates were increased following erroneous trials. Similar to previous lesion studies in monkeys and humans (Kennerley et al., 2006; Camille et al., 2011), these results suggest that the dACC monitors feedback to maintain behaviour. Impairment of anti-saccade, but not pro-saccade, performance suggests that the dACC may be particularly important for maintaining the performance of cognitively demanding tasks.

The ability of the dACC to associate feedback with actions to implement cognitive control is supported by neurophysiological findings. Neurons in the dACC have been shown to signal the presence or absence of reward (Shima and Tanji, 1998; Ito et al., 2003), task difficulty, and the task being performed (Johnston et al., 2007; Sheth et al., 2013; Wisniewski et al., 2015). Individual neurons can also be tuned for both reward size and saccade direction (Hayden and Platt, 2010). Thus, the dACC is well positioned to integrate information to select the appropriate task and implement cognitive control, particularly in cognitively demanding task situations.

How the dACC implements cognitive control and how it interacts with other brain areas for task switching is unclear. The dACC and DLPFC are often associated with each other for cognitive control and are highly and reciprocally connected (Bates and Goldman-Rakic, 1993; Duncan and Owen, 2000; Petrides, 2005). For alternating blocks of pro-saccades and anti-saccades, simultaneous recordings from both areas have shown that task selectivity in dACC neurons was strongest after a task switch and declined throughout the block, whereas task selectivity remained constant in the DLPFC (Johnston et al., 2007). In addition, in an alternating exploration and exploitation task, high gamma power increases in the dACC preceded increases

in the DLPFC after negative feedback and first positive feedback (Rothé et al., 2011). These studies suggest that enhanced activity in the dACC following feedback or changes in task demand recruits the DLPFC. Both brain areas may work together to modulate the activity of other brain areas to perform the appropriate task. Alternatively, the dACC may specify the appropriate task to the DLPFC, and the DLPFC may be subsequently responsible for maintaining the task and regulating other brain areas (Shenhav et al., 2013).

5.2 Caveats and Limitations

5.2.1 Distant effects of reversible cryogenic deactivation

The effects of deactivation are often attributed to the targeted brain area. Although cryoloops effectively deactivate cortical tissue adjacent to a cryoloop, distant brain areas are also modulated. Metabolic tracer studies with 2-deoxyglucose (2DG) have demonstrated that brain areas that receive projections from the cortex targeted by deactivation show reduced 2DG uptake (Vanduffel et al., 1997; Payne and Lomber, 1999). This reduced 2DG uptake is reflective of reduced neural activity and is likely in proportion with the projections' functional impact. As a result, the modulation of distant brain areas may contribute to the observed behavioural effects of reversible cryogenic deactivation. In addition, electrophysiological changes in downstream brain areas may be affected by changes in intermediate brain areas. For example, SC activity can be affected directly by DLPFC deactivation and indirectly by the FEF, which receives input from the DLPFC and sends output to the SC (Everling and Munoz, 2000). Overall, the effects of deactivation are influenced by the deactivated brain area's contribution to function, the contribution of other brain areas to function, and the ability of other brain areas to compensate

for the deactivated area. Nonetheless, reversible cryogenic deactivation is a useful technique for establishing causal relationships between a brain area and function and for examining network interactions.

5.2.2 Non-human primates as an animal model for cognitive control

Non-human primates, particularly macaque monkeys, have been widely used as a model for cognitive control. Invasive techniques, such as lesions, reversible deactivation, intracranial electrophysiology, microstimulation, and neuropharmacology, enable the neural basis of cognitive functions to be examined at high spatial and temporal resolution (Stoet and Synder, 2009). However, inherent differences in methodology, neuroanatomy, and brain function between monkeys and humans present limitations for interpreting studies on cognitive control.

Whereas human task performance is often guided by verbal task instruction, monkeys are highly trained to correctly perform tasks by repetition and rewarded behaviour (Stoet and Synder, 2003). Consequently, monkeys avoid the cognitive demands of maintaining a verbal instruction and may be biased to form stimulus-response associations. Despite training methods that encourage stimulus-response associations, monkeys are capable of applying abstract rules to novel stimuli (Wallis et al., 2001; Stoet and Snyder, 2003). With regard to task switching behaviour, studies have demonstrated conflicting results for switch costs in monkeys (Stoet and Snyder, 2003; Caselli and Chelazzi, 2011), and suggest that mechanisms of task-set reconfiguration may differ between monkeys and humans. Furthermore, neural mechanisms for cognitive control, particularly the role of the dACC, have been difficult to elucidate because of contrasting findings between monkeys and humans. Human functional neuroimaging studies implicate the dACC in conflict monitoring while monkey neurophysiological studies have been

unable to produce evidence of conflict-related signals (Cole et al., 2009). These differences may be attributed to differences in experimental techniques and dACC structure. Taken together, understanding the neural basis of cognitive control requires an evaluation of the similarities and differences between the two species most commonly used to investigate it.

In this thesis, cognitive control was investigated using monkeys performing pro-saccade and anti-saccade tasks. These tasks rely on well understood neural circuitry and reliably produce behavioural and functional neuroimaging results that are comparable between monkeys and humans (Munoz and Everling, 2004; Ford et al., 2009). As a result, these tasks are useful for clarifying similarities and differences between the two species. Here, we demonstrated that monkeys show switch costs comparable to humans and that switch costs may be associated with task difficulty or cognitive demand. In addition, our findings help reconcile discrepancies regarding the dACC and support the idea that the dACC monitors feedback to select the appropriate task and implement cognitive control, particularly in cognitively demanding task situations. Overall, despite differences between species, the macaque monkey remains a suitable model for investigating the neural basis of cognitive control and task switching.

5.3 Future Directions

5.3.1 Switch-related differences in cortical neural activity

Although this thesis describes switch-related differences in SC activity, neural correlates of task switching have not yet been identified in cortical areas that are thought to be involved with task selection, maintenance, and implementation. Neurons in the dACC, DLPFC, FEF, and SEF demonstrate task-selectivity for pro-saccades and anti-saccades (Schlag-Rey et al., 1997;

Everling and Munoz, 2000; Everling and DeSouza, 2005; Johnston et al., 2007), and are appropriate candidates for investigating for further neural correlates of task switching. The time at which switch-related differences occur in these areas during a trial would be informative of each area's specific role in task processing, task switching, and cognitive control. Switch-related differences in the SC support its role in the production of switch costs. Similarly, it is possible that switch-related differences in the dACC support its role in feedback monitoring and task selection and differences in the DLPFC support its role in task maintenance. Identifying neural correlates of task switching would help elucidate the mechanisms of task processing for goal-directed behaviour.

5.3.2 Effects of cortical deactivation on activity in the task switching network

The work presented here demonstrates how reversible cryogenic deactivation can be used to investigate brain function and functional relationships between brain areas. The roles of the DLPFC and dACC in task switching can be further understood by examining the effects of their deactivation on spiking and LFP activity in other brain areas. For example, the effects of DLPFC deactivation on the FEF, which shows similar spiking activity for pro-saccades and anti-saccades to the SC (Everling and Munoz, 2000), could support the hypothesis that the DLPFC regulates target brain areas. Changes in spiking and LFP activity in the DLPFC with dACC deactivation could clarify the relationship between these two critical brain areas for cognitive control. Furthermore, the effects of DLPFC and dACC deactivation on whole-brain activity and functional connectivity can be examined using fMRI to investigate interactions between brain areas in the task switching network at rest and during task performance. Overall, further

deactivation studies can help elucidate how different brain areas contribute to selecting,

maintaining, implementing, and executing the appropriate task-set.

5.4 Concluding Remarks

Throughout this thesis, the contributions of oculomotor and cognitive brain areas to task

switching were examined in non-human primates using the pro-saccade and anti-saccade tasks.

Successful task switching relies on brain areas to integrate information about the external

environment and internal goals, and select, maintain, implement, and execute the appropriate

task-set. The findings presented here help clarify the role of several brain areas at different stages

of task processing. They suggest that the dACC monitors feedback to select the appropriate task

to perform, the DLPFC maintains the task-set and modulates other brain areas, and the SC is

modulated by task switching processes and contributes to the production of switch costs. Further

investigations of these brain areas and other areas in the task switching network using lesions,

functional neuroimaging, and neurophysiology will continue to provide insight into the neural

basis of goal-directed behaviour.

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EDUCATION

Neurology Residency Program   2017 – Present
University of Calgary, Calgary, Alberta, Canada

MD/PhD Program
Doctor of Philosophy   2012 – 2017
Graduate Program in Neuroscience
The University of Western Ontario, London, Ontario, Canada

Doctor of Medicine   2010 – 2017
Schulich School of Medicine & Dentistry
The University of Western Ontario, London, Ontario, Canada

Bachelor of Science (Honours)   2006 – 2010
SSP Life Sciences, Research Stream, Neuroscience Stream
Queen's University, Kingston, Ontario, Canada

RESEARCH EXPERIENCE

PhD Candidate   2012 – 2017
The University of Western Ontario, London, Ontario, Canada
Investigating cognitive control and task switching using the macaque
oculomotor system
Supervisor: Dr. Stefan Everling

Research Assistant   2008 – 2010
York University, Toronto, Ontario, Canada
The prefrontal cortex, attention, and human eye movement suppression
Supervisor: Dr. Joseph DeSouza

Honours Thesis   2009 – 2010
Queen's University, Kingston, Ontario, Canada
Influence of motor cost and reward value in a reaching foraging task
Supervisors: Dr. Michael Dorris and Dr. Randy Flanagan

NSCI 491 Directed Special Laboratory   2009
Queen's University, Kingston, Ontario, Canada
Characterizing superior colliculus neurons by spike width during visual search
Supervisor: Dr. Martin Paré

PEER-REVIEWED PUBLICATIONS

Chan JL, Koval MJ, Johnston K, Everling S (2017) Neural correlates for task switching in the macaque superior colliculus. J Neurophysiol 118:2156-2170.

Adam R, Isabella S, **Chan JL** (2015) Insight into motor control and motor impairment from stroke and beta oscillations. J Neurophysiol 114:3033-3035.

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BOOK CHAPTERS

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ABSTRACTS AND CONFERENCE PRESENTATIONS

Ma L, **Chan JL**, Johnston K, Lomber SG, Everling S (2017) Dorsolateral prefrontal cortex activites following deactivation of anterior cingulate cortex in an antisaccade task in monkeys. 40th Annual Meeting of the Japan Neuroscience Society. Chiba, Japan.

Ma L, **Chan JL**, Johnston K, Lomber SG, Everling S (2017) Dorsolateral prefrontal cortex activites following deactivation of anterior cingulate cortex in an antisaccade task in monkeys. 11th Annual Meeting of the Canadian Association of Neuroscience. Montréal, Québec, Canada.

Chan JL, Johnston K, Lomber SG, Everling S (2015) Effects of anterior cingulate cortex deactivation on dorsolateral prefrontal cortex local field potential activity and the control of task switching. 25th Annual Meeting of the Society for the Neural Control of Movement. Charleston, South Carolina, USA.

Chan JL, Johnston K, Lomber SG, Everling S (2014) Bilateral anterior cingulate cortex deactivation reduces switch costs in the macaque monkey. 44th Annual Meeting of the Society for Neuroscience. Washington, DC, USA.

Adam R, **Chan JL** (2014) Brain busters: Neuromyths and neuroscience in the media. Brain Awareness Campaign Event, 44th Annual Meeting of the Society for Neuroscience. Washington, DC, USA.

Chan JL, Kucyi A, DeSouza JF (2014) Attentional load affects task-related brain activation but not task decoding. 20th Annual Meeting of the Organization for Human Brain Mapping. Hamburg, Germany.

Chan JL, Koval MJ, Womelsdorf T, Lomber SG, Everling S (2013) Effects of prefrontal cortex deactivation on local field potential activity in the superior colliculus. 43rd Annual Meeting of the Society for Neuroscience. San Diego, California, USA.

Chan JL, Koval MJ, Womelsdorf T, Lomber SG, Everling S (2013) Dorsolateral prefrontal cortex deactivation and saccade-related local field potential activity in the superior colliculus. 7th Annual Meeting of the Canadian Association for Neuroscience. Toronto, Ontario, Canada.

Greenberg A, Wang SH, **Chan JL**, Ferrari P, Cheyne D, DeSouza JF (2011) Evoked response may differentiate the preparatory signals associated with pro- and anti-saccades: a MEG study. Centre for Vision Research Conference. Toronto, Ontario, Canada.

Kucyi A, **Chan JL**, Arsenyan D, Soeizi M, DeSouza JF (2010) The effect of preparatory period on pro- and anti-saccade performance using a gap paradigm. 40th Annual Meeting of the Society for Neuroscience. San Diego, California, USA.

Chan JL, DeSouza JF (2010) Neural correlates of impulse control in the prefrontal cortex in a dual attentional task during the antisaccade task. 20th Annual Rotman Research Institute Conference. Toronto, Ontario, Canada.

Chan JL, DeSouza JF (2009) The prefrontal cortex, attention and human eye movement suppression. Canadian Undergraduate Conference on Healthcare. Kingston, Ontario, Canada.

Ovaysikia S, Tahir KA, **Chan JL**, Jobst CJT, Pynn LK, DeSouza JF (2009) A novel stroop effect examining emotional words on facial expressions: an fMRI study. 39th Annual Meeting of the Society for Neuroscience. Chicago, Illinois, USA.

Chan JL, DeSouza JF (2009) The prefrontal cortex, attention and human eye movement suppression. Rising Stars of Research. Vancouver, British Columbia, Canada.

Chan JL, DeSouza JF (2009) Role of the human prefrontal cortex and attention in response suppression of eye movements. Summer Workshop on Attention & Performance. Hamilton, Ontario, Canada.

Chan JL, DeSouza JF (2009) Role of the human prefrontal cortex in the response suppression of eye movements. 3rd Annual Inquiry@Queen's Undergraduate Research Conference. Kingston, Ontario, Canada.

AWARDS AND HONOURS

CIHR MD/PhD Studentship ($132 000 over 6 years)	The University of Western Ontario	2010 – 2016
Western Graduate Research Scholarship ($25 000 total)	The University of Western Ontario	2012 – 2015
NSERC USRA ($5 625)	York University	2010
Dean's Honour List	Queen's University	2006 – 2010
Major James H. Rattray Memorial Scholarship ($1 000)	Queen's University	2009
Delegate's Choice Award: CUCOH Research Poster Competition		2009
Rising Stars of Research Conference Registration and Travel Awards ($500)	University of British Columbia	2009
NSERC USRA ($5 625)	York University	2009
Principal's Scholarship ($10 000 over 2 years)	Queen's University	2006 – 2008
Major James H. Rattray Memorial Scholarship ($1 000)	Queen's University	2008
NSERC USRA ($5 625)	York University	2008

Dean's Honour List with Distinction	Queen's University	2008
W.T. MacClement Memorial Prize (Biology) ($635)	Queen's University	2007