EXECUTIVE FUNCTION AND FRONTO-STRIATAL CIRCUITRY: INSIGHTS FROM ANTISACCADES, TASK SWITCHING, AND PARKINSON'S DISEASE

By

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Abstract

Many studies of 'executive control' have focused on the prefrontal cortex (PFC), which contains the neuronal functional properties, modulatory neurotransmitters, and network connections with sensory and motor regions to make this large brain area a candidate region to provide all the necessary elements to voluntarily control behavior. However, like the motor and premotor cortex, the PFC is integrated with the basal ganglia (BG) in such a similar fashion, that it is impossible not to consider that the PFC might depend on the BG to implement executive control effectively. This thesis draws on knowledge of PFC and BG function, and combines studies that require the instantaneous *top-down* control over motor behavior with a neurological patient group with primarily BG dysfunction (Parkinson's disease), to provide for a new understanding of prefrontal-BG networks sub-serving executive control. The tasks performed by subjects consist of *antisaccade*s (generate a voluntary eye-movement away from a visual stimulus) and those dealing with *task switching* (change behavior after an alternate was previously required). Numerous neural and functional imaging studies have identified key areas of the prefrontal cortex and BG that are critical to antisaccade generation, and studies in task switching have implicated similar neural mechanisms that are involved in overriding one behavior with another. By combining task switching with antisaccades, this thesis specifically examines the neural mechanisms related to suddenly changing behavior, under conditions where one behavior is easier to perform than the other. The methods utilize on-line eye-tracking in healthy young adults and older adults with, and without, Parkinson's disease, to develop theories of a role of the BG in executive control, and to search for specific neural correlates of executive control signals in the PFC, premotor cortex and BG using functional magnetic resonance imaging (fMRI). Together, the conclusions drawn from this thesis point to an important role of the BG in overriding more automatic behavior with behavior that is more difficult to perform. This thesis also suggests that this overriding mechanism occurs through the boosting of cortical executive control signals via net excitatory feedback from the BG.

Co-Authorship

The research in this thesis was conducted by Ian Cameron under the supervision of Dr. Douglas Munoz and Dr. Giovanna Pari. Ian Cameron conceived and designed Chapter 3, and assisted in the conception and designs of Chapters 2, 4 and 5. Ian Cameron collected and analyzed all of the data in Chapters 2, 3, 4, and 5 (except for a portion of control participants in Chapter 5 that were collected by Alicia Peltsch). Ian Cameron wrote all first drafts of Chapters 2, 3, 4 and 5, and was lead author on all subsequent drafts. Dr. Nadia Alahyane designed the experimental paradigm in Chapter 5. Dr. Brian Coe assisted in the methodological designs in Chapters 3 and 5, and implemented the fMRI eye-tracking capability. Dr. Douglas Munoz co-conceived Chapter 2, and assisted in the conception and designs of Chapters 3, 4 and 5. Dr. Giovanna Pari recruited participants with Parkinson's disease for Chapters 4 and 5, and assisted in the designs of Chapters 4 and 5. Dr. Masayuki Watanabe co-conceived and designed Chapter 2, assisted in the methodological designs of Chapters 3 and 4, and designed the paradigms and analysis programs of Chapters 2 and 4. Dr. Patrick Stroman assisted in the methodological designs in Chapters 3 and 5. Drs. Brian Coe, Douglas Munoz, Giovanna Pari, Patrick Stroman, and Masayuki Watanabe provided editorial advice on the writing of Chapters 2,3 and 4, where listed as co-authors in each chapter. Dr. Douglas Munoz also provided editorial advice on the writing of Chapter 5.

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List of Abbreviations and Symbols

AC	anterior commissure
ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
ANOVA	analysis of variance
anti	non-switch antisaccade trial
anti2pro	antisaccade to prosaccade switch trial
anti2pro error	erroneous antisaccade to prosaccade switch trial
BG	basal ganglia
bonf	Bonferroni correction
BOLD	blood oxygen level dependent
cd/m^2	candelas per square meter
CN	caudate nucleus
DA	dopamine
DLPFC	dorsolateral prefrontal cortex
EOG	electrooculography
EPI	echo-planar imaging
Exec	execution period
FA	flip angle
FDR, Q(FDR)	false discovery rate
FEF	frontal eye fields
fMRI	functional magnetic resonance imaging
FOV	field of view
FWHM	full-width at half maximum
GPe	globus pallidus external segment
GPi	globus pallidus internal segment
L	left
L-DOPA	levodopa

LED	light emitting diode
LTD	long-term depression
LTP	long-term potentiation
MD	thalamus (mediodorsal nucleus)
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MP-RAGE	magnetization-prepared rapid gradient-echo
MRI	magnetic resonance imaging
ms	millisecond
MSN	medium spiny neuron
NS	non-switch
PC	posterior commissure
PD	Parkinson's disease
PFC	prefrontal cortex
PEF	parietal eye fields
PET	positron emission tomography
PFC	prefrontal cortex
prep	preparatory only trial
pro	non-switch prosaccade trial
pro2anti	prosaccade to antisaccade switch trial
pro2anti error	erroneous prosaccade to antisaccade switch trial
R	right
s	second
SC	superior colliculus
SD	standard deviation
SE, SEM	standard error of the mean
SEF	supplementary eye fields
SNr	substantia nigra pars reticulata

SNpc	substantia nigra pars compacta
SRT	saccade reaction time
STN	subthalamic nucleus
TE	echo time
TMS	transcranial magnetic stimulation
TR	repetition time
UPDRS	Unified Parkinson’s Disease Rating Scale
val	value
VLPFC	ventrolateral prefrontal cortex
vs.	versus
WSR	Wilcoxon signed rank test
~	approximately
©	copyright
$	dollar
=	equal
>	greater than
<	less than
%	percentage
±	plus or minus
*, **, †	to highlight statistical significance or importance where described

Chapter 1: General Introduction

When Alfred Nobel left in his will the financial means to establish annual awards "to those who, during the preceding year, shall have conferred the greatest benefit on mankind" [1], the Nobel Prize in Physiology or Medicine was designated to go an individual who made the "most important discovery" within the domain of physiology or medicine. Embodied under his original conception were the desires society had (and still have today) for groundbreaking discoveries that bring forth significant scientific impacts that, in the case of the biological sciences, become canonical principles of function. Over a century later, the Nobel Prize in Physiology or Medicine remains one of the most significant forces of motivation to scientists working in biological sciences for finding that *one* principal discovery. With 100 awards since its conception (awards were not always presented during the World War years and in the 1920s), a surprisingly large number have been given to neuroscience, as this young field was laying down general principles of biological computation. Prizes awarded in the early third of the 20th century went to very basic principles following Nobel's wishes; Golgi and Cajal received theirs for *structure of the nervous system* in 1906, and Sherrington and Adrian for *function of neurons* in 1932. Subsequently, a large quantity in the 1960's and 1970's (Fig. 1.1) were awarded for work during a 'golden age' of neuroscience in the mid 20th century where the field was rapidly expanding and still making discoveries that were no less rudimentary in nature. In fact, when Hubel and Wiesel received theirs in 1981, it was for *discoveries concerning information processing in the visual system*, and this award was shared with Sperry for identifying the *functional specialization of the cerebral hemispheres*. Thus, it is apparent that major, fundamental discoveries were made over the past century regarding the most complex organ and biological computation device in nature. For this trend to continue, one would assume that there needs to be more discoveries that result in unchallenged determinations of functions; something that may, or may not, be possible as the field now advances in many directions dealing with more complex questions that are difficult to define precisely, like 'consciousness' or '*executive functions*', which will be investigated in this thesis. We are in an era where rules of how the brain mechanistically performs a particular operation are becoming difficult to establish without considering numerous alternative solutions,

[1] http://www.nobelprize.org, © Nobel Web AB, 2009

as we now have a better appreciation of the roles of multiple neuron networks that span the entire brain. Perhaps, this is why two of the awards in Physiology or Medicine in the past 30 years have gone to *physical* science methods that provided researchers with tools to ask more comprehensive questions related to the nervous system, such as how multiple brain regions can work together under larger, more complex computations. Cormack and Hounsfield received their prize for *computer assisted tomography (CAT)* in 1979, and Lauterbur and Mansfield for *magnetic resonance imaging (MRI)*, in 2003. We may well witness more awards in Physiology or Medicine to major technological advances, as the methods we utilize now become even more important, as we aim to map brain networks in complex behaviors that may not provide a concrete substrate upon which to build a unitary principle of function, like those mediating *executive control*, described in Section 1.1. Thus, quite possibly, a future Nobel Prize in Physiology or Medicine may go to S. Ogawa and K.K. Kwong, the two scientists credited with discovering functional magnetic resonance imaging (fMRI), as it has provided those of us working in behavioral neuroscience with a tool to make giant leaps in our study of the neural mechanisms underlying the production of complex human behavior that would not be possible otherwise. However, for such a award to occur, fMRI would need to demonstrate its long-lasting significance to the "betterment of mankind", and as such, its direct implications to neuroscientific conclusions will need to become unchallenged, as we in the behavioral neurosciences will need to show that our discoveries using this technique can lead to establishing principal findings of neural function, and not just giant leaps in interpretation.

Because of the complexity of fMRI as a technique, as well as with what it is typically used to study, the past two decades since its scientific explosion have also been accompanied by reactions of disappointment and dismissal not unlike those related to phrenology in the 1800's. This is because in 2010, modern imaging methods still have no way of actually measuring a response in a single neuron – the basic computational architecture behind behavior – and thus to some, are no more than million-dollar calipers. But those of us in the behavioral neurosciences who have embraced the field with all its shortcomings do so with the philosophy that fMRI can fill in the missing links between the neurons and human behavior, with a technique that is unrivalled

in the versatility of questions that can be asked in a variety of human populations. We do so, also, because the imaging field is continually improving; one needs to only attend an annual brain-imaging meeting before they are struck with awe with just how fast this field builds upon itself and is brought closer to neural computations. Questions about what the brain is doing provoke questions about what improvements can be made to the methodology; and the development of new methods stimulates novel questions that are then asked about brain function. In this sense, the impacts of Ogawa's and Kwong's original discoveries are already apparent. The past decade has seen a drive towards interpretations that break from regional specialization of function, to those aiming to understand distributed networks of processing, as decades of evidence from animal neurophysiology have demonstrated. Advances in computational modeling, combined with new imaging techniques more sensitive to the timings of neural processing (e.g., magnetoencephalography) and with methods that can focally manipulate function in a network (e.g. transcranial magnetic stimulation), will ensure that fMRI will remain be one of the most widely used techniques to study the human brain – even if only as a complementary first-pass analysis to identify the regions and networks involved in larger, more complex neuronal processes demanding more fine-grained exploration. This exploration may be accomplished by other methods; or, it may bring about new developments in imaging and insights into the use of other applications that would not have arisen otherwise. In any case, for complex, neuronal operations to be understood, the entire neuroscience community will need to integrate their individual methods and discoveries in order for some global 'Eureka' moment to arise.

1.1 Prefrontal Cortex (PFC) and Executive Function

The integration of functional brain imaging (fMRI as well as positron emission tomography) with clinical, animal, and computational approaches is critical to the study of the one of the most important and complex forms of neural function in humans: those of *executive control*. These high-level cognitive functions, (defined as the neural processes important to guiding voluntary behavior when specific plans of action must be formulated) (Baddeley, 1986; Owen, 2004), should not be interpreted without taking a network approach (Gazzaley and D'Esposito, 2007), and as such will ultimately demand the use of methodologies that will enable this. This is

because they encompass everything from sensory processes related to assessing whether a given object should evoke a behavior, to the 'internal' representation of what behaviors can be linked to a given stimulus, to the actual execution of a motor response. As such, it is difficult to isolate any particular brain region as being the only site of a given executive process. However, it is apparent that when there is a *problem* in executive functioning (as described below), there are specialized brain functions that are better described as not being sensory or motor in origin, but as being some sort of hybrid process such as *working memory* (the maintenance of information in the brain that may no longer exist in the environment, but may be used to guide future behavior) (D'Esposito et al., 1995). It is also appropriate to consider that processing *'hubs'* exist in the networks that span the sensory and motor systems, and in this way do provide anatomically identifiable substrates of executive control processes that can be explored using fMRI. We know these hubs exist because many pathologies of the nervous system cause focal lesions rather than distributed degeneration, and have provided snapshots into the compartmentalization of many components of executive function that are neither sensory nor motor per se, and that reveal distinct processes that can be dissociated from one another depending on the site of the lesion (Gazzaley and D'Esposito, 2007; Badre et al., 2010). Thus, regional specialization within the executive control network does exist to some degree, and modern fMRI studies are continuing to prove useful in mapping the locations of these specific processes onto processing hubs, particularly within the prefrontal cortex (Gazzaley and D'Esposito, 2007).

Today, the most famous example of executive functions still comes from a startling example of executive *dys*function following a frontal lobe lesion to railway worker Phineas Gage in 1848. As described by his physician, John M. Harlow, with Mr. Gage

> "the equilibrium or balance, so to speak, between his intellectual faculties and animal propensities seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity, manifesting but little deference to his fellows, impatient of restraint or advice when it conflicts with his desires, at times perniciously obstinate, yet capricious and vacillating, devising many plans of operation which are no sooner arranged than they are abandoned in turn for others appearing more feasible…" (Harlow, 1993).

Harlow's assessment was conducted years before the first fMRI studies showed frontal lobe changes in blood oxygenation could be attributed to executive functions (D'Esposito et al., 1995), or before the first quantifiable neuropsychological lesion studies were performed in a modern

experimental approach (Milner, 1963). Nevertheless, the description by Harlow still stands today as a basic, but unitary observation of what the frontal lobe contributes to high-level neural functions that are so crucial to human behavior. It has been well established since Gage that the prefrontal cortex (PFC) is a brain region that is universal to these high-level executive operations, and now modern lesion and imaging studies are shedding light on subcomponents of executive functions (many of which are the same as those described in Gage's behavior) that can be roughly aligned to divisible prefrontal sub-networks (e.g., Guitton et al., 1985; Miller and Cohen, 2001; Gazzaley and D'Esposito, 2007; Badre et al., 2009). It is also apparent, however, that executive hubs exist beyond the boundaries of the PFC, and these different brain regions become more important depending on the question; if one is interested in studying memory processes to guide future behavior, then the hippocampus must be considered (Bast, 2007), on the other hand, if one is interested in attentional filtering of irrelevant information to a behavioral goal, then the parietal lobe needs to be incorporated (Colby and Goldberg, 1999). However, in all cases, critical hubs also exist in the PFC, meaning that it effectively has a role as a central processing region mediating the flexible control over behavior. Gage's lesion, which encompassed the PFC bilaterally, produced behavioral changes related to the general operations governing voluntary behavioral control: in particular, in that *easier* behaviors (or those that appear to be more automatic or impulsive) were performed more often that would be desired. More specifically for the goals of this thesis, Gage's brain lesion affected the functioning of executive operations required when a *rule* specifies the *selection* of a particular behavior, out of alternative behaviors that may be in direct competition. The ability to plan and generate an appropriate behavior based on a given environmental condition is a critical component of executive control, and is the basis of the experiments in Chapters 2-5.

A rule can be anything delivered to an animal from the environment that should evoke a particular response (e.g. green: eat, black: do not eat). In many cases (especially in laboratory experiments), the rules constitute the generation of arbitrary *stimulus-response mappings* (e.g., green: press left button, black: press right button). They require the integration of information from any of the sensory modalities, combined with information accessed from memory, and the

retrieval of an internal model of how to behave, or in some cases, the generation of new plans of how to behave. These plans can be referred to as *task sets* (Sakai, 2008) and their formation and maintenance constitute the hallmark of executive functions involved in generating goal-directed behavior, and implicate the PFC as being central to their formation (Miller and Cohen, 2001; Gazzaley and D'Esposito, 2007). A decision process is often required in which the animal must first integrate the environmental information to establish a task set, to then select an appropriate action to perform from numerous competing possibilities – and often with millisecond timing. The selection choices can be simple, such as to approach or avoid a stimulus, or they can be complex if, for example, they require previous knowledge of what a given environmental context means, or require the inclusion of intermediate steps or use of a tool, such as to brake or steer an automobile to avoid an obstacle.

As with all studies of executive function, sensory information, working memory and attention cannot be neglected, meaning that one should consider the influence of other brain regions (as will be described below). Specifically, it is not clear in how separable the 'selection' is (i.e., the internal planning of a future motor behavior based on a given rule) from actual response programming and execution. Nevertheless, because the PFC is a critical central processor to all of these functions, and because all of these functions contribute to rule processing, it is logical to focus on this region as a central brain region to rule processing. However, to understand how rule processing can lead to the programming of a behavioral response, the integration with the motor system requires deeper exploration. This is of particular importance, as to study executive *control,* we need to extend rule processing to behavioral execution. Experimentally, we can do so by creating conditions in a laboratory setting whereby one neural sub-process (e.g., rule processing) can be isolated from some other operation (e.g., response programming). This is often done, especially in the case of fMRI, by contrasting two or more conditions that we hypothesize differ in the type or requirement of a given process.

For a goal-directed behavior to be produced, the brain must be able to rapidly incorporate information both from the environment as well as from an internal model of how to achieve the goal with the application of a particular motor response. Suppose what is required is a routinely

automated task, such as to orient one's gaze to attend to a given object; the appropriate stimulus-response mapping is a simple one, and presumably, a motor behavior is produced with little requirement for executive control. However, should the desired behavior be something that is novel, or that goes against competing alternatives that may be more automatic to perform (demanding less 'cognitive effort'), the brain must have the mechanisms to override the tendency to the more automatic behavior, and produce what is desired. This simplified scenario of executive processes involved in response selection under relatively automatic, versus relatively complex, conditions is an excellent framework to work with in a laboratory setting, because it provides for the quantifiable comparison between stimulus-response mappings that are very strong (thus demanding little executive control), with those that are perhaps more difficult to achieve (demanding greater executive control). Any delay in execution, increase in the frequency of erroneous responses, or other measureable behavioral parameters that allow for the evaluation of how *efficient* a goal-directed behavior was performed, provides the experimenter with a substrate that is simple enough to form the basis of an fMRI study, a neurophysiological recording study, or a computational model, because it contains a simple "condition A versus condition B hypothesis" that can be directly tested. An example of this is the *antisaccade* task, which requires one to suppress the automatic tendency to look towards an abruptly appearing visual stimulus, and to execute an eye movement (saccade) in the opposite direction (Hallett, 1978; Munoz and Everling, 2004). Indeed, neurological correlates associated with this task have been explored in numerous human imaging (e.g., Sweeney et al., 1996; Luna et al., 1998; Connolly et al., 2002; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Connolly et al., 2005; Ford et al., 2005; Brown et al., 2006) and animal studies (e.g., Everling et al., 1998; Everling and Munoz, 2000; Everling and DeSouza, 2005; Watanabe and Munoz, 2009; Watanabe and Munoz, 2010), and the executive sub-processes involved generally hinge upon neural networks involving the PFC being required in: a) establishing an antisaccade task set, b) suppressing the competing response (prosaccade), c) directing attention to the desired location for which to direct behavior, and d) programming the desired motor response. While the nuances of these steps pertain to a specific goal-directed oculomotor response, they do map onto executive processes that are

thought to be universal to generating any voluntary behavior, and outcompeting more automatic alternatives. Moreover, they fit with general theories of how PFC networks act as sources of *top-down* signals that can modulate processing in other brain regions (Desimone and Duncan, 1995; Miller and Cohen, 2001; Gazzaley and D'Esposito, 2007).

To explore the neural mechanisms and to more precisely identify the critical brain regions in these processes, it helps to consider computational models of executive control, as they can suggest plausible solutions to a black-box problem. In one general model of how top-down signals can result in the selection of an appropriate behavior, Dehaene and colleagues (1998) proposed that there exists in the brain a large spanning network termed the *global 'workspace'*, consisting of long-range cortical connections with the frontal cortex, centered, in particular around the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). This conceptual workspace receives and sends connections to 'processor' modules, that constitute sub-networks that assign a given a rule to a given sensory input, and thus generate a *stimulus-response mapping*. For tasks that are highly automated, the processors can produce the appropriate behavior with minimal influence from the higher-level workspace. However, when novel, less automatic or more complex tasks are required, the workspace acts as a modulator to these processors (Dehaene et al., 1998). This model is not far from the one proposed by Norman and Shallice, in which attention has a role as a 'supervisor' of sub-processing modules in goal directed behavior (Norman and Shallice, 2000). The idea of a higher-level network providing top-down signals to lower-level networks provides a means for classification of executive sub-processes that map onto specific neural substrates, described in the following sections. Importantly, however, the workspace model fits with general descriptions of PFC function (Gazzaley and D'Esposito, 2007), such that it can *enhance* processing in some lower networks and *suppress* processing in others. This concept will be a key framework on which the experiments in this thesis were designed, and for why the basal ganglia (BG) (Section 1.3) might be critically important in making these fundamental operations possible.

1.2 Modelling Executive Function

The 'workspace' in the Dehaene and colleagues (1998) model incorporates signals that can activate and suppress the appropriate and inappropriate processing units, respectively, and contains internal connections that can maintain an active state for a goal-directed behavior, but switch to a different state if negatively evaluated. Only one such state can be active at a given time, meaning that parts of the workspace related to other states are inhibited; therefore, this provides a conceptual model of the maintenance of an established *task set*. The idea of limited executive resources to maintain one task set is an important hypothesis, that fits with many of the findings in this thesis (Chapters 4 and 5) pertaining to the execution of an inappropriate response in Parkinson's disease, when the desired task set is overridden, erroneously, with an alternative.

This basic architecture provides a simple, but insightful model of how a given task-set can be maintained, and how the selection of a given behavior can be implemented in a neural network model. Indeed, it was demonstrated that it could model a shift from automatic behavior in the Stroop task (read a written word) (Stroop, 1935), to the more effortful behavior (state the name of the font color of the written word), providing a framework for executive processes related to controlling voluntary behavior in situations that would be similar to those in the antisaccade task described previously. What is most interesting to note was that the workspace was not needed for the automatic word naming response, such that the automatic behavior (and task set) were activated by the lower processor modules alone. However, the more dominant nature of an automatic task set results in an initial bias amongst the processor modules so should the workspace *not* successfully activate the alternative task set, the more automatic behavior is executed in error. Thinking in this fashion is beneficial to our interpretation of executive dysfunction observed in Phineas Gage, as well as in many neurological disorders implementing prefrontal cortical networks, such as Parkinson's Disease (PD) (Chapters 4 and 5), and Attention Deficit Hyperactivity Disorder (ADHD) (Owen, 2004; Sergeant, 2005). A problem with this model, however, is that it is based on some learning mechanism to reset the system to a novel behavior that gets closer to perfect performance with each iteration. Thus this, and other learning models like this, cannot explain how a human brain could instantly choose the appropriate response upon

the first exposure. The evidence from biological experiments (and from everyday life) that the brain, in particular the PFC, can do this is without debate: how else could one perform the color naming Stroop response or an antisaccade on the very first instance after receiving only a verbal instruction to do so?

One possibility is that contained within the executive and motor networks is something analogous to a 'library' of possible task sets and behaviors from which to choose. However, certain task sets are more difficult to assemble, requiring increased processing time, and/or a greater integration of information from the environment, memory, and motor planning. Novel task sets may not even exist in the library, and may need to be created through the rapid integration of new information upon first experience, and then stored for more efficient execution the next time they are required. The more complex or novel the task sets are, the more the executive system must work to achieve their establishment in neural executive networks (such as in the concept of a 'workspace'). For this reason, first-time behaviors likely depend on environmental feedback to acknowledge that the desired behavior was achieved, or not. The next time the brain experiences the identical conditions, these states would benefit from any *boosting* mechanisms in which the desired activation patterns can be rapidly selected and strengthened over the alternative, more dominant, possibilities. While this proposal has not yet been proven, experimental and anatomical evidence shows that the PFC is cable of mediating the translation of sensory information into internal representations to guide motor behavior (Gazzaley and D'Esposito, 2007), however whether the PFC does this alone is questionable, and unlikely, as explained in the following section.

1.3 Basal Ganglia (BG) and Executive Function

The basal ganglia (BG) could provide a boosting mechanisms to cortical processes, having both the means to increase the strength (firing rate) of PFC signals, suppress competing signals, and to also enable the rapid selection of previously learned behavior, which is critical to performing movements in sequence that have become automatic (such as typing or bicycle riding) (Wise et al., 1996; Hikosaka, 1998; Redgrave et al., 1999; Wu and Hallett, 2005; Doyon, 2008). Moreover, the BG also have the means to globally suppress the response system very

rapidly (Mink, 1996; Nambu, 2004; Nambu, 2005), perhaps allowing for the PFC to establish the novel, first-time task set and generate the appropriate response.

BG circuits are interconnected with the motor as well as prefrontal cortices in positive feedback loops (Alexander et al., 1986; Wise et al., 1996) and have been shown to be crucial in regulating the voluntary control of motor behavior (Hayes et al., 1998). Basic models of the basal ganglia posit that the two component pathways, the direct and indirect, participate in the selection of a desired motor program; activation of the direct pathway results in dis-inhibition of thalamo-cortical and brainstem circuits, where as activation of the indirect and hyperdirect pathways results in increased inhibition (Mink, 1996; Nambu, 2005) (Fig. 1.2A). These models were developed based on evidence from motor (Mink, 1996) and oculomotor control (Hikosaka et al., 2000), but the parallel architecture that includes prefrontal and limbic 'loops' suggest that it functions, in general, as a selector for a given pattern of cortical activity (Alexander et al., 1986), with the looped architecture supporting positive feedback of the same cortical *modules* that provided signals to the BG input nuclei originally (Wise et al., 1996). The process of signal selection is thought to occur first through widespread inhibition of thalamo-cortico and brainstem circuits via a fast pathway that increases inhibitory output (the hyperdirect pathway) that prevents the execution of all movements. Subsequently, focused dis-inhibition of a desired motor program ensues by the direct pathway, with the indirect pathways assisting in further focusing (Mink, 1996). Indeed, the fast stopping process, through the hyperdirect pathway (involving the sutbthalamic nucleus as the input to the BG and not the striatum) has been established in recent human fMRI studies (Aron and Poldrack, 2006), as well as in anatomical and neurophysiological experiments (Monakow et al., 1978; Fujimoto and Kita, 1993). Moreover, it has been shown through lesion studies of individual BG nuclei, as well as with pathologies affecting the BG, that cells in motor cortex do behave under these circumstances, as they would be expected if they are, in fact, receiving less thalamic excitation (Mink, 1996); specifically, the peak level of activity in motor cortical neurons is reduced, and the time to reach the peak is delayed (Doudet et al., 1990; Watts and Mandir, 1992). As explained above, this basic architecture has been demonstrated physiologically in the oculomotor channel (Hikosaka et al., 2000), which uses the

same input (caudate nucleus (CN)) and output (substantia nigra pars reticulata (SNr)) nuclei as the prefrontal 'executive' loop.

The BG circuits are themselves modifiable, such that the strength of a given cortico-BG module can be enhanced by learning mechanisms (Wise et al., 1996). This enables even initially novel behaviors to become more automated after specific cortico-striatal synapses are strengthened. Dopaminergic inputs to the dendrites of the striatal medium spiny neurons (MSNs) provides for the enhancement of the specific cortico-striatal synapses of the direct pathway, and in turn, for stronger, more focal dis-inhibition of a given behavioral module (Mink, 1996; Schultz, 2001). Evidence does suggest that as novel actions become well-learned, the BG becomes more important in their execution (Wu and Hallett, 2005; Doyon, 2008), and the BG's direct and indirect pathways provide the basic architecture to produce patterned or sequencing behaviors (Berns and Sejnowski, 1998). It has also been hypothesized that dopamine signaling in the striatum eventually decreases if a behavior becomes more established, once the cortico-striatal synapses have become strengthened (Horvitz et al., 2007) to the point of automatization. Taken together, this suggests that the BG can both function as a mechanism to boost the selection process of the task set signals of the PFC, and then once *automaticity* has occurred, the BG can function more in a direct means to produce motor behavior, perhaps through motor cortical-BG channels (Graybiel, 1998; Badre et al., 2010). In this sense, an automatic task set could be considered to be directly coupled to motor behavior, and mediated through BG motor circuits activating well-learned behavioral modules. Non-automatic task sets might be established in prefrontal/premotor cortex, and depend on BG signaling for suppression of competing task sets, and for mechanisms to *become* automated.

Direct experimental evidence that the BG plays an important role in executive control in humans is also well established, given that patients with BG disorders such as Parkinson's and Huntington's disease display deficits in decision making, planning and working memory (Owen, 2004; Wolf et al., 2009) with corresponding signal differences in the BG and PFC when patients with Parkinson's disease perform tasks related to flexibly changing behavior (Monchi et al., 2004). The interplay between the PFC and the BG is extremely important to executive control (Baddeley,

1986; Hikosaka, 1998; Miller and Cohen, 2001; Owen, 2004; Wager et al., 2004; Aron and Poldrack, 2006; Cools et al., 2006; Aron et al., 2007), and modern lesion and fMRI studies now are aiming to better understand the relative anatomical components in cortical and subcortical structures.

Given all the evidence that the PFC and BG together constitute critical networks governing executive control, it is possible that a hierarchy exists such that the further a behavior is removed from immediate motor execution, such as task set establishment, the PFC is the originator of the control mechanisms (Wise et al., 1996; Gazzaley and D'Esposito, 2007); but, the PFC might require signals from the BG to keep the goal-relevant activity maintained, and thus would benefit from the BG's ability to select and inhibit signals that pertain to competing behaviors (as suggested by the experiments in this thesis). However, incoming information, if highly salient or ingrained into a well-learned task set, can result in the rapid re-selection of an alternative cognitive state (Miller and Cohen, 2001), preparing the motor system for an alternative behavior to be performed. Indeed, attention signals have been included in the Dehaene and colleagues (1998) model as something that can reset the workspace to a different state, and are also known to induce a dopamine burst in the BG (Horvitz et al., 2007) perhaps helping to reset the task set when novel information is introduced.

1.4 Outline of Experiments

Under the framework of PFC and BG operations described above, the goal of this thesis is to investigate the role of the BG in executive control; specifically, to examine how the BG might assist the PFC by providing mechanisms to suppress, and/or dis-inhibit, cortical signals related to preparing for and generating a desired voluntary behavior. Four studies were conducted to understand the role of PFC-BG circuitry in tasks when one behavior needed to be overridden with another, because this principle represents a cognitively demanding scenario in which a desired task set needs to be rapidly established and the response system 'reconfigured' (Rogers and Monsell, 1995). I utilized tasks that each constituted some, or all of the following principles: a) two behaviors in competition with one another, with a selection process required, b) the distinction between task set establishment and motor response programming, and c) differences in

automaticity between two behaviors. We did this by developing novel *task-switching saccade tasks* that built upon the already well-established pro and antisaccade tasks, but also incorporated principles from the study of task switching that are more useful for studying task set competition (Rogers and Monsell, 1995; Meiran et al., 2000). The use of the saccadic eye-movement system provided us with a well established motor system that is well understood at the physiological level (Scudder et al., 2002; Sparks, 2002; Munoz and Everling, 2004) and that contains known regional hubs to enable us to make predictions about their relative roles in executive control processes. The application of fMRI conducted concurrently with online eye-tracking enabled us to measure behavior in an environment in which the subject cannot otherwise move. Based on the known neural substrates involved in saccade generation, the imaging studies were conducted with a targeted approach, providing us with a Region of Interest (ROI) method to investigate the brain networks involved in executive functions pertaining to successfully executing a desired response.

The results from Chapter 2 show that flexibly switching from one behavior to another is accompanied by a quantifiable measure, the 'switch cost', that is, interestingly, more tied to motor processes rather than cognitive processes related to task set establishment. Following this, Chapter 3 confirms similar switching behavior in an fMRI experiment, and shows that the BG is involved in switching from one prepared response to another, but with particular importance in switching from more automatic to more voluntary behavior. Thus, Chapters 2 and 3 demonstrate that neural processes required to successfully change behavior map onto circuits involving the BG, but that the particular involvement of the BG is in switching to a non-dominant motor response. However, despite Chapters 2 and 3's findings that parameters related to executive control processes (the switch costs) are more identifiable during *motor* preparation and execution, it might be that these signals originate from the PFC, with assistance of the BG in tuning into the proper task set signals when an inappropriate motor behavior is imminent. Thus, in Chapter 4, patients with Parkinson's disease perform a similar experiment to Chapter 2, but with manipulations to push participants towards the execution of an initially instructed behavior. Doing so means that the appropriate task set must then be able to be reestablished for the appropriate

response to be executed. The results show that deficits in establishing the non-dominant task set arise in Parkinson's disease, fitting with deficits in executive control. Finally, in Chapter 5, it is shown that behavioral deficits in suppressing automatic behavior in Parkinson's disease correlates with fMRI signals related to the failed establishment of the non-dominant task-set in the prefrontal and pre-motor cortices, and this is shown to be independent of motor execution. Taken together, Chapters 3, 4 and 5 suggest that prefrontal-BG circuitry is important in overriding automatic behavior with more voluntary behavior, with the influence of automaticity apparent at the task set stage. Combined with Chapter 2, this thesis suggests that the BG provide the mechanisms to activate and suppress the appropriate and inappropriate neural signals related to a given behavior, so that the desired behavior can be implemented efficiently. This gating mechanism assists the prefrontal cortex in selecting the appropriate task set whenever goal-directed behavior is required suddenly.

1.5 Publication of Chapters

Chapter 2 (Cameron et al., 2007), Chapter 3 (Cameron et al., 2009a) and Chapter 4 (Cameron et al., 2010) have been published in peer-reviewed journals. For citation purposes, please reference these original publications. Preliminary data from Chapter 5 has appeared in abstract form (Cameron et al., 2009b). The following changes have been made to the chapters in this thesis with respect to the original publications. In Chapter 2, minor editorial changes have been made for continuity with other chapters in the thesis, as well as to correct an error in reporting degrees freedom in one-way ANOVA statistical tests. Editorial changes include: 'nonswitch' to 'non-switch'; 'P' to '*P*'; 'F' to '*F*'. The changes in the reporting of degrees of freedom are: 'F(1,2)' to '*F*(2,33)'. In Chapter 3, minor editorial changes have been made for continuity with other chapters in the thesis. These changes include: 'Supporting Fig.' to 'Supplementary Fig.'; 't_{df}' to '*t*'. Finally, in Chapter 4, minor editorial changes have been made for continuity with other chapters in the thesis, which include: 'pro-to-anti' to 'pro2anti'; 'anti-to-pro' to 'anti2pro';'t(df)' to '*t*'.

Chapter 2: Contrasting Instruction Change with Response Change in Task Switching

2.1 Abstract

Switching between two tasks results in 'switch costs,' which are increased error rates and response times in comparison to repeating a task. Switch costs are attributed to a change in 'task set,' which is the internalized rule of how to respond to a stimulus. However it is not clear if this is because the instruction about which task to perform has changed, or because a programmed response has changed. We examined this question by changing the instruction about whether to perform a pro or an antisaccade to a stimulus, before or after the stimulus was presented. As a saccade response is specified by instruction plus stimulus position, changing the instruction after the stimulus was present resulted in a change in the specified response, whereas changing the instruction beforehand did not. Three experiments investigated i) if changing instruction alone or changing the specified response produced switch costs; ii) if predictability of switching instruction influenced switch costs; and iii) if predictability of stimulus position influenced switch costs. Regardless of instruction or stimulus predictability, switch costs for both pro and antisaccades consistently resulted if the specified response switched. This suggests that a pro or antisaccade motor program was automatically programmed based on a presented instruction and stimulus position. Therefore, the given physical information drove switch costs, even if subjects could predict a change in task. This study demonstrates that switch costs result if changing an instruction changes a programmed response.

2.2 Introduction

The choice to perform one task instead of another is a hallmark of human executive functioning. However, flexibly changing from one task to another results in impairments in performance. In the laboratory setting this is explored by monitoring performance when two or more tasks are interleaved. Namely, subjects are slower to respond if the task on the current trial is different from the task on the previous trial (Jersild, 1927; Spector and Biederman, 1976; Allport et al., 1994; Rogers and Monsell, 1995). Subjects also make more errors when the task switches from one trial to the next. These increases in response time and error rates when switching task are referred to as 'switch costs'.

Switch costs represent a basic but fundamental measure of the ease in which the brain can flexibly control behavior. Functional Magnetic Resonance Imaging (fMRI) studies suggest that flexibly switching task is mediated by the prefrontal cortex, the pre-supplementary motor area, basal ganglia and parietal cortex (Monchi et al., 2001; Brass and von Cramon, 2004; Miller et al., 2005; Yeung et al., 2006). Lesions or degeneration in these areas can lead to task-switching impairments (Milner, 1963; Miller and Cohen, 2001; Monchi et al., 2004). However the precise neural origins of switch costs are unclear.

There is substantial evidence that switching task requires executive processes to switch 'task set.' 'Task set' refers to the internalized rules about how to respond to a stimulus (Allport et al., 1994; Rogers and Monsell, 1995; Schuch and Koch, 2003). Evidence suggests that 'task set' can be subdivided into components that can be configured endogenously in advance of stimulus presentation, and into other components that are triggered upon presentation of the stimulus to act upon (Rogers and Monsell, 1995; de Jong, 2000; Matthews et al., 2002; Monsell, 2003; Barton et al., 2006). Meiran (2000) proposed that task set can be divided into 'stimulus set' (prepared based on an instruction) and 'response set' (pertaining to the execution of a response to the stimulus). Therefore it is possible that task set prepared based on an instruction may simply be a rule about what to do; whereas task set triggered by the target stimulus may be a response program that is automatically prepared. The aim of the current study is to investigate how switching only an internalized rule differs from switching a programmed motor response.

Recent studies have investigated how switch costs are related to selecting and executing a response (Meiran, 2000; Schuch and Koch, 2003; Wylie et al., 2004; Koch and Allport, 2006). These studies have used methods such as: priming the subject to execute one motor response over another (e.g., hit left key), interleaving no-go trials (where a response was not executed on the previous trial), and examining the interference from two responses that share a common response mapping (e.g., hitting left key as a valid response to either task). However, in each case the comparison (switch versus repeat task) is made between the current trial that includes an instruction and a response, and the previous trial that also included an instruction and a response. Therefore, these studies cannot directly examine the difference between *switching* a

response process versus switching only a rule. Comparing across trials mixes both processes, and can include other sources that affect responding, such as previous saccade direction and previous stimulus location (Fecteau and Munoz, 2003).

In the present study, we used a *mid-trial* change of instruction that could occur before or after the target stimulus was presented. On each trial, a colored fixation point dictated to perform a prosaccade to a peripheral stimulus, or an antisaccade away from the stimulus. If this fixation point changed color before the stimulus was present, it did not constitute a change of response, only a change in the rule about what task to perform on that trial. However if the instruction changed after the stimulus was present, the required response was also changed.

We used prosaccades and antisaccades because distinct responses (saccade left or saccade right) are dictated by an instruction plus stimulus position. A large body of literature exists on their neurophysiological processes, and we know that the presentation of a stimulus will automatically evoke response processes (Dorris and Munoz, 1998; Everling and Munoz, 2000; Munoz and Everling, 2004; Everling and DeSouza, 2005). Secondly, studies have shown that the prefrontal cortex is involved in configuring to the appropriate saccade task using fMRI of humans (DeSouza et al., 2003) and neurophysiology in monkeys (Everling and DeSouza, 2005). Furthermore, there are no issues of overlapping stimulus response mappings, as on each trial the leftward saccade response is exclusively associated with one task, and the rightward response is exclusively associated with the other task.

In Experiment 1, we investigated how manipulating when the instruction change occurred affected when switch costs occurred. Importantly, we could classify the instruction change as before or after a response could be programmed. In Experiment 2, we investigated the effect of prior information suggesting whether the instruction would change or remain the same, in order to determine if predicting instruction change would result in switch costs if a response could be voluntarily programmed in advance of stimulus presentation. Finally, in Experiment 3 we examined the possibility that subjects could prepare a saccade response in advance of the stimulus, if they could predict where the stimulus would appear.

Our results suggest that the appropriate saccade response was automatically prepared based on the instruction (fixation point color) and stimulus position. Switching the motor program (either prosaccade or antisaccade), and not switching the rule alone, was the critical element in switch cost production.

2.3 Experiment 1: Effect of Instruction Change

In Experiment 1 we established when a change of instruction during the trial produced switch costs. We varied the time at which the change in instruction could occur, henceforth known as 'switch time,' before stimulus onset, concurrently with stimulus onset, or after stimulus onset (Fig. 2.1). We also controlled for the fact that changes in fixation color or luminance alone could be responsible for switch costs, even if they did not convey instruction.

2.3.1 Methods

Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board, and adhere to the Declaration of Helsinki. Twelve individuals with normal or corrected-to-normal vision were recruited from the Queen's University population and provided their informed consent prior to participating. They were compensated for their participation ($10/hour). Three of the participants were male, and the age range of the participants was 20-25.

Design and Procedure

Horizontal eye position was monitored online with DC-electrooculography (EOG). To minimize DC drift the skin was cleaned with rubbing alcohol and the subjects wore the electrodes for approximately 5-10 minutes before the experiment began. Additional DC drift was corrected manually during the experiment. Stimulus presentation and monitoring of eye position were done using REX Version 5.4, sampling at 1000 Hz (Hays et al., 1982). Prior to data collection the EOG signal was calibrated to 10° left ,10° right and 0°. Eye-movement and statistical analyses were conducted in MATLAB 7.0 (The Mathworks).

Subjects were seated 1m from a tangent visual screen immediately behind an array of LED stimuli. A head rest was used to maintain head position. All of the experiments were conducted in the dark, however the screen was diffusely illuminated for 600 ms between trials to

prevent dark adaptation. The subjects performed a saccade task that required them to initiate a saccade to or away from a stimulus (red or green LED; dual red/green diode, red: 5.0 cd/m^2, green: 15.0 cd/m^2), that appeared 10° to the left or right of center. The basic parameters of the task remained the same across three separate days of the experiment, and are illustrated in Fig. 2.1. All twelve subjects participated in all three days, and performed either an interleaved pro-antisaccade task, or a blocked pro-antisaccade task depending on the day.

Interleaved pro-antisaccade task.

Each trial began with the presentation of a fixation point at center (red or green LED, tri red/green/blue diode, red: 8.0 cd/m^2, green: 3.0 cd/m^2) (Fig. 2.1). Subjects were told that one fixation color dictated to perform a prosaccade (look towards) to the 10° stimulus, and the other color dictated to perform an antisaccade (look away) from the stimulus. Instruction color was counterbalanced between subjects, but for each subject the 10° stimulus was always the identical color as the prosaccade instruction color at fixation. The stimulus was presented pseudorandomly to the left or right 1300 ms after the subjects fixated the central fixation point. At five variable times relative to stimulus appearance ('switch times'), the central fixation point was extinguished for 100 ms, and then reappeared as either the same or opposite color. 50% of the trials incorporated this switching of fixation color. The onset of this second fixation point was -800, -400, -200, 0, 200 ms with respect to stimulus appearance, corresponding to the five different switch times in the experiment (recall that on only half the trials did the instruction actually switch). Early switch times were included to be sure we allowed sufficient time for a rule to be changed in advance of stimulus presentation (e.g., -800ms). Note that on the 0 and +200 ms switch time trials the second fixation point appeared concurrently with (0) or after (+200) stimulus appearance. Therefore, subjects were told to obey the second instruction, and be sure to wait for its appearance before initiating the appropriate response. The 100 ms gap in fixation allowed us to compare trials in which the second fixation point was the same ('non-switch') to those in which it switched ('switch'), at each of the five switch times. The 100 ms gap also ensured that both switch and non-switch trials had a change in stimulation at fixation.

Subjects were required to perform 200 correct trials per block, and completed 3 blocks in total. Before completing the 600 correct trials, subjects were given a practice block that consisted

of non-switch trials only of interleaved pro-antisaccades. Subjects were required to complete 100 correct practice trials.

Blocked pro-antisaccade task.

The blocked pro-antisaccade task was conducted to control for the fact that switch costs were not driven only by a change in fixation color, but required a change in task instruction. Subjects performed blocks of prosaccades and antisaccades using the same parameters as in the interleaved pro-antisaccade task, but they did not have to use the instruction given by the fixation color, since they knew which task to perform for the entire block. The second fixation color always corresponded with a pro or antisaccade in each block, even though 50% of the trials were switch trials. Subjects were informed that the first fixation point may be a different color from the second however they were to always execute prosaccades or antisaccades depending on the block. Subjects performed two blocks of 150 pro trials, and two blocks of 150 anti trials. Pro or anti-block order was counterbalanced across subjects. Subjects were instructed to perform the desired saccade, making sure to wait until the second fixation light had appeared.

Order of Tasks

All twelve subjects participated in the three sessions on three separate days, and performed the pro-antisaccade tasks in the following order: blocked pro-antisaccade task (Day1), interleaved pro-antisaccade task (Day2), blocked pro-antisaccade task (Day3).

Analysis

Failure to fixate the first fixation point within 5 s, failure to maintain fixation, failure to initiate a saccade, and failure to fixate the saccade target for at least 160 ms were recorded as 'rejection errors' and removed from analysis. Responses were analyzed such that pro and antisaccade trials refer to the saccade dictated by the second fixation color. For example, prosaccade switch trials are those in which the first fixation color indicated an antisaccade, and the second fixation color indicated a prosaccade. Prosaccade non-switch trials are those in which both the first and second fixation color indicated to make a prosaccade. Response time was defined as the time from when the stimulus appeared to when the first saccade away from fixation exceeded 30°/s. This meant that response times at the +200ms switch time included a delay of 200 ms while the subjects waited to receive the second fixation point.

The errors of primary interest were those in which subjects executed the wrong saccade based on the second instruction (a prosaccade on anti instruction and vice versa), and errors in which the subject anticipated the response (executed a saccade on +200ms trials before or within 70 ms of the onset of the second fixation instruction). These errors were labelled as 'direction' and 'anticipatory errors', respectively, and were analyzed separately. The percentage of direction and anticipatory errors were calculated by dividing the errors by the total number of valid trials (correct trials + direction error trials + anticipatory error trials).

Switch costs and switch benefits (for response time and direction errors) at each switch time were calculated by subtracting the mean of non-switch trials from the mean of switch trials of the twelve subjects (see Supplementary Table 2.S1). A positive value indicated a switch cost, and a negative value indicated a 'switch benefit'. A priori, we wished to examine when switch costs were found across the switch times. T-tests were used for response time and Wilcoxon Signed Rank tests were used for direction errors. We also examined how switch costs depended on Day (blocked or interleaved tasks). Therefore, oneway ANOVAs were performed at each switch time to compare how switch costs were affected by task (e.g. blocked or interleaved). For direction errors, we used this used the simple subtraction as an index of switch costs. For response time, however, we used a normalized index in the following way:

$$\text{switch cost index} = \frac{\text{MEAN}_{\text{switch}} - \text{MEAN}_{\text{non-switch}}}{|\text{MEAN}_{\text{switch}} - \text{MEAN}_{\text{non-switch}}| + \sqrt{(\text{SD}_{\text{switch}})^2 + (\text{SD}_{\text{non-switch}})^2}}$$

This index incorporates variability in response times, in addition to mean response times (Prince et al., 2002). We did not assume the variability in response time would be the same at each switch time or the same in the blocked and interleaved tasks. If the difference of the means is large and the variance is small, this index is close to ±1 depending on which mean is larger. However, if the variance is large, the switch cost indices are smaller.

A repeated-measures ANOVA across the switch times was not conducted, as the 200 ms delay would alter the statistical tests, and we were not interested in such interactions.

2.3.2 Results

Supplementary Table 2.S1A, B, C show when significant switch costs and switch benefits developed for Days 1, 2 and 3, respectively. Corresponding statistical tests are shown.

Response time

Large switch costs of 94 ms for prosaccades were found in the interleaved task (Day 2) at the +200ms switch time (Fig. 2.2A, top-middle panel). Similarly, large switch costs of 88 ms for antisaccades were found at +200ms. Switch costs were not found before stimulus onset in either the blocked or interleaved tasks ($P > 0.14$), however switch benefits did occur at the -800ms and -400ms switch times (Fig. 2.2). There was an effect of whether subjects performed the blocked task or the interleaved task, such that switch costs were largest in the interleaved task at the +200ms switch time (Fig. 2.2B). One-way ANOVAs demonstrated that these switch costs were significantly larger in the interleaved task than in the blocked-task (prosaccades, $F(2,33) = 6.00$, $P < 0.01$; antisaccades, $F(2,33) = 5.25$, $P < 0.05$) (Fig. 2.2B). Paired t-tests revealed that switch costs did not differ between pro and antisaccades at any switch time in either the blocked or interleaved tasks ($P > 0.07$). To summarize, response time switch costs did not develop before stimulus onset, however some significant switch benefits were found. Switch costs were significantly larger in the interleaved task (Day2).

Direction and Anticipatory Errors

Direction error rates followed the same trends as response times. Switch costs occurred at the 0ms and +200ms switch times on Day 2 (Fig. 2.3A and B), and did not occur at pre-stimulus switch times. Switch costs were significantly larger in the interleaved task (Day 2) ($P < 0.01$) (Fig. 2.3B). Significant switch benefits of were found at the -400ms switch time, $P < 0.01$ (Fig. 2.3A, bottom-middle panel). This resulted in a marginally significant difference of switch benefits between pro and antisaccades at this switch time only ($P < 0.05$). No other switch costs or benefits were significant at any other switch time for either the blocked, $P > 0.09$, or interleaved task, $P > 0.075$.

Post-hoc analysis showed that subjects made significantly more errors altogether on prosaccade trials (switch + non-switch) in the interleaved task than in the blocked task (t-test, $P < 0.01$). There was a significant difference in overall antisaccade direction errors in comparison to prosaccades at the +200ms switch time in the interleaved task ($P < 0.05$). There was no

significant differences at any other switch time ($P > 0.07$). There was not a significant difference between antisaccade direction errors across the 3 days, except at +200ms ($P < 0.01$).

In the blocked tasks subjects made significantly more anticipatory errors, accounting for the low percentage of direction errors at the +200ms switch time on Days 1 and 3. We subdivided these anticipatory errors into “anticipatory congruent” and “anticipatory incongruent” with reference to the first instruction (Fig. 2.4). Anticipatory congruent errors refer to those that were in the correct direction (towards or away from the stimulus) associated with the color of the first instruction. Incongruent refer to those errors that were in the direction against what was associated with the first instruction. For the blocked tasks, subjects consistently made significantly more anticipatory-congruent errors on non-switch trials than on switch trials ($P < 0.05$) (Fig. 2.4, left and right panels). In contrast, subjects made significantly more anticipatory incongruent errors on switch trials than on non-switch trials ($P < 0.05$) (Fig. 2.4, left and right panels). In all cases, there was a significantly greater percentage of incongruent errors than congruent errors on switch trials ($P < 0.05$). In addition, there was a greater percentage of congruent errors than incongruent errors on non-switch trials ($P = 0.05$). In the interleaved task, anticipatory errors were less than 12% (Fig. 2.4, middle panels). There was only a significant difference of more anticipatory congruent errors for non-switch prosaccades that switch prosaccades ($P < 0.05$). For the non-switch prosaccades, anticipatory congruent errors were greater than incongruent ($P < 0.05$). To summarize, anticipatory errors were high in the blocked task, such that on switch-trials subjects made mostly anticipatory incongruent errors, whereas on non-switch trials subjects made mostly anticipatory congruent errors with respect to the first instruction. This is consistent with the requirement to perform only pro or antisaccades depending on the block.

2.3.3 Discussion

Switch benefits

Recent studies using interleaved pro and antisaccades have revealed response time switch benefits for antisaccades (Cherkasova et al., 2002; Manoach et al., 2002; Fecteau et al., 2004; Barton et al., 2006). Barton and colleagues (2006) suggested that the origin of these switch benefits results from persisting response-system inhibition from the previous antisaccade which

required inhibiting a reflexive saccade to the stimulus. Antisaccades that follow prosaccades (switching task) do not have to overcome this inhibition (Barton et al., 2006). We observed switch costs and switch benefits regardless of pro or antisaccade (see Figs. 2.2 & 2.3), suggesting that inhibition related to one task alone cannot explain our findings. We believe that in our task, subjects were volitionally controlling both pro and antisaccades, based on the difficulty of the interleaved task. We found that prosaccade response times were slower in comparison with those found in basic reflexive- prosaccade tasks (Fischer and Weber, 1992; Fischer and Weber, 1997; Munoz et al., 1998). Increased latency in both pro and antisaccades has also been found in other saccade studies of countermanding, dual-task performance and task-switching (Kristjansson et al., 2001; Hunt and Klein, 2002; Matthews et al., 2002). As shown in Fig. 2.2, prosaccade response times were consistently faster in the blocked tasks than in the interleaved tasks ($P < 0.05$).

We cannot explain what is driving the switch benefits from this experiment. One possibility is that while we controlled for a temporal warning effect with the 100 ms gap, the saliency of a change of instruction prior to stimulus appearance may have had some additional effect on increasing the readiness to respond. This could lead to subjects executing the response faster on trials in which the instruction switched early in the trial.

Switch costs

We controlled for the fact that switch costs might be mediated by the changing color or luminance at fixation. There were small response time switch costs in the blocked tasks on Day 1 and 3, however these costs were much smaller than on Day 2 and were not present in direction errors (Figs. 2.2 and 2.3). Secondly, anticipatory errors suggest that subjects were not influenced by the first instruction in the blocked task (Fig. 2.4). If a high proportion of anticipatory congruent errors had resulted for either switch or non-switch trials, this would suggest that the subjects had generated a response based on the color of the first fixation point, rather than simply failing to delay responding. This indicates that color change alone did not change task set.

The results from the interleaved task (Day 2) suggest that: i) physical information is strong enough to drive switch costs, and ii) switch costs do not result before the stimulus is present. Since the switch-trial probability was 50%, the first instruction carried no response-

related information, so subjects had to rely on the instruction carried by the second fixation color to execute the correct response. Importantly, switch costs were still found for both prosaccades and antisaccades after stimulus onset. This suggests that the first instruction automatically induced a corresponding task set. The motivation of Experiment 2 was to examine the role of voluntarily changing task set. If switching of instruction could be predicted, switch costs might result at the negative switch times because subjects could use this information to change task set in advance of the stimulus. If this occurred, it would also demonstrate that the instruction induced a task set, before the stimulus was present.

2.4 Experiment 2: Effect of Switch Trial Probability

In Experiment 1, switch costs resulted despite the subjects having no information about whether the instruction would change or remain the same. In Experiment 2 we manipulated the probability that the current trial would include a change in instruction. Previous studies have demonstrated that switch costs are reduced if one is able to predict that a switch will occur (Rogers and Monsell, 1995; Monsell, 2003). We predicted that switch costs might decrease, or reverse to switch benefits, if the subjects expected a switch of instruction, and therefore could switch task set. For example, switch benefits at +200ms might imply that the subjects configured a task set against the first instruction, using the information that the instruction would likely switch.

2.4.1 Methods

Participants

Twelve different participants performed the interleaved pro-antisaccade task, in which the probability that the first fixation color would switch was varied. Two of the participants (IC and MW) were co-authors on the paper. Eight were male, and the age range was 20-28.

Design and Procedure

Three sessions of the task were run, such that switch-trial probability in each session was either 25%, 50% or 75%. Subjects performed the experiment across three separate days, and the order in which each subject received the three versions was counterbalanced. Subjects were not informed of the switching probability by the experimenter.

The experimental conditions were identical to those of Experiment 1, however nine of the subjects performed the task in a different laboratory, where they were seated 80 cm from the

screen. For these subjects, stimulus eccentricity was 15°. The performance of the nine subjects in the second laboratory was compared to the performance of three subjects in the first laboratory (1m from screen, 10° targets) and did not show behavioral differences. To control for any differences between the laboratories, experimental conditions and subjects, we replicated the 50% interleaved pro-antisaccade task from Experiment 1 in addition to exploring the effects at 25 and 75% switch probability. Subjects were required to perform 200 correct trials per block, and completed 3 blocks in total as in Experiment 1. 100 correct practice trials (interleaved pro-antisaccades of non-switch trials only) were given beforehand.

2.4.2 Results

Supplementary Table 2.S2 shows significant switch costs and switch benefits and statistical tests for Experiment 2.

Response time

As shown in Fig. 2.5A and B, increasing the switch probability from 25%, to 50% and to 75% meant that switch costs decreased at the post-stimulus switch time. Large response time switch costs were always found at the +200ms switch time ($P < 0.01$), however as the switch probability increased to 75%, switch costs decreased, $F(2,33) = 7.69$, $P < 0.01$. For antisaccades, switch costs were also largest in the 25% condition at 0ms, $F(2,33) = 11.31$, $P < 0.001$, and +200ms, $F(2,33) = 8.34$, $P < 0.01$ (Fig. 2.5B). Switch costs were also consistently found at the 0ms switch time in the 50% and 25% switch probability conditions, $P < 0.01$. However, switch costs at the 0ms switch time were less than the switch costs found at the +200ms switch time.

In the 25% switch probability condition, small switch costs of 17 ms were found before stimulus onset at -200ms for prosaccades (Fig. 2.5A, top-left panel). This was the only instance in which switch costs were found before stimulus onset.

Switch benefits were found at the -800ms switch time for both prosaccades and antisaccades in all three probability conditions ($P < 0.05$). Switch benefits were also found at the -400ms switch time in the 50% switch probability (Fig. 2.5A, middle panels), and at -200ms for antisaccades at 75% switch probability (Fig. 2.5A, bottom-right panel). Response time switch benefits were not significantly modulated by switch probability ($P > 0.08$).

Switch costs were marginally higher for prosaccades in the 25% switch probability condition at the -200ms switch time (t-test, $P < 0.05$). In the 50% switch probability condition, switch costs were significantly higher for prosaccades at the +200ms switch time ($P < 0.01$). Similarly in the 75% condition, switch costs were significantly higher for prosaccades at 0ms, $P < 0.001$, and at +200ms, $P < 0.01$.

Direction Errors

Figure 2.6 shows how the occurrence of direction errors changed systematically across the three switch-trial probabilities. Significant switch costs were consistently found at +200ms in all conditions ($P < 0.05$) (Fig. 2.6A), but reduced as the probability of switching instruction increased (Fig. 2.6). This resulted in switch costs being significantly largest in the 25% condition, and smallest in the 75% condition for antisaccades at +200ms, $F(2,33) = 3.58$, $P < 0.5$ (Fig. 2.6B). Switch benefits for direction errors never occurred, $P > 0.21$.

Subjects made at most 3.8% anticipatory errors in Experiment 2, and thus will not be described further (t-test, $P > 0.13$). There was no significant difference in error rate switch costs between pro and antisaccades, however there were marginally greater switch costs for antisaccades at the 0ms switch time in the 25% condition (t-test, $P < 0.05$).

2.4.3 Discussion

Significant switch costs were consistently found at the +200ms switch time regardless of switch trial probability. Information *supporting* switching could not eliminate switch costs. Therefore, while switch costs were affected by prior information, a component of task set appears to be triggered automatically by the color at fixation. We speculate that the first instruction biased the system to automatically program the corresponding response when the stimulus appeared. This occurred despite information suggesting the instruction would switch to the opposite task. Therefore, switch costs may result from the switching of a response program, automatically prepared at stimulus onset. Information related to switch probability modulated switch costs, suggesting that there is a second component of task set that was volitionally controlled. As there were small response time switch costs that appeared before stimulus onset (-200ms, prosaccades, 25% switch probability) this suggests that the subjects were able to adopt a task set (internalized rule) based on the first instruction before stimulus onset.

2.5 Experiment 3: Effect of Stimulus Location Probability

If switch costs result from the switching of a programmed motor response, switch costs also may result if the stimulus itself changes a motor program. Previous evidence has demonstrated that stimulus predictability can reduce pro and antisaccade latencies toward, or away from, the predicted stimulus location (Carpenter and Williams, 1995; Dorris and Munoz, 1998; Koval et al., 2004). Therefore, it is possible that a saccade response could be prepared to a predictable stimulus location. Switch costs might result before stimulus onset if the change in instruction changes a programmed response to this location. Alternatively, prior information relating to the stimulus location may not be able to change switch costs, if the instruction at fixation and stimulus have the strongest effect of triggering a response process.

2.5.1 Methods

Participants

Twelve different participants performed Experiment 3. Three were male and the age range was 19-28. The laboratory was identical to the one used in Experiment 1 for all subjects.

Design and Procedure

Two sessions were run and the order was counterbalanced for the twelve subjects. In one session the stimulus appeared at the left and right location with equal probability. In the other session, the stimulus either appeared 75% on the left and 25% on the right for six subjects, or 25% on the left and 75% on the right for the other six subjects. Therefore, for each subject we had trials where the stimulus appeared at a low probability location (25%) and trials where the stimulus appeared at a high probability location (75%). These low and high probability locations were then compared to the second session of 50% stimulus probability, identical to Experiment 1 and Experiment 2. All other aspects of the analysis were identical to Experiment 1, and the probability that the instruction would switch was 50%. Subjects were not informed of the instruction switching or stimulus location probability.

The experimental conditions were identical to those of Experiments 1 and 2. Subjects were required to perform 200 correct trials per block, and completed 3 blocks in total. Practice trials were given as in Experiments 1 and 2.

2.5.2 Results

Supplementary Table 2.S3 shows statistically significant switch costs and benefits for Experiment 3.

Response Time

The manipulation of stimulus location probability did not significantly affect the magnitude of switch costs (Fig. 2.7B), $F(2,33) < 2.28$, $P > 0.11$, or when switch costs developed with respect to stimulus onset (Fig. 2.7A). As shown in Fig. 2.7A, response time switch costs and benefits followed similar trends to the 50% switch trial probability condition in Experiments 1 and 2. For instance, switch costs were consistently found at the +200ms switch time ($P < 0.01$). Significant switch benefits occurred at the -800ms and -400ms switch times, but not at other switch times (Fig. 2.7A)

Switch costs at the +200ms switch time for prosaccades were significantly greater than those for antisaccades at the high stimulus probability location ($P < 0.05$). The difference in switch costs at the 0ms switch time between pro and antisaccades for the low stimulus probability location was also significant ($P < 0.05$).

Direction Errors

As in response time analysis, there were no significant differences in switch costs or benefits between the three probability conditions $F(2,33) < 1.62$, $P > 0.21$ (Fig. 2.8B). Significant switch costs were observed at the +200ms location in the 50% stimulus probability condition for antisaccades (Fig. 2.8B, bottom-middle panel), and this switch cost for antisaccades was significantly greater than for prosaccades ($P < 0.01$) at +200ms. Significant switch costs were also observed at +200ms in the 75% stimulus probability location for prosaccades and antisaccades ($P < 0.05$).

Subjects made altogether more errors in the 25% stimulus probability location for antisaccades than they did for prosaccades. These are errors in which the subjects looked to the stimulus (a prosaccade) which appeared in the low probability location. This was significant across all switch times except at +200ms ($P < 0.01$). These errors were not significantly different across the probability locations, $P > 0.09$, other than at -800ms, $P < 0.01$. Response times for these errors were greater than 210 ms in all instances.

2.5.3 Discussion

We predicted that if subjects had prior information suggesting that the stimulus will appear at one location, they may be able to use this information to program a saccade in advance of the stimulus. Therefore, switch costs might result before stimulus onset if the change in instruction changed a programmed saccade. The trend of antisaccade error rates across the probability locations suggests that subjects at least learned the location probability, and this affected their performance. However, the pattern of switch costs was identical to Experiments 1 and 2 (50% switch probability). This suggests that stimulus predictability was not enough to drive switch costs, and the main effect was from the change of instruction after the stimulus and first instruction specified a response.

2.6 General Discussion

We identified in Experiment 1 that switching a response program driven by physical information is a fundamental property of task switching performance. Experiment 2 demonstrated that prior information about an instruction switching can influence switch costs, but switch costs still result when a specified response changes. Experiment 3 verified that switch costs are related to switching a physically specified response, and not due to response preparation based on probable stimulus location. We believe that a saccade response was automatically programmed based on a combination of physically available information of fixation point color and stimulus location. Switch costs result when the response is changed.

2.6.1 Accumulator Model

A useful method to illustrate saccade response programming is with an 'accumulator model.' An accumulator model considers a response program as a neural signal that begins at a baseline of activity, rises toward a threshold level of activity, and triggers a response. The baseline level of activity and the rate of rise to threshold can influence when the response is executed, and whether this response can be inhibited by competing programs (Carpenter, 1981; Logan et al., 1984; Carpenter and Williams, 1995; Hanes and Schall, 1996; Hanes and Carpenter, 1999; Sinha et al., 2006). These principles have been validated in neurophysiological recordings of saccade-related neurons in the frontal eye-fields (FEF) and superior colliculus (SC)

(Hanes and Schall, 1996; Dorris and Munoz, 1998; Pare and Hanes, 2003; Munoz and Schall, 2004) two critical areas for saccade generation (Schiller et al., 1980).

In the current experiment, response time switch costs can be modeled as saccade response signals that cross threshold later on switch trials than on non-switch trials (Fig. 2.9A). We suggest that when the stimulus appears after the first instruction, a neural response signal (pro or antisaccade) is automatically initiated from baseline activity (following a delay in sensory to motor processing). On switch trials, the change in instruction requires the alternate saccade response signal to be initiated. Thus, switching the instruction after stimulus presentation requires reprogramming a new response and suppressing the old response. This is not required on non-switch trials, resulting in non-switch trial signals triggering a response earlier in time than switch trial signals. On a switch trial, if the saccade signal related to the original instruction is not inhibited and crosses the threshold, a direction error is triggered corresponding to an error rate switch cost.

On non-switch trials, response signals that are initiated before the second instruction result in 'correct' trials provided the saccades are executed 70 ms after the second instruction (anticipatory if they cross before this time). If the saccade response is initiated to the first instruction, this would reduce the mean response time on correct non-switch trials, but would reduce the mean response time of direction errors on switch trials. To examine this possibility behaviorally, we analyzed the response time of direction errors in the interleaved tasks at the +200ms switch time. The mean response time for direction errors on antisaccade switch trials was significantly shorter than on antisaccade non-switch trials in Experiments 1 (Day 2), Experiment 2, and Experiment 3 at the 50% stimulus location probability ($P < 0.05$). This trend was similar for prosaccades, however it was only significant in Experiment 2. (Recall that the percentage of direction errors was consistently below 5% for non-switch prosaccade trials, resulting in highly variable and sparse data for analysis). This supports the proposal that response signals initiated to the first instruction that cross threshold result in short latency correct non-switch trials, but switch trial direction errors.

We propose that information related to the probability that the instruction will switch can affect the rate of rise of response signals initiated upon stimulus onset. This corresponds to a voluntary component of task set. Upon presentation of the second instruction there would be a difference in the level of activity depending on switch probability (Fig. 2.9A). It has been shown when the 'go' signal to execute a saccade is presented, the initial level of activity in the FEF and SC negatively correlates with saccade response times (Dorris et al., 1997; Dorris and Munoz, 1998; Everling and Munoz, 2000). It has also been shown that pre-stimulus activity in some FEF and SC saccade neurons can be biased by saccadic probability (Dorris and Munoz, 1998). Therefore, when the probability of switching is low (25%), response related activity may increase to a higher level before the second instruction is delivered (Fig. 2.9B), resulting in increased switch costs. The small response time switch costs that occurred at -200ms in the 25% probability condition suggest that the possibility that at stimulus onset, another signal, related to the first rule, might be at a higher level than the signal related to the second rule. Therefore, if activity related to the representation of the first rule is still higher upon stimulus presentation, switch costs may result as the response signal on non-switch trials would be initially closer to threshold. Indeed, Sinha and colleagues (2006) proposed a two-stage model of task-switching, such that recognizing an instruction to switch was a rise-to-threshold process that in turn dictated when the saccade response signal commences. We cannot discount other explanations however, such as: reconfiguration to the new instruction takes longer than 200 ms and therefore is reconfigured after stimulus presentation on switch trials. This reconfiguration time might vary with switch probability, accounting for why this occurred only in the 25% switch condition (Rogers and Monsell, 1995; Monsell, 1996).

2.6.2 Switch Benefits

Unlike switch costs, switch benefits were not influenced by instruction probability, and therefore do not reflect a change in task set. They may result from an altering effect that might alter the baseline activity or rate of rise to threshold, resulting in the response signals triggering a saccade earlier on switch trials.

2.7 Conclusions

We propose that switch costs result from the switching of a response program, defined by a combination of physically available information of stimulus position plus the presented instruction. Voluntary signals related to instruction probability can modulate switch costs; however switch costs are still driven by the physical information. Switch costs do not result from switching an instruction alone. This suggests that we have the flexibility to change task set related to rule representation, however we are impaired at switching task if a response processes is engaged.

Chapter 3: Role of the Basal Ganglia in Switching a Planned Response

3.1 Abstract

The ability to perform an appropriate response in the presence of competing alternatives is a critical facet of human behavioral control. This is especially important if a response is prepared for execution, but then has to be changed suddenly. A popular hypothesis of basal ganglia (BG) function suggests that its direct and indirect pathways could provide a neural mechanism to rapidly switch from one planned response to an alternative. However, if one response is more dominant or "automatic" than the other, the BG might have a different role depending on switch direction. We built upon the pro- and antisaccade tasks, two models of automatic and voluntary behavior (respectively), and investigated whether the BG are important for switching any planned response in general, or if they are more important for switching from a more automatic response to a more difficult response to perform. Subjects prepared either a pro or antisaccade, but then had to switch it unexpectedly on a subset of trials. The results revealed increased striatal activation for switching from a pro to an antisaccade, but this did not occur for switching from an anti to a prosaccade. This activation pattern depended on the relative difficulty in switching, and it was distinct from frontal eye fields, an area shown to be more active for antisaccade trials than for prosaccade trials. This suggests that the BG are important for compensating for differences in response difficulty, facilitating the rapid switching of one response for another.

3.2 Introduction

The ability to choose an appropriate response when competing alternatives exists is a critical facet of behavioral control. Think of a football (soccer) player on defence who needs to rapidly change her planned response, if she was "tricked" by an offensive player's fake movement. To do this effectively requires effort; as an initial response is already in preparation for execution. We recently modelled this situation using a variant of the *pro* and *antisaccade* paradigm (Cameron et al., 2007). Subjects were instructed to prepare a prosaccade (look towards) or antisaccade (look away) to a peripheral stimulus that appeared on a visual screen (Hallett, 1978). Unpredictably, on a subset of trials, the subjects were required to switch their planned response when the instruction changed suddenly. This resulted in response time and

error rate “switch costs”, corresponding to response reconfiguration processes that commenced after the initial response was in preparation, and took time to complete (Cameron et al., 2007). Several of these task switching experiments *across trials* have been conducted previously (Jersild, 1927; Allport et al., 1994; Rogers and Monsell, 1995; Monchi et al., 2001; Cools et al., 2004; Isoda and Hikosaka, 2008), however, we suggest that the method of Cameron et al. (2007), in which the switch occurs *within a trial*, is a better model of neural mechanisms required to change a response in preparation.

We showed in Cameron et al. (2007), that switch costs resulted when subjects prepared either a pro or antisaccade to a stimulus, and then had to switch it to the alternative. Switch costs did not result if the instruction changed before the peripheral stimulus was presented, suggesting that a response was required to be in preparation for these behavioral costs to occur. What was most interesting was that switching from the more difficult antisaccade to the more “automatic” (or dominant) prosaccade produced switch costs that were similar to those when subjects switched in the opposite direction. This finding was intriguing, as the BG is associated with suppressing the visually triggered prosaccade on antisaccade trials in the oculomotor field (Briand et al., 1999; Munoz and Everling, 2004; Chan et al., 2005; Peltsch et al., 2008). Thus, it would be predicted that switching from an anti to a prosaccade should be a relatively simple process, void of BG control since no prosaccade needs to be suppressed. Alternatively, switch costs when switching to a prosaccade is sensible if one considers that the indirect pathway of the BG might be important for suppressing *any* competing response, and the direct pathway might be important for dis-inhibiting the *desired* response (Mink, 1996; Nambu, 2004), even if it highly automatic. From this, we hypothesized that similar switch costs should be accompanied by similar activation patterns in the caudate nucleus (CN), the area of the BG that receives competing pro and antisaccade response signals (Alexander et al., 1986; Hikosaka et al., 2000) that would undergo a selection process by the direct and indirect pathways.

However, our results show in a first experiment, that correctly switching from a pro to an antisaccade resulted in greater CN activation, but that this did not occur for switching from anti to pro. When subjects failed to switch to the antisaccade, the CN activation pattern differed,

suggesting a correlate between CN activation and successfully switching to the antisaccade. In a second experiment, we confirmed that the greater striatal activation for switching from a pro to an antisaccade was due to response difficulty. We suggest that rather than acting as a general selector between competing response signals (Mink, 1996; Nambu, 2004), the BG have a particular role in boosting weaker response signals to override dominant response signals.

3.3 Materials and Methods

All experiments were approved by the Research and Ethics Board of Queen's University, and adhered to the principles of the Canadian Tri-council Policy Statement on Ethical Conduct for Research Involving Humans and the principles of the Declaration of Helsinki (1964). Subjects were recruited from the Queen's University community, and gave their written and informed consent.

3.3.1 Experiment 1

The goal of the first experiment was to determine if the BG are involved in switching a planned response in general, or if they are differentially involved in switching from automatic to more difficult behavior.

Subjects

Ten subjects (age 22-28) participated in a two-session experiment at the Queen's University MRI facility, with each session 1.5 to 2 hours in duration. Nine subjects had normal or corrected to normal vision, and the 10th subject verified that she could distinguish the stimuli without her glasses. All were right-handed, and 5 were male. Subjects did not report any history of neurological or psychiatric disorders, or color blindness.

Paradigm

Subjects lay supine in the scanner and viewed visual stimuli back-projected onto a screen located at the head-end of the scanner. A mirror attached to the head coil and angled at approximately 45° allowed them to view the screen. Subjects were presented with a text screen informing them to prepare for the onset of each experimental run containing 16 trials.

The timings of stimuli are shown in Fig. 3.1A. Each trial began with a blue cross ('Neutral Cross', 0.5° of visual angle) at center for 3 s that did not convey any instruction, other than to

fixate. Then, the cross changed to a green (instructing a prosaccade) or red (instructing an antisaccade) cross having the same size and luminance. We chose these colors explicitly, to take advantage of the familiarity from traffic signals. This did not require participants to learn unfamiliar rules that might confound the interpretation of erroneous responses. The green or red crosses were present for 3 s. Next, a peripheral stimulus (blue circle, 0.5° of visual angle) pseudorandomly appeared 5.5° to the left or right, and was also present for 3 s. Subjects were instructed to execute a prosaccade (look towards) to the stimulus, or an antisaccade (look away) from the stimulus based on the instruction (pro or anti). In 50% of the trials, the red or green cross changed to the opposite color 100 ms (25% of total trials) or 200 ms (25% of total trials) after the peripheral stimulus appeared. Previous work (Cameron et al., 2007) demonstrated that these times are within a critical time period for producing switch costs, suggesting that one response was prepared and then changed subsequently (Nakamura et al., 2005). Subjects were told to obey the new instruction, to be as quick and as accurate as possible, and if they executed the wrong response, to correct themselves. Subjects were asked to hold their gaze at the target position until the peripheral stimulus disappeared, and simultaneously, a blue 'Neutral X' appeared at center to redirect their fixation. This 'Neutral X' was present for 12 s to allow the hemodynamic response to return to baseline. Each trial was 21 s in duration. Subjects performed 12 runs (divided over two separate sessions of 6 runs each) of 16 trials: 4 non-switch antisaccade trials ('anti'), 4 non-switch prosaccade trials ('pro'), 4 anti-to-prosaccade switch trials ('anti2pro', 2 with a 100 ms switch time, and 2 with a 200 ms switch time) and 4 pro-to-antisaccade switch trials ('pro2anti', 2 with a 100 ms switch time, and 2 with a 200 ms switch time). The trials were presented in a pseudorandom order by the following method: four distinct pseudorandom trial sequences were created prior to the experiment. Subjects received these sequences in random order, such that identical sequences could not precede one another, and subjects were not given more than 2 of each sequence on a given day. Subjects were given one run of practice in front of a computer monitor on each day, and eye movements were not recorded during this practice run.

Our goal was to test whether differential fMRI activation would result despite similar switching behavior. Thus, our approach was to utilize data only from the subjects (N=7) who

showed similar switch costs for switching to the pro or antisaccade (Fig. 3.1B,C). Therefore, 3 of the 10 subjects were removed from further analysis because they produced greater than 75% errors on pro2anti switch trials. These 3 subjects demonstrated a large behavioral bias to the prosaccade response, emphasizing the differences in response automaticity. However, their deficit in switching to the antisaccade confounded our interpretation of BG activation; we were interested specifically in examining whether differential BG activation would result depending on switch direction, *despite* similar switching behavior. If this occurred, it would suggest that the BG has a role mediating one response over the other. Individual data from all 10 subjects is shown in Supplementary Fig. 3.S1.

Eye tracking and visual display

Visual stimuli were generated using E-PRIME software (Psychology Software Tools Inc., Pittsburgh, PA) running on a PC, and an NEC LT265 DLP video projector (Tokyo, Japan) was used to back project the image onto a custom-build screen. The projector had a refresh rate of 60Hz and a resolution of 1024 X 768. Eye tracking was conducted using an ISCAN ETL-400 camera (Burlington, MA) running DQW software v1.10X and sampling eye position at 120Hz. The camera was positioned next to the screen, approximately 50 cm from the bore of the magnet to view the right eye of the subject in the mirror. An infrared fiber-optic illuminator was fixed to the head-coil prior to the subject entering the bore of the scanner. This illuminated the subject's right eye from an angle of approximately 45° below the eye. Prior to the first functional scan, calibration of the eye-tracker was conducted using a 9 point calibration routine such, with the 9 points covering the maximum available visual field on the screen (approximately 16° in width).

fMRI parameters

All MRI scans were conducted with a Siemens 3T Magnetom Trio system, with a 12 channel receive-only head coil, using methods based on BOLD contrast (Ogawa et al., 1990; Kwong et al., 1992). High resolution anatomical images were collected with a T1-weighted MPRAGE sequence, with an anterior-posterior phase encoding direction. The voxel size was 1 mm in all 3 directions. The field of view (FOV) was 256 mm X 256 mm, and the matrix size was 256 X 256. The flip angle was 9°, the TE was 2.2 ms and the TR was 1760 ms.

Functional scans were collected using a T2* weighted echo-planar imaging sequence, with slices acquired in the transverse orientation, and with an anterior-posterior phase encoding direction. Each volume contained 11 slices of 3.3 mm isovoxels (3.3 mm thick slices), centred by the operator in the transverse plane to include the entire head and body of the caudate nucleus (CN) identified from the anatomical images. We specifically focused on the CN, the main input stage of the BG, using the highest temporal resolution possible (TR = 750 ms) to image the entire structure. This afforded us with the ability to examine in greater detail the time courses of the BOLD activation patterns in the CN for each response type. The FOV was 211 mm X 211 mm, and the matrix size was 64 X 64. The flip angle was 56°, and the echo time (TE) was 30 ms (in order to optimize for the sensitivity of the BOLD contrast). A saturation band was used and applied across the subjects' eyes to prevent motion artefacts from the eye movements. On the first trial of every run, the neutral cross was present for a total of 4.5 s, allowing an additional 1.5 s (2 TRs) to achieve steady-state longitudinal magnetization.

Statistical Methods

Behavioral data was analysed using custom programs in MATLAB 7.4 (The MathWorks Inc., Natick MA). Saccade reaction time (SRT) was defined as the first saccade away from fixation after stimulus onset, when the velocity exceeded the mean + 3 times the standard deviation of the background velocity. Direction errors were those in which the first saccade was against that of the final instruction. SRTs of < 90 ms were considered anticipatory (Munoz et al., 1998), and were excluded from behavioral analysis, however, these rarely occurred (< 1.5% for any subject). Errors in which subjects failed to fixate the instruction, failed to maintain fixation (measured by saccades in any direction during the fixation period), failed to initiate a saccade, or executed multiple saccades during the response period were also removed from behavioral analysis, but modelled separately as "null trials" in the fMRI analysis (see below). Direction errors were only analyzed if the subject corrected the error (failure to correct errors occurred < 5% of the time for any subject, and these trials were also placed in the null category). The percentage of direction errors was calculated by dividing the errors by the total number of valid trials. Finally, entire runs were excluded if the subject had more than 25% of their trials removed for any of the

above reasons or if successful eye-tracking was not possible. This occurred once for 2/7 subjects, and 3 times for 1/7 subjects. In total, all subjects provided between 9 and 12 functional runs, and no subject had more than 19% of their trials excluded from further analysis for any given run that was included.

Paired t-tests (non-directional) were conducted to compare mean SRTs and mean % direction errors across subjects between anti and pro trials, anti and anti2pro trials, and pro and pro2anti trials, at each switch time. Left and right target responses were combined to increase statistical power. *P* values were corrected for multiple comparisons (Bonferroni, $P < 0.05$).

Analysis of the functional brain data was conducted using BrainVoyager 1.9 (Maastricht, the Netherlands). Functional images were first pre-processed to remove motion artifacts and linear drift (high pass filtered at 3 cycles/time course, motion corrected by aligning the images of the time series to the first volume in the series, and corrected for slice timing differences by means of a sinc interpolation). The first two volumes were removed from analysis in order to include only data obtained with a steady-state longitudinal magnetization.

Each subject's high resolution anatomical scan was transformed into Talairach coordinates (Talairach and Tournoux, 1988), first using cubic spline interpolation to align the anatomical images into the AC-PC plane, then using trilinear interpolation to transform the anatomical images into Talairach coordinates. An average of all the subject's individual anatomical images in Talairach coordinates was computed to create a reference volume on which to overlay the functional volumes in Figs. 3.2,3.3,3.4,3.6,3.7,3.8,3.9 and 3.10.

The events of interest were modelled with boxcar predictors with a width of the 3 s 'Response' period (Fig. 3.1A), convolved with BrainVoyager's canonical (2 gamma) hemodynamic response function to map the BOLD response time locked to the onset of the visual stimulus, and spanning into the 12 s period ('Neutral X') following the Response Period. A total of 8 predictors for the Response Period were created based on: instruction (switch or non-switch), response (prosaccade or antisaccade), and performance (correct direction or erroneous direction that was subsequently corrected). For our main analyses, the 100 ms and 200 ms switch time trials were combined. However, we performed a post-hoc analysis whereby the 100

and 200 ms switch times were separated, and all error trials were grouped together under a separate predictor. This was conducted to explore whether there was a difference in CN activation for switch trials that were less difficult (100 ms switch time) and more difficult (200 ms) (Fig. 3.3F-H). Note that the execution of two saccades during the 'Response' period (erroneous switch trials) was contrasted with the execution of one saccade during the 'Response' period (correct non-switch trials), as erroneous trials were only included if subjects corrected the error (Figs. 3.4,3.8,3.10). However, as this occurs for both erroneous switch trial types, any differences in BOLD activation patterns between the two erroneous switch trial types cannot be attributed to the execution of a second saccade. In addition, the initial 'Instruction' period, was also modelled with separate predictors (pro = green, or anti = red). Finally, all "null trials", plus trials in which tracking was lost, trials in which the subject made multiple eye movements, failed to correct an error (5%), or 'uncorrected' a correct response (< 2%) were modelled with a separate "null predictor" in the Response Period. This was done so that trials that could not be classified as a correct trial or corrected error were still modelled so not to affect the calculation of the BOLD signal change from baseline.

Group analysis was conducted using a fixed-effects general linear model (GLM), with separate subject predictors, Bonferroni corrected for multiple comparisons at $P < 0.05$ and cluster-sized corrected at $P < 0.05$ (yielding a cluster threshold of 8 contiguous voxels, as estimated using BrainVoyager's Cluster-level Statistical Threshold Estimator at 1000 iterations). Paired t-tests (non-directional) were conducted using MATLAB 7.4 on the beta weight values (GLM parameter estimates) for comparisons described in the Results section and Figure legends. We specifically examined the BOLD signal time courses for non-switch and switch trials that shared a common preparatory period (e.g., pro, pro2anti, pro2anti error), allowing us to be certain that differences in CN activation did not related to differences in the preparatory periods. BOLD signal time courses were aligned to the onset of the peripheral stimulus, and the baseline was averaged from the final 3 time points (including the time point at stimulus onset) of the 'Instruction' period.

3.3.2 Experiment 2

A second experiment was conducted to control for the difference in switching difficulty between pro and antisaccades. The paradigm and stimuli remained identical to Experiment 1, however the switch times were staircased by +/- 50 ms based on performance (described below in Paradigm and fMRI Parameters) to converge on 50% accuracy for switching either response. This manipulation made switching to a pro or antisaccade similar in difficulty, but did not affect the nature of the responses executed (e.g., visually directed prosaccade and internally guided antisaccade). The frontal eye fields (FEF) were scanned along with the CN as they constitute an area that has shown greater BOLD activation for generating an antisaccade relative to generating a prosaccade (Connolly et al., 2002; Curtis and D'Esposito, 2003; Ford et al., 2005; Brown et al., 2007), and thus FEF activation could be compared to CN activation which is hypothesized to reflect a response switching mechanism rather than an antisaccade generation mechanism.

Subjects

11 different subjects (to avoid confounds from prior experience with 100 and 200 ms switch times), 5 male, age 22-30, were recruited. All subjects were right handed and reported no history of neurological or psychiatric disorders or color blindness.

Paradigm and fMRI Parameters

FEF was scanned in conjunction with the CN, using 16 slices of 3.3 mm isovoxels tilted between the transverse and coronal plane to center on FEF, and include the head and body of the CN. Subjects first performed a task consisting of blocks of antisaccades and prosaccades contrasted with periods of fixation in order to locate FEF using the Siemens Neuro3D software, whereby a GLM contrast of saccades minus fixation was conducted.

For the main experiment, the TR was 1 s (due to the greater number of slices), and the flip angle was 62° (Ernst angle), to optimize the signal to noise ratio for a TR of 1 s. The initial instruction of the first trial was presented for 5 s (additional 2 TRs) to allow the longitudinal magnetization to reach a steady state. All other scanning parameters remained the same as in Experiment 1.

The initial switch time was 200 ms after stimulus onset for both switch trial types, but this increased by 50 ms if the given switch trial was executed correctly, or decreased it by 50 ms if the given switch trial was executed incorrectly. Switch times were allowed to staircase to a minimum

of 50 ms and to a maximum of 500 ms after stimulus onset. If on a given run the subject executed all switch trials incorrectly, or executed all switch trials correctly, they were provided with verbal feedback to improve accuracy, or improve speed, respectively. These runs were then excluded from analysis because the switch time could not be reliably close to the subject's performance threshold. In addition, we were only interested in subjects for which no more than 60% errors and no less than 40% errors on either switch trials were achieved. As shown in Fig. 3.5A, 7 subjects produced this behavior, and thus 4 subjects were excluded from further analysis for failure to perform to criterion (Fig. 3.5A and Supplementary Fig. 3.S3). Performance of the removed subjects could not be reliably close to their threshold for switching successfully. As such, their behavior confounded our interpretation of CN BOLD activation that was hypothesized to relate to switching difficulty. In the end, 6 of the remaining 7 subjects participated on both days of the experiment, each providing a total of 9 to 12 runs (9 for one subject, 10 for one subject and 11 for 2 subjects due to runs being excluded for reasons listed previously). The 7th subject was only available for 1 session, and contributed 5 viable runs.

Subjects were given one run of practice outside the magnet prior to each session, with the switch times set at 100 ms and 200 ms as in Experiment 1.

Statistical Methods

A fixed-effects GLM, with separate subject predictors was conducted, Bonferroni corrected for multiple comparisons at $P < 0.05$ and cluster-sized corrected at $P < 0.05$ (yielding a cluster threshold of 7 contiguous voxels). All other analysis methods remained identical to Experiment 1.

3.4 Results and Statistical Analysis

3.4.1 Experiment 1

Behavior

All subjects produced switch costs in either switch direction; saccade reaction times (SRT) were greater on switch trials than on non-switch trials, and subjects often failed to switch successfully (Fig. 3.1B,C, Supplementary Fig. 3.S1). For the 7 subjects used in further analysis, antisaccades were more difficult to perform than prosaccades, despite similar switching behavior: non-switch antisaccades ('anti' trials) were slower than non-switch prosaccade ('pro' trials) (t =

2.96, $P = 0.025$, corrected for multiple comparisons) (Fig. 3.1B), and error rates were greater for anti trials than for pro trials ($t = 4.14$, $P < 0.01$, corrected) (Fig. 3.1C).

fMRI

The initial contrast conducted examined whether greater BOLD activation resulted in the CN for switch trials compared to non-switch trials. Correct anti and pro trials were pooled into non-switch trials and subtracted from correct anti2pro and pro2anti trials that were pooled into switch trials. Group activation maps from the GLM of the 'Response' period (Fig. 3.1A) are shown in Fig. 3.2A, demonstrating that switch trials resulted in greater CN activation than non-switch trials, $t \geq 4.57$, $P < 0.05$, corrected for multiple comparisons. Our a priori interest was to identify if switching from anti to pro, and/or pro to anti resulted in greater CN activation. Thus, we extracted the mean beta weight values across subjects for the 4 response types (Fig. 3.2B). Switching from pro to anti (comparison between pro2anti and pro trials) resulted in significantly greater BOLD activation (right CN: $t = 7.02$, $P < 0.001$, left CN: $t = 4.95$, $P < 0.01$). Switching from anti to pro did not (comparison between anti2pro and anti trials, right CN: $t = 0.34$, $P = 0.75$, left CN: $t = 1.55$, $P = 0.17$). In order to further understand the nature of these contrasts, we extracted the mean % BOLD signal changes across subjects for the 4 correct trial types, as well as for the erroneous switch trials (Fig. 3.2C), and grouped the trials according to identical preparatory periods. (It has been shown previously with BOLD fMRI that frontal areas critical to antisaccade generation show differences in activation upon antisaccade instruction (Connolly et al., 2002; DeSouza et al., 2003; Connolly et al., 2005). Thus, it was important to account for any possible effects in CN activation that might relate to differences in *preparatory set*, rather than response switching). On pro2anti trials, the activation profile was greater than on pro trials, whereas on anti2pro trials the activation profile showed little difference from anti trials (Fig. 3.2C). Interestingly, the activation profiles on erroneous anti2pro and pro2anti trials increased initially relative to the correct trials, with pro2anti error trial activation rising sharply to a peak, but then blunting in comparison to the correct pro2anti trials.

Subsequently, we performed separate GLMs, comparing anti and anti2pro trials, and pro and pro2anti trials. These contrasts are more justified, since the contrast maps compare trials that have identical preparatory conditions. However, we also directly contrasted anti to pro trials, to

confirm the trend shown in Fig. 3.2B, that performing a non-switch antisaccade did not result in greater BG activation relative to a prosaccade in the current experiment. Contrast maps are shown in Fig. 3.3A-C, demonstrating that only pro2anti trials resulted in greater BOLD activation relative to pro trials (Fig. 3.3C), $P < 0.05$, corrected for multiple comparisons. Fig. 3.3D shows the mean BOLD signal time courses from this contrast. A distinctly greater % BOLD signal change for pro2anti trials compared to pro trials is evident. This effect was significant across subjects (right CN: $t = 7.59$, $P < 0.001$, left CN: $t = 5.64$, $P < 0.01$) (Fig. 3.3E). A region of interest (ROI) analysis of the CN was conducted (see Supplementary Fig. 3.S2). This analysis consisted of a GLM, but did not utilize a contrast map to define a region; rather, the left and right CN were defined anatomically. The results also showed that pro2anti trials were significantly greater in activation relative to pro trials in the right CN (right CN: $t = 3.64$, $P < 0.05$, left CN: $t = 1.40$, $P = 0.21$), but that anti trials were not greater than pro trials (right CN: $t = -0.017$, $P = 0.92$, left CN: $t = -1.47$, $P = 0.19$). This confirmed that failure to find an increased activation for anti2pro trials relative to anti trials (Fig. 3.3B) cannot be attributed to greater activation for anti trials relative to pro trials.

Next, we performed a separate GLM analysis in which the 100 ms and 200 ms switch trials were not pooled, to examine whether there was a difference in switching from a pro to an antisaccade at 100 ms or 200 ms post stimulus onset. Fig. 3.3F illustrates the mean BOLD signal time course from pro2anti switch trials from the CN clusters in Fig. 3.3C. It is evident that the BOLD response is greater on pro2anti trials at the 200 ms switch time than at the 100 ms switch. Next, we directly contrasted pro2anti 200 ms to pro2anti 100 ms switch trials. Figs. 3.3G and H show that in bilateral regions of the dorsal CN, pro2anti 200 ms switch time trials resulted in significantly greater BOLD activation than pro2anti 100 ms switch time trials. To correct for multiple contrasts, the less conservative false discovery rate method was used (Fig. 3.3H), $Q < 0.05$.

Finally, we analyzed erroneous switch trials to evaluate whether BG activation is critical to mediating this switching behavior. We directly contrasted erroneous responses on switch trials to correctly executed non-switch trials. Fig. 3.4A and C demonstrate that greater CN activation occurred during erroneous anti2pro trials (corrected by a prosaccade) relative to correct anti trials

(mean beta values: right CN: $t = 3.48$, $P < 0.05$, left CN: $t = 3.32$, $P < 0.05$). The contrast of pro2anti error trials to pro trials did not result in significantly greater activation in the CN (Fig. 3.4B).

In summary, similar switch costs were found in both directions, indicating that the initially instructed response was prepared, and there were costs to switching it (Cameron et al., 2007). However, increased CN activation occurred only for switching correctly from a pro to an antisaccade. Thus, the differential activation for switch direction may result from a greater demand on BG processes to switch from a more automatic response to a more difficult response. Experiment 2 was conducted subsequently to test whether the differences in CN activation depended on the fact that subjects elicited a visually directed saccade in one condition, and an internally guided saccade in the other. We staircased the switch times based on performance (see 3.3 Materials and Methods), equalizing for the difference in switching difficulty. If the CN activation pattern changed relative to Experiment 1, it would dissociate the influence of switching difficulty from the execution of a visually driven or an internally guided saccade.

3.4.2 Experiment 2

Behavior

As shown in Fig. 3.5A, 7 of 11 subjects demonstrated error rates on switch trials between 40 and 60%, allowing us to examine behavior when switch direction was similar in difficulty. For these 7 subjects, anti trials were not slower statistically than pro trials ($t = 0.79$, $P = 0.46$) (Fig. 3.5B), however there was still evidence of prosaccade dominance, as error rates were greater on anti trials compared to pro trials ($t = 4.38$, $P < 0.01$, corrected) (Fig. 3.5C). Subjects produced significant error rate and SRT switch costs (all $t > 4.99$, $P < 0.01$) (Fig. 3.5B,C). Reaction times of erroneous saccades on switch trials are shown in Supplementary Fig. 3.S3. As a result of the staircasing procedure, the average switch time of the instruction for pro2anti trials was 193 ms, and the average switch time for anti2pro trials was slightly slower at 205 ms (across subjects), suggesting that switching difficulty was equalized. However, these values were not significantly different from one another ($t = 0.61$, $P = 0.56$).

fMRI

Switch trials resulted in greater CN activation relative to non-switch trials (Fig. 3.6A). Fig. 3.6B,C shows that anti2pro trials resulted in greater activation than anti trials (right CN: $t = 3.54$, $P < 0.05$, left CN: $t = 3.65$, $P < 0.05$), and pro2anti trials resulted in greater activation relative to pro trials in the right CN (right CN: $t = 4.06$, $P < 0.01$, left CN: $t = 1.77$, $P = 0.16$). Different BOLD signal time courses resulted between anti2pro error and pro2anti error trials (Fig. 3.6C); anti2pro error trials resulted in a noticeably greater increase in % BOLD signal change relative to both correct anti2pro and anti trials, but BOLD activation for pro2anti error trials was delayed in onset.

Separate GLM contrasts of anti to pro trials revealed no greater activation for either response in the CN (Fig. 3.7A), as in Experiment 1. Contrasting anti2pro trials to anti trials revealed greater activation in the right CN (Fig. 3.7B,D,E) that was significant across subjects' mean beta weight values ($t = 3.62$, $P < 0.05$). However, contrasting pro2anti trials to pro trials revealed no increased activation in the CN (Fig. 3.7C). Analysis of erroneous responses showed greater activation for erroneous anti2pro trials compared to correct anti trials (Fig. 3.8A,C) (right CN: $t = 3.94$, $P < 0.01$, left CN: $t = 4.67$, $P < 0.01$), but did not show greater activation for erroneous pro2anti trials compared to correct pro trials (Fig. 3.8B).

An anatomical ROI analysis of correct trials was conducted on the CN as in Experiment 1. The ROI analysis showed that the comparison of anti2pro to anti trials revealed greater activation for anti2pro trials in both the right and left CN (right CN: $t = 2.29$, $P < 0.05$, left CN: $t = 3.10$, $P < 0.05$), and the comparison of pro2anti to pro trials revealed greater activation for pro2anti in the right CN ($t = 2.88$, $P < 0.05$) (Supplementary Fig. 3.S4).

Finally, the frontal eye fields (FEF) were analyzed in a similar fashion to the CN, in order to examine a region hypothesized to have a greater role in antisaccade generation, rather than in task switching. In brief, imaging data from FEF (Figs. 3.9 and 3.10) demonstrate that performing an antisaccade (either on an anti, pro2anti, or pro2anti error trial) resulted in greater activation relative to performing a prosaccade. However, performing an anti2pro or anti2pro error trial did not result in greater activation relative to performing an anti trial. This pattern of activation mirrors previous saccade studies of FEF in antisaccade generation (Connolly et al., 2002; Curtis and

D'Esposito, 2003; Ford et al., 2005; Brown et al., 2007), and most importantly, is distinct from activation in the CN (which did not show greater activation for anti trials relative to pro trials).

3.5 Discussion

We showed in both Experiments that the BG is involved in switching a planned response, as CN BOLD activation was greater on switch trials compared to non-switch trials. However, we suggest that the BG are more important for switching from an automatic or dominant response to a non-dominant response, as greater activation resulted only for switching to the antisaccade in Experiment 1 (Figs. 3.2 and 3.3), despite similar switching behavior (Fig. 3.1B,C). Importantly, this increase in activation correlated with switch time difficulty (Fig. 3.3F-H). We then showed in Experiment 2 that the CN activation patterns on switch trials changed when differences in switching difficulty were equalized. Therefore, CN activation did not correspond to a general response switching mechanism (Mink, 1996; Nambu, 2004). We suggest instead that the CN activation related to switching difficulty, implying that the BG have a specific role in overriding a dominant action with an alternative action.

Prosaccades are more automatic, and easier to perform than antisaccades, in terms of habituation, and demand on attentional and cognitive resources (MacLeod, 1991; Dafoe et al., 2007; Ettinger et al., 2008). Antisaccades also require suppression mechanisms against responding automatically, (Everling et al., 1998; Everling and Munoz, 2000), preventing the execution of a visually driven saccade to the stimulus. This suppression mechanism has been interpreted to drive the greater BOLD activation seen in FEF for antisaccades relative to prosaccades (Connolly et al., 2002), which fits with our findings of greater FEF activation when executing an antisacccade relative to a prosaccade (Fig. 3.9). Note that FEF were consistently more active for antisaccades compared to prosaccades, even when a corrective antisaccade was made following an erroneous prosaccade (Fig. 3.10B,C). This suggests that the FEF activation related to the underlying differences between visually directed saccades and internally guided saccades, and several previous imaging studies have shown greater activation in FEF for antisaccades relative to prosaccades (O'Driscoll et al., 1995; Sweeney et al., 1996; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Connolly et al., 2005; Ford et al., 2005; Miller et al.,

2005; Brown et al., 2006; Brown et al., 2007). Because we did not observe greater CN activation for anti trials relative to pro trials (Figs. 3.3A, 3.7A, Supplementary Figs. 3.S2, 3.S4), CN activation cannot be attributed to these same processes. This finding is also supported by the fact that in Experiment 2, the switch time manipulation did not change the actual responses elicited, however the CN activation patterns changed (compare Figs. 3.2,3.3 with 3.6,3.7).

We propose that CN activation is driven, at least in part, by mechanisms similar to the Stroop task, in which subjects must perform an unusual response under interference from a dominant and more automatic response (e.g., respond with the color of the font that is incongruent with the word that is written). Models of the Stroop effect posit that the dominant response exerts the greatest interference (MacLeod, 1991), and it has been shown that performing the *less* dominant response results in greater CN activation (Peterson et al., 2002). In our study, the greatest interference results on a pro2anti trial whereby the dominant prosaccade is explicitly instructed to be planned. This would explain why there was not greater activation on anti relative to pro trials, as the pro response was *not* explicitly instructed to be planned. Under the proposed framework, switching to an antisaccade requires subjects to instantly override a more automatic response, and this is more difficult to accomplish. Conversely, switching to a prosaccade is in the direction of a more automatic response that is easier to perform. The stair-casing method of Experiment 2 only yielded a significant increase in anti2pro trials relative to anti trials at the contrast level in the right CN (Fig. 3.7A-C). However, it can be seen in Fig. 3.6 that activation was greater on anti2pro relative to anti trials, as well as on pro2anti relative to pro trials. Thus, the biggest effect of the stair-casing method appears to be increasing the difficulty of switching from anti2pro, making it similar in difficulty to switching from pro2anti. Experiment 1 did not result in increased anti2pro activation, suggesting that with fixed switch times, switching difficulty was asymmetric.

Examination of erroneous switch trials provides valuable insight into the underlying mechanisms. In both experiments, greater CN activation was seen for erroneous anti2pro trials relative to correct anti trials. In this situation, the antisaccade response overcame any interference from the more automatic prosaccade, as it was executed despite the change in

instruction. Thus, increased CN activation might result if the corrective prosaccade needs to overcome *response-system inhibition* (e.g., suppression against eliciting a saccade to the stimulus), that had biased the response system against its execution during the initial antisaccade instruction (Vink et al., 2005; Barton et al., 2006; Woodward et al., 2006; Manoach et al., 2007). In contrast, in both Experiments 1 and 2, erroneous pro2anti trials (that were subsequently corrected with an antisaccade) did not result in greater CN activation relative to correct pro trials (Figs. 3.4,3.8), measured by group contrasts. Note, however, that the BOLD activation profiles in Figs. 3.2 and 3.6 (derived from the contrast of switch minus non-switch) showed that in Experiment 1, a sharp increase in BOLD activation for pro2anti error trials occurred initially, but then blunted in comparison to correct pro2anti trials. In Experiment 2, the BOLD activation pattern on pro2anti error trials was delayed in onset, and did not result in greater activation relative to correct pro2anti trials. Together, these different activation patterns between pro2anti and pro2anti error trials suggest that switching successfully to the antisaccade is a process that is mediated, at least in part, by the BG. However, the differences in pro2anti error activation patterns across the experiments might also be reconciled by a response-system inhibition hypothesis: we cannot discount possibility that during the *pro* instruction in Experiment 1, subjects adopted a "wait-and-see" strategy given that switch times were predicted within 200ms, effectively inhibiting the response system against eliciting the programmed prosaccade. The result was an increase in BOLD activation when the volitional, non-dominant antisaccade was executed, even if a prosaccade was executed in error first. On a correct non-switch prosaccade trial, the subjects 'released*'* the programmed response, resulting in a less BOLD activation. We hypothesize that in Experiment 2, no wait-and-see strategy could be employed, and no response-system inhibition was imposed on the prosaccade instruction. This resulted in the reduced BOLD activation on correct pro2anti and pro2anti error trials relative to Experiment 1, but still contained an effect of task-switching, driving greater BOLD activation on correct pro2anti trials relative to pro trials (Fig. 3.6C).

So what neural networks might produce the BOLD activation seen in the CN? The dorsal CN receives overlapping projections from FEF and dorsolateral prefrontal cortex (Alexander et

al., 1986; Cui et al., 2003; Gerardin et al., 2003), and several studies have implicated the dorsolateral prefrontal cortex in voluntary saccade control (Guitton et al., 1985; Everling and DeSouza, 2005; Pierrot-Deseilligny et al., 2005; Brown et al., 2007; Ettinger et al., 2008). Thus, CN activation could be driven in part by processes related to rule representation and attentional set, and in all: processes related to instantly selecting the appropriate response signals from FEF (Redgrave et al., 1999; Hikosaka et al., 2000; Monchi et al., 2001; Peterson et al., 2002; Cools et al., 2004). Future studies should try to dissociate these components, in particular investigating whether the CN activation is related to cancellation or reprogramming mechanisms. However, cancellation processes alone should not produce the activation patterns seen on erroneous anti2pro trials. Secondly, cancellation should be a fast-acting process, possibly mediated by a "hyper-direct" pathway from cortex to the subthalamic nucleus, bypassing the CN, and exciting the substantia nigra pars reticulata, resulting in increased inhibitory output of the BG against responding (Mink, 1996; Aron and Poldrack, 2006; Isoda and Hikosaka, 2008). A reprogramming explanation suggests we are measuring increased activation for amplifying weaker or previously inhibited response signals. Thus, we propose that greater CN activation is related to switching to a most effortful response on a given trial: an antisaccade when a prosaccade is more automatic, or either response if the response system was biased against its execution.

3.6 Conclusions

The BG have been implicated in the inhibition of inappropriate response signals and the dis-inhibition of appropriate response signals pertaining to a desired action; however it has not been tested previously how the BG are involved in switching from one response in preparation to another instantly. Here, we have demonstrated that differences in response difficulty resulted in differential CN activation for switching. When we controlled for the difference in response difficulty, CN activation changed. Therefore, we suggest that the BG are important for effectively switching planned behavior, by overriding biases in the response system towards a particular action. This mechanism is necessary, should a more dominant behavior become inappropriate, and a new course of action be needed immediately.

Chapter 4: Executive Impairment in Parkinson's Disease: Response Automaticity and Task Switching

4.1 Abstract

Patients with Parkinson's disease (PD) show slowed movement initiation and can have deficits in executive function, leading to impairments in controlling involuntary behavior. This results in difficulties performing an *antisaccade*, which requires one to suppress an automatic eye movement (a *prosaccade*) to a visual stimulus, and execute a voluntary eye movement in the opposite direction. Antisaccade deficits are similar to those seen in *task switching*, whereby one is required to change a response after performing a different behavior. Both antisaccade (Hood et al., 2007) and task switching (Cools et al., 2001) deficits in PD have been attributed to fronto-basal ganglia (BG) dysfunction. Previously, we demonstrated with functional magnetic resonance imaging that BG circuitry is important to both task switching and voluntary saccade generation, as greater caudate activation was seen when healthy young adults first prepared a prosaccade, but then switched to an antisaccade (Cameron et al., 2009a). Therefore, we hypothesized that PD patients would have difficulty switching from one saccade response to the other, with particular impairment in switching from a pro to an antisaccade. Here, we not only confirmed this prediction, but also showed that PD patients performed better than controls in switching from an anti to a prosaccade. This suggests that task switching deficits in PD are particularly pronounced when more automatic behavior needs to be overridden with alternative behavior. We suggest that this occurs primarily at the level of establishing the appropriate *task set*, which is an internalized rule that governs how to respond.

4.2 Introduction

Parkinson's disease (PD) involves the degeneration of dopamine producing cells in the substantia nigra pars compacta that input to the striatum (Betchen and Kaplitt, 2003). The consequence of this is altered neuronal firing in the two principal pathways of the basal ganglia (BG): the *direct* and *indirect*, which leads to a net increase in inhibitory output from the BG on thalamo-cortical circuits, and on the superior colliculus (Mink, 1996; Hikosaka et al., 2000; Schultz, 2001; Dagher and Nagano-Saito, 2007). This results in the hallmark motor symptoms of bradykinesia (slowed movement execution) and akinesia (impaired movement initiation), and is

thought to contribute to executive dysfunction often observed in PD which resembles that following frontal lobe damage (Lewis et al., 2003; Owen, 2004). Accordingly, tasks that require both an initiation of a motor response as well as executive control over behavior unearth deficits in behavioral control in PD. In the *antisaccade* task, PD patients fail to suppress an automatic *prosaccade* to a visual stimulus more frequently than normal healthy adults, resulting in erroneous eye movements in the direction of the stimulus (Briand et al., 1999; Chan et al., 2005; Amador et al., 2006; Hood et al., 2007). PD patients are also slower to initiate an antisaccade. The antisaccade task is one of the simplest models of behavioral control, and deficits in PD suggest that deficient dopaminergic (DA) input to the BG disrupts the suppression and focusing mechanisms (Mink, 1996) of the BG on cortical (e.g., frontal eye fields, dorsolateral prefrontal cortex) signals critical to generating a voluntary saccade and suppressing an automatic saccade (Munoz and Everling, 2004). Importantly, these antisaccade deficits highlight an asymmetric impairment in PD, in which an *unimpaired* automatic response interferes with the execution of an alternative, voluntary, response. Some evidence exists that this impairment might occur at a more cognitive stage, during which an antisaccade *task set* (a rule about how to respond) is established prior to response programming (Rivaud-Pechoux et al., 2007). However, most previous studies have focused on the failure to suppress an automatic prosaccade to a peripheral stimulus, and on the slower programming of the voluntary antisaccade away from the stimulus in PD. More work is needed to understand how the easier prosaccade task set might compete with the more difficult antisaccade task set, setting-up a person with PD for an incorrect or impeded response before a response is programmed.

To explore this, we now draw on studies of *task switching* that have been more optimally designed to explore the interaction between competing task sets. Task switching experiments have also shown that PD patients have deficits in behavioral flexibility that can be explained, at least partially, by fronto-BG dysfunction. Deficits include slowed reaction times when the appropriate response changes across trials (Cools et al., 2001; Cools et al., 2003), perseveration errors in the Wisconsin Card Sorting Task (Milner, 1963; Lees and Smith, 1983) related to the inability to change task set, and impairments in working memory resulting in deficits manipulating

rule representations (Owen, 2004; Lewis et al., 2005). Importantly, it has been demonstrated with functional magnetic resonance imaging (fMRI) that fronto-BG circuitry is important to task switching (Cools et al., 2006) and that differences in cortical as well as BG activation are seen when comparing PD patients and control subjects performing switching tasks (Monchi et al., 2004; Monchi et al., 2007). However, unlike the antisaccade task, studies in task switching typically rely on participants to switch between stimulus-response mappings learned in a given experiment, and do not contrast highly automatic behavior to alternative, more difficult, behavior to perform. An exception to this is a study by Woodward and colleagues (2002) who showed in a Stroop paradigm that patients with PD had greater reaction time 'costs' than controls when they first performed the more automatic word reading response, but then subsequently performed the more difficult color naming response. Thus, deficits in task switching in PD may relate to how 'easily' one can switch between two behaviors that differ in automaticity.

We previously created a paradigm in which participants were prompted to plan one response (pro or antisaccade) but then switch it, unexpectedly, to the alternative on a subset of trials (Cameron et al., 2007). Importantly, the switching difficulty was asymmetric, meaning that subjects could be switching to a response that was either more automatic (prosaccade), or less automatic (antisaccade), to perform. Moreover, the time in a given trial in which the switch occurred varied with respect to peripheral stimulus onset, such that if the switch in instruction occurred in advance of stimulus onset, it would constitute a change of task set alone. Using a version of this paradigm, we also showed with fMRI that activation in the caudate nucleus (CN), the BG input nucleus in the oculomotor system, correlated with switching difficulty (Cameron et al., 2009a). A greater increase in CN activation occurred when subjects first planned a prosaccade, but then had to switch to an antisaccade, than when subjects first planned an antisaccade, but then had to switch to a prosaccade. This demonstrated that activation of the CN correlated with switching from a more automatic to a more difficult behavior. Based on previous findings from the antisaccade and task switching literature, we hypothesize that PD patients in a similar task will show greater difficulties (increased reaction time and error rates) on antisaccade trials compared to control subjects, greater difficulties in switching task, and greatest difficulties in

switching from a pro to an antisaccade. We are also interested in determining if deficits exist when only task set is changed.

The results show that PD patients had an underlying bias towards the more automatic prosaccade response that interacted with their task switching behavior: patients were overall superior at prosaccade performance, but impaired at antisaccade performance. Thus, patients showed poorer performance in switching from a pro to an antisaccade in comparison to the controls, but showed superior performance in switching from an anti to a prosaccade. Interestingly, their poorer performance in switching from a pro to an antisaccade occurred only when a change in task set was required. Therefore, we suggest that enhanced biases towards more automatic or habitual behavior exist prior to programming a response in PD, and this can explain some of the deficits observed in both antisaccade and task switching experiments.

4.3 Methods

4.3.1 Participants

All experimental procedures were reviewed and approved by the Queen's University Human Research Ethics Board and adhered to the Declaration of Helsinki. 26 individuals (14 PD, 12 age-matched control participants) with normal or corrected-to-normal vision were recruited. All participants were permitted to wear corrective lenses if required, and all participants provided written informed consent and were compensated for their participation ($10/hour). PD patients (mean age = 60.1, 10 males) were recruited from GP's movement disorder clinic at the Kingston General Hospital, and age-matched controls (mean age = 59.9, 5 males) were recruited from the Kingston community. PD patients were considered early/moderate stage based on a mean Hoehn and Yahr score of 2.2. Clinical data and participant demographics are shown in Table 4.1.

PD patients were medicated and were not asked to interrupt their medication on the days of recording, due to the difficulty of the task (expected to produce a large percentage of error trials), and the fact that antisaccade deficits have been shown to occur in PD even while taking dopaminergic medications (Briand et al., 1999; Chan et al., 2005; Hood et al., 2007; Cameron et al., 2009b). Medication information for each patient is given in Table 4.1. All control participants reported no history of neurological, psychiatric or visual disorders (other than refractive error),

and did not differ as a population in terms of age and years of education. Finally, all participants underwent an evaluation of mental status, using the Mini Mental State Examination (MMSE) by IC. A score of 26 or lower was used as exclusion criteria.

4.3.2 Design and Procedure

Horizontal eye position was monitored online with DC-electrooculography (EOG). To minimize DC drift the skin was cleaned with rubbing alcohol and participants wore the electrodes for approximately 5-10 minutes before the experiment began. Additional DC drift was corrected manually during the experiment. Stimulus presentation and monitoring of eye position were done using REX Version 5.4, sampling at 1000 Hz (Hays et al., 1982). Prior to data collection the EOG signal was calibrated by having subjects look between targets that were located at 10° left,10° right and center position. Data analyses were conducted with custom software developed in MATLAB 7.4 (The Mathworks, Natick, MA).

Participants were seated 1m from a tangent visual screen and an array of LED stimuli was positioned just in front of the screen. A head rest was used to minimize any change in head position. All of the experiments were conducted in the dark however the screen was diffusely illuminated for 600 ms between trials to prevent dark adaptation.

Blocked design

Participants first performed a prosaccade task that required them to initiate a saccade to a peripheral stimulus (target) that appeared 10° to the left or right of a central fixation point (FP) that marked the onset of the trial (Fig. 4.1). The FP was a light emitting diode (LED), colored red (8.0 cd/m^2) or green (3.0 cd/m^2), because subjects would subsequently perform an antisaccade task with the opposite fixation color (described below), and fixation color was counterbalanced across subjects. In the end, 5/12 controls and 7/14 PD patients received the red fixation instruction for the prosaccade task. The target appeared 900 ms after participants fixated the fixation point, and was the same color as the central fixation point. Participants were required to look to the target as soon as it appeared and to hold their gaze on the target for 160 ms before the target disappeared and the screen was illuminated for 600 ms to end the trial. Participants were required to complete 100 correct trials (defined by direction and by reaction time of < 1000 ms from target onset).

Next, the participants performed a block of 100 correct antisaccade trials. The parameters of the antisaccade block were identical to those in the prosaccade block, however the participants were required to refrain from eliciting a saccade to the target, and instead, to make a saccade to the mirror location. The target remained the same color as in the prosaccade block but the FP was now the opposite color to instruct an antisaccade.

Task switching design

The basic experimental setup remained the same as the blocked design, with each trial beginning with the onset of the red or green FP corresponding to the same instructions as in the blocked design. However, on 33 % of the trials, the initial fixation color switched to the opposite color at 4 variable 'switch times' relative to target appearance: -200, -100, 0 and +100ms (Fig. 4.1). When this occurred, subjects were required to switch task, and these trials are referred to as 'switch trials'.

We chose the 4 switch times to investigate how behavior would differ if subjects had more or less time to switch task. Greater percentage direction errors and increased saccade reaction time (SRT) on switch trials relative to non-switch trials are referred to as 'switch costs' and it was expected that switch costs should be greater when participants had less time to switch (Cameron et al., 2007). Importantly, two of the switch times occurred before target onset (-200 and -100ms) meaning that if PD patients have difficulty in establishing a new *task set* (a rule about which action to perform) (Sakai, 2008), switch costs might be greater than controls, and a deficit at these switch times would suggest impairments in executive function primarily. In contrast, the 0 and +100ms switch times involved a change in task concurrent with, or after, the target had appeared, meaning that a pro or antisaccade response to the target may have already been in preparation (Cameron et al., 2007). Thus, greater switch costs in PD at these times would suggest a deficit in overriding one prepared response with another.

Participants were asked to perform 4-5 blocks of 100 correct trials. However, no subject was required to perform more than 200 trials (correct or error) per block, and no subject was required to perform more than 1000 trials in total. In the end, 11/12 control participants achieved 400 correct trials in the task switching design with one achieving 250. For PD patients, 8/14

achieved 400 correct trials, 2 achieved 300 correct trials, and 2 achieved 150 correct trials. The remaining 2 PD participants (numbers 13 and 14 in Table 1) could not perform the task (executed close to 100% errors on all switch trials), and were excluded from further analysis, yielding the comparison of 12 PD participants (mean age = 60.3 years, 8 male, see Table 1) to 12 age-matched controls.

4.3.3 Analysis

Failure to fixate the first fixation point within 5000 ms, failure to maintain fixation, failure to initiate a saccade within 1000 ms, and failure to fixate the saccade target for at least 160 ms were removed from analysis. SRT was defined as the time from when the target appeared to when the first saccade away from fixation exceeded 30°/s. Saccades with reaction times < 90 ms were also excluded, representing anticipatory errors as defined by a previous study in the same laboratory that showed that prosaccades of human subjects less than this value were initiated with only 50% accuracy (Munoz et al., 1998).

The errors of primary interest in the current study were those in which participants executed the wrong saccade to the target based on the current instruction (a prosaccade on anti instruction or vice versa). These errors were labelled as 'direction errors', and the percentage of direction errors was calculated by dividing the errors by the total number of valid trials (correct trials + direction error trials) for the pro or antisaccade condition. Errors that qualified as failures to initiate a saccade were also analyzed by dividing these errors by the total number of all trials.

Reaction times and percentage direction errors on non-switch and switch trials were analyzed first with omnibus 3-way repeated measures ANOVAs in SPSS Statistics version 17.0, with a between-subject factor of 'Group' (2 levels: PD and Control), a within-subject factor of 'Switch Time' (5 levels: non-switch, -200, -100, 0, +100), and a within-subject factor of 'Initial Task' (2 levels: pro and anti). To test our a priori hypothesis, subsequent 2-way repeated measures ANOVAs were conducted between (i) non-switch prosaccade trials and pro-to-antisaccade ('pro2anti') switch trials, and (ii) non-switch antisaccade and anti-to-prosaccade ('anti2pro') switch trials, to contrast trials that that began with the identical initial instruction, and

thus, with an identical initial task set. The significance level for all tests was set at $P < 0.05$, and the Greenhouse-Geisser (ε) correction was used if the sphericity of variances was violated.

To specifically understand differences in task switching between PD patients and controls, 'switch costs' in SRT and percentage direction errors were calculated by comparing non-switch trials to switch trials of an identical initial task (e.g., non-switch pro trials, and pro2anti switch trials). Switch costs were presumed to reflect the requirements of the brain to override one behavior with the alternative. For direction errors, switch costs at each switch time were calculated by subtracting the mean of non-switch trials from the mean of switch trials for a given switch time for each participant. A positive value indicated a switch cost. For SRT switch costs, we used a normalized index:

$$\text{switch cost index} = \frac{\text{MEANswitch} - \text{MEANnon-switch}}{|\text{MEANswitch} - \text{MEANnon-switch}| + \sqrt{(\text{SDswitch})^2 + (\text{SDnon-switch})^2}}$$

which incorporated variability in reaction times in addition to mean reaction times (Prince et al., 2002). We did not assume that variability in reaction times would be the same across patients and controls, and across non-switch and switch trials. If the difference of the means was large and the variance was small, this index was close to ±1 depending on which mean was larger; if the variance was large, the switch cost indices were smaller. For switch costs, a 2 X 4 ANOVA was conducted, with a between-subjects factor of Group (PD and Control) and a within-subjects factor of Switch Cost with 4 levels (-200, -100, 0, +100). Post-hoc *t*-tests (independent, two tailed) were conducted at individual switch times to compare PD patients with controls for a given response where stated.

For the blocked design, paired *t*-tests were used to compare SRTs within subjects for pro and antisaccades, and independent *t*-tests were used to compare across groups, $P < 0.05$, corrected for multiple comparisons (Bonferroni). Mann-Whitney U tests (*Z*) were used for direction errors due to the fact that very few errors on prosaccade trials were made, meaning that the distribution of prosaccade error rates was non-parametric around a floor value of zero (Kolmogorov-Smirnov test, $P < 0.05$). Finally, Pearson's *r* values were used for correlation analyses.

4.4 Results

Blocked design

Both PD patients and controls made more errors on antisaccade trials than on prosaccade trials, PD: $Z = 3.06$, $P < 0.01$, control: $Z = 2.67$, $P < 0.01$ (compare Fig. 4.2A and C). There was a greater percentage of direction errors on antisaccade trials for PD (21%) compared to controls (13%) (Fig. 4.2C), however this did not reach significance, $Z = 1.65$, $P = 0.10$. Both PD and control participants had greater SRTs for antisaccade trials relative to prosaccade trials, PD: $t = 5.65$, $P < 0.01$, control: $t = 4.79$, $P < 0.01$ (compare Fig. 4.3A and C). Finally, PD patients were slower to respond than control participants for both prosaccade trials (299 ms vs. 247 ms), $t = 3.04$, $P < 0.01$, and antisaccade trials (395 ms vs. 331 ms), $t = 2.64$, $P < 0.05$. These results show that PD patients were significantly slower to respond overall, and exhibited behavior that fits with previous findings (Briand et al., 1999; Chan et al., 2005; Hood et al., 2007).

Task switching design

Changing from the blocked design to the task switching design increased the percentage direction errors significantly for both non-switch pro (Fig. 4.2B) and antisaccade (Fig. 4.2D) trials, and for both PD patients and control subjects, $Z > 1.96$, $P < 0.05$. SRT on non-switch pro and antisaccade trials also increased significantly for controls $t > 6.11$, $P < 0.01$, and on non-switch prosaccades for PD patients, $t = 3.13$, $P = 0.01$ (Fig. 4.3B,D). PD patients did not have a significantly greater SRT on non-switch antisaccade trials relative to the blocked design, $t = 1.80$, $P = 0.17$.

A test of normality (K-S) revealed that > 75% of the direction errors at each switch time were normally distributed. Therefore, the ANOVA as described in the Methods was used because we were most interested in interactions between ‘Group’ and ‘Switch Time’, highlighting the differences between the two groups (Fig. 4.2B,D and Fig. 4.3B,D). However, the Mann-Whitney U test was used for post-hoc tests at each switch time for percentage direction errors. The Group X Switch Time X Initial Task ANOVA revealed no significant interaction for direction errors $F(4,19) = 1.87$, $P = 0.16$, or for SRT, $F(4,19) = 0.57$, $P = 0.69$. There was, however, a main effect of Group for SRT, $F(1,22) = 4.54$, $P < 0.05$. Two-way ANOVA’s were subsequently conducted to determine the influence of switching from an initially planned behavior to the alternative, as described above.

4.4.1 Pro and Pro-to-Antisaccade trials

For direction errors, there was a significant Group X Switch Time interaction, $F(4,19) = 4.49$, $P < 0.01$, and there was a main effect of Switch Time, $F(2.74, 60.59) = 143.28$, $P < 0.01$. There was no main effect of Group $F(1,22) = 1.18$, $P = 0.29$. As shown in Fig. 4.2B, this demonstrates that PD patients did not make greater errors overall in comparison to control subjects, however, the interaction shows that PD patients made fewer errors on non-switch prosaccade trials (4% vs. 8%), but greater errors on pro-to-antisaccade ('pro2anti') switch trials (average 78% vs. 70% across the switch times). Post-hoc Mann-Whitney U tests confirmed that PD patients made significantly fewer non-switch prosaccade errors than controls, $Z = 2.37$, $P < 0.05$, and greater pro2anti errors at the -200 ms switch time, $Z = 2.31$, $P < 0.05$. At the -100 ms switch time, the difference approached significance, $Z = 1.73$, $P = 0.08$. Percentage direction errors did not differ between groups at the 0 and +100 ms switch time, $P > 0.67$.

For SRT, there was not a significant Group X Switch Time interaction, $F(4,19) = 0.61$, $P = 0.66$. However, there was a main effect of Switch Time, $F(4,88) = 55.6$, $P < 0.01$, and there was a main effect of Group, $F(1,22) = 4.35$, $P < 0.05$, illustrating that PD patients were slower to respond overall, but showed a similar switching behavior to the controls (Fig. 4.3B).

Figure 4.4A shows that both groups produced switch costs in error rates for pro2anti trials (Y axis > 0), with the switch costs being greater (close to significance) across the switch times in PD patients, $F(3,20) = 2.42$, P = 0. 096. The main effect of Group was also close to significance, $F(1,22) = 3.27$, $P = 0.08$. Importantly, the early switch times had significant differences between the groups, $t > 2.40$, $P < 0.05$, whereas the latter two did not, $t(22) < 0.831$. There was no difference in SRT switch costs between the two groups $F(3,20) = 1.46$, $P = 0.26$, nor was there a main effect of Group, $F(1,22) = 0.52$, $P = 0.48$ and at -200ms, switch costs were not significantly greater for PD patients, $t = 1.64$, $P = 0.11$ (Fig. 4.5A).

To summarize, PD patients showed greater direction error switch costs and greater errors on pro2anti switch trials at the -200 and -100 switch times compared to the controls. PD patients also had fewer errors on non-switch prosaccade trials, but were slower to respond overall and did not show greater SRT switch costs.

4.4.2 Anti and Anti-to-Prosaccade trials

There was no significant Group X Switch Time interaction for percentage direction errors, $F(4,19) = 2.13$, $P = 0.12$, but as above, there was a main effect of Switch Time, $F(1.43, 31.40) = 16.39$, $P < 0.01$. There was no main effect of Group $F(1,22) = 0.90$, $P = 0.35$. As seen in Fig. 4.2D, PD patients made greater errors relative to controls on non-switch antisaccade trials (49% vs. 37%), but fewer errors than controls on anti-to-prosaccade ('anti2pro') trials overall, and also showed less of a change in error rates across the switch times than did the controls. PD patients showed significantly fewer anti2pro errors at the -200 ms, $Z = 2.04$, $P < 0.05$, and at the +100 ms switch time, $Z = 1.99$, $P < 0.05$, relative to controls.

For SRT, there was no significant Group X Switch Time interaction, $F(4,19) = 1.05$, $P = 0.41$. However, there was a main effect of Switch Time, $F(2.15,47.38) = 19.06$, $P < 0.01$. The main effect of Group approached significance, $F(1,22) = 3.59$, $P = 0.07$. As with pro and pro2anti switch trials, this suggests that PD patients were slower to respond overall (Fig. 4.3D).

Analysis of switch costs showed that PD patients had enhanced switch *benefits* in direction errors relative to control subjects, $F(3,20) = 2.94$, P = 0.06 (Fig. 4.4B), approaching significance, $t = 1.9$, $P = 0.07$, at the +100 ms switch time. The main effect of Group did not reach significance however, $F(1,22) = 2.53$, $P = 0.13$. For SRT, there was no difference in SRT switch costs between the two groups, $F(3,20) = 0.42$, $P = 0.74$, main effect of Group, $F(1,22) = 0.26$, $P = 0.62$ (Fig. 4.5B).

In summary, an opposite pattern of behavior emerged for switching from an anti to a prosaccade than for switching from a pro to an antisaccade with respect to percentage direction errors (Figs. 4.2B,D): PD patients showed a performance deficit on the non-switch trials (anti), but a performance advantage on the switch trials (anti2pro) relative to the control subjects.

4.4.3 Correlation with disease severity and medication

For each patient, their UPDRS motor score (Table 1) was correlated against SRT and direction errors in the blocked and task switching designs. Data was collapsed across the 4 switch times. All correlations, except for SRT on anti2pro switch trials, were in the positive direction (i.e., greater SRT and greater percentage direction errors corresponded to a greater UPDRS score) however no correlation had an *r* value greater than 0.48, indicating that there was

no correlation between UPDRS motor score and performance. Years from initial diagnosis (Table 1) were also correlated to SRT and direction errors in the same way, and all correlations were also in the positive direction, with significant correlations resulting for non-switch anti SRT, r = 0.80, $P < 0.01$, in the task switching design, and for pro-to-antisaccade SRT in the task switching design $r = 0.60$, $P < 0.05$.

On average, control subjects failed to initiate a saccade on 2.4% of all trials, whereas PD patients failed to initiate a saccade on 12.2 % of all trials. There was no correlation between the percentage of these errors and with the UPDRS motor score, $r = 0.21$.

Correlations to medication regimen were not conducted due to the heterogeneous medications across subjects, however the switch costs of the 4 patients who were not taking L-DOPA (patients 1,2,11 & 12 in Table 1) were compared to the remaining 8 who were. (Note that these 4 patients were also on average less advanced in terms of years with diagnosed PD). There was a significant Group X Switch Time interaction for the anti2pro direction error switch costs, $F(3,8) = 4.17$, $P < 0.05$, and a main effect of Group, $F(1,10) = 5.14$ $P < 0.05$, such that the 4 non-L-DOPA patients had a reduced prosaccade switch benefit, that reached significance at the -100, 0 and +100ms switch times (all P's < 0.05). This effect arose not from significant differences in non-switch anti error rates ($P = 0.17$), but from significantly greater anti2pro error rates at these 3 switch times in the non-L-DOPA participants (all P's < 0.05). These 4 patients also had reduced pro2anti SRT switch costs at +100ms, $t = 3.98$, $P < 0.01$. No other comparisons were significant.

4.4.4 Supplementary Analysis of Task Switching

We focused the above analysis on the switch costs related to changing an initially planned behavior in comparison to maintaining the initially planned behavior. As such, these switch costs are akin to the switch costs reported in our previous fMRI study (Cameron et al., 2009a), and to the fMRI activation patterns reported in a card sorting task, in which trials where PD patients had to maintain a given behavior, were subtracted from trials in which PD patients had to change behavior based on feedback (Monchi et al., 2004). However, an alternative method to measure switch costs is to compare trials that share identical responses (e.g., non-

switch anti trials and pro2anti switch trials), to measure the time required for, and ability of, executive processes to reconfigure to the appropriate task set. If PD patients have a deficit in this reconfiguration process, they would be expected to produce enhanced switch costs. However, if there is an underlying bias towards one behavior (e.g., prosaccades), this might not reveal switch costs because the identical saccade response is compared.

Under this analysis, no significant differences in task switching behavior were found between the groups, except for an interaction that approached significance between Group and Switch Time for direction error *reconfiguration* costs derived from comparing pro trials to anti2pro trials, $F(3,20) = 2.94$, $P = 0.06$. This interaction arose from the fact that PD patients showed reduced reconfiguration costs at the later switch times, but that were not individually significantly different from the controls, $P > 0.11$. A main effect of Group for SRT reconfiguration costs approached significance, $F(1,22) = 3.13$, $P = 0.09$, indicating that PD patients showed a trend for increased SRT reconfiguration costs overall for anti2pro trials. The full results of this analysis are described in Supplementary Analysis 4.A1 including Supplementary Figs. 4.S1 and 4.S2 that illustrate reconfiguration costs for direction errors and SRT, respectively.

4.4.5 Summary

The results taken together demonstrate a strong prosaccade bias in PD patients; they made fewer errors when executing a prosaccade, or switching to a prosaccade, but they were significantly impaired at executing an antisaccade in comparison to controls. Patients were slower at responding overall. There was no correlation of UPDRS motor score to saccade behavior, however the 4 patients not taking L-DOPA showed a reduced prosaccade advantage compared to the 8 who were. Correlations involving years since diagnosis showed that the patients with fewer years since initial diagnosis executed antisaccades faster than patients with more years since initial diagnosis.

4.5 Discussion

We hypothesized that if PD patients had an underlying deficit in task switching, they would have shown increased switch costs in both SRT and the occurrence of direction errors. However, PD patients only showed greater direction error switch costs when switching from the

more automatic prosaccade to the less automatic antisaccade. Instead, PD patients showed an advantage over the controls in terms of errors when switching *towards* the more automatic prosaccade. Additional analysis showed that because reconfiguration costs were not greater in PD than in control subjects, there was not a generalized impairment in task switching in PD; rather, deficits arose depending on the relative automaticity between two tasks. Together the findings point to a task set bias towards the more automatic behavior, which underlies their difficulty in generating alternative, voluntary behavior.

Previous studies have shown deficits in antisaccade performance in PD (Chan et al., 2005; Hood et al., 2007), and have attributed these deficits to greater difficulty in suppressing the automatic prosaccade. However these studies were unable to make predictions about a prosaccade *advantage* in PD, because percentage direction errors on pro trials are typically few in blocked designs (e.g., Fig. 4.2A). In the current study, a prosaccade advantage in PD was seen as consistently fewer direction errors on trials where a prosaccade was required (Fig. 4.2A,B,D) , in particular at the +100ms switch time on ant2pro trials where this effect was most pronounced. Reconfiguration costs occurred in both groups at this switch time (see Supplementary Content), which are expected given that the alternative antisaccade task was initially instructed, and these trials were compared to the simplest trials: non-switch prosaccades. However, only the PD patients showed a *switch* benefit in terms of correct performance at this time (Figs. 4.2D,4.4B), suggesting that even if an antisaccade response could be prepared based on the target being present, PD patients were still advantaged by switching to a prosaccade. This might suggest a speed-accuracy trade-off in PD (SRT switch costs did occur), if PD patients withheld their responses upon antisaccade instruction, perhaps as compensation for their known difficulty in antisaccade generation. However, being slower to respond (explained in the following section) may have worked to their advantage in switching to the more automatic response. In either case, an antisaccade impairment (resulting in prosaccade execution) in PD occurred on trials where an antisaccade was required (Fig. 4.2B,C,D), except on those trials that involved switching from a pro to an antisaccade *after* target onset (Fig. 4.2B, Supplementary Fig. 4.S1A).

This suggests that biases towards a more automatic task set exist in PD, and these biases interfere with the setting of the appropriate task set prior to programming a response.

Task set can be thought of as the configuration of neural signals related to rule representation and preparatory processes that govern how one should respond to a stimulus (Wallis et al., 2001; Sakai, 2008). Because no information existed about the direction of the saccade response on trials with negative switch times, the behavioral deficits observed in PD at these switch times must have occurred at the level of establishing an antisaccade task set. Results from a recent study by Rivaud-Pechoux and colleagues (2007) suggested that simultaneous activation of both pro and antisaccade task sets in an interleaved design might contribute to the greater error costs for antisaccades in PD in comparison to a standard blocked design. However, because there were also prosaccade costs associated with performing the interleaved design by Rivaud-Pechoux and colleagues (2007) (as well as in the current study, Fig. 4.2A,B), we cannot conclude that the antisaccade error costs are associated with interference from the prosaccade task set by comparing blocked to interleaved designs. In contrast, differential switch costs and switch benefits highlight the asymmetric interference that one task set has over the other in producing, or reducing, error rates when the task switches mid-trial. Taken together, our results suggest that a stronger bias towards the more automatic prosaccade task set in PD made it more difficult for PD patients to override automatic behavior with an alternative behavior.

4.5.1 Neurological Substrate Underlying Behavior

Our results are consistent with models of BG dysfunction in PD that posit that deficits in behavioral control are the result of increased inhibitory output from the BG on downstream motor structures (i.e., the superior colliculus) and on thalamo-cortical circuits (Alexander et al., 1986; Mink, 1996; Betchen and Kaplitt, 2003; Nambu, 2005). We hypothesize that impairment in establishing the antisaccade task set in PD is the result of changes in neural signaling in the frontal cortex due to increased BG inhibition on the excitatory cortical afferents from the thalamus. Voluntary saccade control is mediated by frontal cortical regions which include the dorsolateral prefrontal cortex (DLPFC), supplementary eye fields (SEF) and frontal eye fields (FEF) that input

to the SC and brain stem (Munoz, 2002; Pierrot-Deseilligny et al., 2004). Preliminary results from our laboratory show that there is a generalized hypo-activation in the DLPFC, SEF, and FEF as PD patients prepare and execute antisaccades (Cameron et al., 2009b), which fits with findings of hypo-activation in executive and attention networks of the frontal cortex in PD (Dagher and Nagano-Saito, 2007). If the frontal cortex is under-activated in PD, the establishment of the more voluntary antisaccade task set may be impaired and the automatic prosaccade task set predominates. The FEF, SEF, and in particular, the DLPFC, are critical to presetting the saccade network for an antisaccade and overriding automatic prosaccades (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991; Sereno, 1996; Condy et al., 2007), and correlates of antisaccade task set in the FEF (Everling and Munoz, 2000; Munoz and Everling, 2004) and DLPFC (Connolly et al., 2002; DeSouza et al., 2003; Everling and DeSouza, 2005; Johnston and Everling, 2006) have been identified with monkey neurophysiology and fMRI. Recent evidence also shows that inactivation of the principal sulcus (anatomical location of DLPFC in monkeys) increased errors on antisaccade trials, but decreased errors on prosaccade trials, when animals were instructed to establish and maintain a pro or antisaccade task set prior to target appearance (Koval et al., 2009). Similarly, it has been shown in humans that a single pulse from transcranial magnetic stimulation (TMS) over the DLPFC increased antisaccade errors when applied at -100 ms (with respect to target onset), but not at 0 or +100 ms (Nyffeler et al., 2007). Taken together, studies do show that disruption of DLPFC processing during task set establishment biases the subject towards prosaccade behavior. Importantly, the DLPFC has also been shown to be involved in shifting attention and task set (Rogers et al., 1998; Rogers et al., 2000; Monchi et al., 2001), and has been implicated in other forms of executive dysfunction in PD (Owen et al., 1998; Monchi et al., 2004; Monchi et al., 2007), in particular those involving planning, strategy and manipulation of items in working memory (Owen, 2004).

The slower SRT in PD in the current study can be also predicted by a model of increased BG inhibition. Saccade neurons in the SC are under tonic inhibition from the substantia nigra pars reticulata (SNr), and there is a pause in this inhibition prior to saccade initiation (Hikosaka and Wurtz, 1983; Hikosaka et al., 2000; Basso and Wurtz, 2002). If the pausing of SNr neurons in the

BG's direct pathway is impeded in PD, or if saccade related activity in the SC must overcome increased inhibition (due to an enhanced indirect pathway) (Nambu, 2004; Nambu, 2005), then both pro and antisaccades should be slower to elicit. Thus, increased SRT in the current study in PD can be explained by increased BG inhibition on the SC, which is consistent with results from another laboratory (Hood et al., 2007). Based on these simple models, suppression of SC saccade neurons via the indirect pathway through the BG should assist in the prevention short latency prosaccades, and should predict decreased errors on antisaccade trials in PD. However, because it takes longer to respond in PD means that there is more time available for the visual signal from the stimulus to trigger a prosaccade error at longer latencies. We observed that the mean SRTs of erroneous prosaccades in PD patients were greater than 300 ms across all 4 switch times, showing that PD patients were not executing a high percentage of short-latency errors on antisaccade trials. Thus, it is possible that the enhanced prosaccade bias in PD could be explained by failure of the frontal cortex to establish, or maintain antisaccade task set, and also by the fact that the target stimulus is continually providing inputs to SC saccade neurons from areas (e.g., visual cortex) independent of the BG impairment. Together this might also contribute to their advantage in switching to the prosaccade at the +100ms switch time.

In summary, we suggest that the ability to establish the antisaccade task set takes place in neural networks in the frontal cortex involving the DLPFC that receive positive feedback signals via BG thalamo-cortical channels (Alexander et al., 1986). These signals may be weaker in PD, resulting in reduced activation of the antisaccade task set, and consequently, reduced inhibition against eliciting a prosaccade. Our findings are similar to those reached by other tests of behavioral control. For example, in the Stroop task (Stroop, 1935), the tendency to perform the more automatic response (word reading) interferes with the required task of reading font color, and the more automatic word reading response impedes the reading of color, and is often executed erroneously (MacLeod, 1991). Indeed, it has been observed that PD patients show response time deficits in the Stroop task, specifically when having to *switch* to the less automatic color naming response after performing the word reading task (Woodward et al., 2002). Similarly, it has been shown that monkeys given chemical lesions to the substantia nigra (pars compacta)

by 1-methyl-4-phenyl-1,2,3,6-terahydropyridine (MPTP) displayed perseverative errors in switching from 'go' to 'no-go' behavior, indicative of fronto-BG dysfunction in executive control (Slovin et al., 1999).

4.5.2 Limitations and Future Directions

A methodological limitation in our study is that patients were taking dopaminergic (DA) medications, and heterogeneous medication regimens. However, their scores of motor function on the UPDRS, and their antisaccade deficits that mirror previous studies of patients in either an 'on' or 'off' medication state (Chan et al., 2005; Hood et al., 2007; Cameron et al., 2009b), suggest that the DA therapy was not sufficient in bringing the patients' performance up to the level of the controls. Moreover, withholding DA medication 12-18 hours prior to testing (as is typical practice in many experiments) may contain residual effects of DA, especially with the agonists taken by a subset of patients (Cools, 2006). Interestingly, an association with medication was observed. Our comparison of the 4 patients who were not taking L-DOPA showed that these 4 patients had a significantly reduced prosaccade advantage making them look more like the controls than the remaining 8. Thus, there may be a medication effect due to L-DOPA, however these results are more likely due to the fact that these patients were less advanced in PD, as L-DOPA was not prescribed to patients in the earlier stages of the disease. Nevertheless, we are planning future studies whereby patients will participate in an on-off medication design of the current experiment in conjunction with fMRI. It is important to consider the effects of medication, because executive dysfunction in PD may depend on levels of dopamine in the frontal cortex itself, either due to pathology or adverse effects from therapy (Owen, 2004; Cools, 2006). In addition, patients with PD may over-activate motor areas in fMRI studies of simple motor responses (Dagher and Nagano-Saito, 2007), perhaps related to compensation for increased BG inhibition (Mallol et al., 2007). Thus, fMRI may be able to identify a correlate of hyper-activation in PD related to their prosaccade advantage.

4.6 Conclusions

We employed a saccade switching paradigm to identify an underlying bias in PD towards a more automatic prosaccade response that influenced their ability to switch task. Specifically, PD

patients performed with impairment or superiority relative to controls, depending on the switch direction. Our results suggest that an underlying deficit in setting a task set towards a non-habitual and voluntary motor task can explain behavioral deficits in PD when a required voluntary behavior competes with an automatic behavior. We suggest that for PD patients to improve performance in daily activities, assistance from externally triggered behavior can be utilized where available (a well known phenomenon) (Martin, 1967; Oliveira et al., 1997). Conversely however, performance on non-automatic tasks can be ameliorated if steps in concentration or improving attention are taken to avoid the detrimental interference from habitual tasks that are more automatic in nature (Morris et al., 1996; Cunnington et al., 1999).

Chapter 5: Impaired Pre-Setting of Motor Brain Regions in Parkinson's Disease

5.1 Abstract

Recent evidence has shown that patients with Parkinson's disease (PD) often display deficits in executive functions, such as planning for future behavior, and that these deficits may stem from pathologies in prefrontal cortex and basal ganglia networks that are critical to executive control. Here we show that when the preparatory 'readiness' to perform a given action is dissociated from the actual execution of that action, PD patients (off and on dopamine medication) display behavioral impairments and reduced cortical brain activation that cannot be explained by a pathology related to dysfunction in movement execution. Rather, they show that the appropriate pre-setting of these regions is the critical element that if not effectively in place results in impairments in the control of subsequent voluntary movement.

5.2 Introduction

To perform a voluntary movement requires not only that the brain is functioning optimally to guide its execution, but that the brain is also properly *pre*set in order for the correct movement to be initiated. In Parkinson's disease, the traditional focus has been on understanding the well-known deficits in motor execution and tremor (Betchen and Kaplitt, 2003), but recent evidence has pointed to the importance in understanding deficits in executive control that often surface in Parkinson's disease (PD) (Leh et al., 2010). We now provide direct evidence that these *cognitive* deficits may be more important to the impaired control of voluntary movements in PD than previously thought. With the *antisaccade task,* we utilize a well-characterized measure of the ability for people to override an automatic response with an alternative, voluntary response that is novel to participants and more difficult to perform.

Participants are required to refrain from initiating an automatic eye-movement in the direction of an abruptly appearing visual stimulus (a prosaccade), and to instead initiate a saccade guided voluntarily in the opposite direction (Munoz and Everling, 2004). To do this successfully, a network of cortical and sub-cortical brain regions, including dorsolateral prefrontal cortex (DLPFC) (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991), frontal, parietal and supplementary eye-fields (FEF, PEF and SEF) (Connolly et al., 2002; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Ford et al., 2005; Brown et al., 2007), and the basal ganglia (BG)

(Ford and Everling, 2009; Watanabe and Munoz, 2009) is required to come online prior to the appearance of the visual stimulus in order that the motor system is preset towards the appropriate action.

We (Chan et al., 2005; Cameron et al., 2010) and others (Briand et al., 1999; Amador et al., 2006; Hood et al., 2007; Rivaud-Pechoux et al., 2007) have shown that PD patients display deficits in the antisaccade task, such that they are slower to initiate the response, and also execute the prosaccade in error on antisaccade trials, with greater frequency. Recent evidence has also shown that hypo-activation measured with functional Magnetic Resonance Imaging (fMRI) occurs throughout the brain during antisaccade performance in PD (Rieger et al., 2008), following general observation of hypo-activation in the brains of PD patients during complex tasks demanding attentional control (Dagher and Nagano-Saito, 2007). In the present study we provide the first evidence that hypo-activation in fMRI occurs more prominently in motor areas during the presetting stage, rather than during the execution of the actual response. We suggest that this corresponds to failure to establish and maintain the appropriate '*task set*', providing for a correlation to the behavioral deficits observed in PD when performing voluntary actions.

5.3 Results

PD patients, on and off (>18h from the previous dose) their regular dopaminergic medication, and age-matched control subjects participated a rapid event-related fMRI design with pro and anti *saccade* trials interleaved with pro and anti *instruction only* ('prep') trials (Fig. 5.1A). This design allowed us to examine activation related to establishing an antisaccade task set, separately from actually executing the antisaccade response. It also and allowed us to use a deconvolution-based fMRI analysis (see 5.5 Methods), in which correctly performed anti trials were compared to correctly performed pro trials, as well as to erroneous antisaccade trials (executed a prosaccade), to examine the differential patterns in brain activation across the groups for each of these response types.

Fig 5.1

5.3.1 Behavior

Shown in Fig. 5.1C-F, the behavioral patterns on anti and prosaccade trials observed in previous studies of PD were replicated (Briand et al., 1999; Chan et al., 2005; Amador et al., 2006; Hood et al., 2007; Cameron et al., 2010). Specifically, PD patients executed a higher proportion of direction errors on antisaccade trials, such that they were more biased to executing the automatic prosaccade response instead (as exemplified in the sample eye-traces in Fig. 5.1B). Correspondingly, this behavioral bias resulted in superior prosaccade performance in terms of percentage direction errors in comparison to control subjects (Fig. 5.1C). PD patients also appeared to be faster at initiating a prosaccade (reduced saccade reaction time (SRT)), but slower at initiating an antisaccade (Figs. 5.1D) though neither comparison reached significance across the groups ($P > 0.23$). PD patients also displayed a higher proportion of pro 'express saccades' than the controls (Fig. 5.1E), which are the very short-latency population of automatic saccades, with latencies typically described between 90 and 140 ms (Fischer et al., 1993; Dorris et al., 1997). Interestingly, it can be seen in the SRT distributions in Fig. 5.2A that PD patients off medication clearly display a bimodal (if not trimodal) peak of short-latency as well as long-latency prosaccades (including those labeled as being in the typical express range), and the proportion of these short-latency prosaccades is reduced in the on meds group, and further in the controls. Fig. 5.2B highlights the prosaccade bias in PD patients (e.g., slower antisaccade SRT, but faster prosaccade SRT for both correct prosaccades and prosaccades executed in error on antisaccade trials). Finally, PD patients were also more variable in responding on prosaccade trials (Fig. 5.1F), which has been reported previously in our laboratory (Chan et al., 2005). Overall, the behavior is consistent with previous studies, and most importantly, highlights the fact that PD patients are biased towards the prosaccade behavior, and thus, against the antisaccade behavior. Note also that medication did not result in significant improvements in performance, though it did make the behavior of PD patients more control-like.

5.3.2 fMRI

From the behavior, it is evident that there should be correlates in brain activation related to the antisaccade deficits in PD. Because fMRI responses are best understood to reflect a greater 'recruitment' of neural processes in one condition compared to another, we based the

Fig 5.2

analyses on comparing correctly performed pro trials to anti trials (see 5.5 Methods), with the hypothesis that activation should be greater in areas critical to the implementing the voluntary components of antisaccade generation (automatic response suppression, attention redirection, saccade vector inversion), which are not required in prosaccades (Munoz and Everling, 2004). We also compared correctly performed antisaccade trials to erroneously performed antisaccade trials, to confirm that areas deemed critical to antisaccade processing would show reduced activation when an antisaccade was not performed correctly. By these methods, fMRI correlates of antisaccade deficits in PD were revealed when these *within*-group contrasts were compared across the groups, as described in the following paragraphs.

An initial contrast of prosaccade trials subtracted from antisaccade trials was made for all three groups (Fig. 5.3A) in order to identify oculomotor regions previously shown with fMRI to display greater activation for antisaccades compared to prosaccades (DLPFC, FEF, SEF, PEF and caudate nucleus (CN)) (Sweeney et al., 1996; Luna et al., 1998; Connolly et al., 2002; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Connolly et al., 2005; Ford et al., 2005; Brown et al., 2006). (Supplementary Fig. 5.S1 shows activation maps for pro and antisaccade trials in the absence of a contrast with one another). Because we were using a deconvolution method, the contrasts illustrated were created by utilizing the three time points that encompassed the region of peak activation determined by inspection, and not by convolution with a canonical hemodynamic response function (see 5.5 Methods). These three time points corresponded to the 5^{th}, 6^{th}, and 7^{th} time points from trial onset, occurring at approximately, 7.7, 9.2 and 10.8 s, respectively (exemplified in Fig. 5.3B). This antisaccade minus prosaccade contrast revealed brain regions displaying significantly greater activation for antisaccades, including our five oculomotor regions of interest (Fig. 5.3A, Talairach locations of peak activations given in Supplementary Table 5.S1). From these regions of interests (ROIs), we subsequently extracted the magnitudes of BOLD activations (as beta-weight parameter estimates from the general linear model) from two critical sub-processes of pro and antisaccade generation: *task set establishment* and *response execution*. Because these individual processes are difficult to separate with BOLD

Fig 5.3

fMRI in whole saccade trials, the instruction only 'prep' trials provided us with the ability to segregate these overlapping sub-processes as best as possible, as prep trials contain only the task set establishment component. We expected the prep trials to correspond to the same preparatory state that would also be present in the first part of whole saccade trials, since the subjects did not know whether a given trial would be a saccade or prep trial upon trial onset (see Fig. 5.1A). Therefore, prep trial activation levels in ROIs defined by whole saccade trial contrasts should nevertheless reveal the same underlying component of task set.

ROI analysis

First, the relative magnitudes of activation related to pro and antisaccade task set establishment were calculated by running a second random effects analysis of the peak locations within the DLPFC, SEF, FEF, PEF and CN ROIs, for pro prep and anti prep trials. The results are displayed in Fig. 5.4A. One-way ANOVAs revealed that significant group differences resulted for pro prep in SEF, $F(2,36) = 8.28$, $P < 0.01$, and CN, $F(2,36) = 5.75$, $P < 0.01$ and marginally/significant differences resulted for anti prep in SEF, $F(2,36) = 2.64$, $P = 0.09$, PEF, $F(2,36) = 3.19$, $P = 0.05$ and CN, $F(2,36) = 7.27$, $P < 0.01$. Subsequently, independent *t*-tests were performed to compare one group to another (uncorrected; shown in Fig. 5.4). Generally, it can be seen that the two frontal motor areas involved in antisaccade programming, SEF and FEF (Hanes and Schall, 1996; Schlag-Rey et al., 1997; Everling and Munoz, 2000), had greater activation for both pro and anti preparation in the controls, with the magnitude being greatest for anti preparation. A similar trend was shown in the PEF and CN.

A subsequent analysis explored the activation patterns related only to the response execution component of a pro or antisaccade (Fig. 5.4B). To do this, the same ROIs shown in Fig. 5.3A were used as in Fig. 5.4A, however, for this second random effects analysis, prep trials were first subtracted from saccade trials, prior to pro being subtracted from anti, thereby isolating the components related to target onset and saccade execution (henceforth referred to as 'execution' component). Specifically, the values were derived from isolating values around the peak, shifted forward by one time point compared with the prep trials (see 5.5 Methods). No statistical differences between the group responses were observed, $F(2,36) = 2.50$, $P > 0.09$,

Fig 5.4

other than between PD patients off- and on-meds in PEF for prosaccades ($P < 0.05$, *t*-test, Fig. 5.4B).

'Prep' trial and 'execution' period contrasts

To further investigate the differences between activation related to preparation and activation related to execution, contrast maps for these components were produced separately. Pro prep trials were subtracted directly from anti prep trials (Fig. 5.5A, Talairach locations of peak activations given in Supplementary Table 5.S2), and pro execution components were subtracted directly from the anti execution components (Fig. 5.5B, Talairach locations of peak activations given in Supplementary Table 5.S3). In all cases only correctly performed trials were used. While this analysis is similar to the ROI analysis in Fig. 5.4, the importance of the direct contrast is that it allows us to directly identify brain regions, at the population level, showing greater activation for anti task set compared to pro task set, as the ROIs identified from the whole saccade trial contrasts (Fig. 5.3) contain also the component of saccade execution.

The results show that there was greater activation for anti preparation throughout in the frontal ROIs (FEF, SEF, DLPFC) in controls and in PD on-meds (Fig. 5.5A), but not in PD off-meds. (For PD patients off meds, greater anti preparation activation in the oculomotor ROI's was only seen in the CN and left PEF). Supplementary Table 5.S2 lists all brain regions that showed greater activation for anti or pro preparation that may not have been illustrated in Fig. 5.5A.

Similar to the ROI analysis in Fig. 5.4B, when examining the execution components, no significant increases in anti compared to pro resulted in any of the ROIs, other than in a putative left DLPFC region in the PD off-meds group, and in the left FEF in controls (Fig. 5.5B, Supplementary Table 5.S3). Thus, the significant differences across the groups between pro and antisaccade processes at the contrast level were more apparent during preparation.

BOLD response curves on correct and error trials

To determine if greater preparatory activation correlates to performance, subsequent analysis was conducted to compare the BOLD response curves in the oculomotor ROIs on correct and erroneous antisaccade trials, to establish first, if there would be differences in BOLD activation, and second, if the differences arose during the time points corresponding more to the

Fig 5.5

preparatory rather than to the execution component. From the saccade trial contrast maps in Fig. 5.3A, BOLD signal curves were extracted from a second random effects analysis that included the pro and antisaccade error trials. Shown in Fig. 5.6, PD patients off-meds did not display differences in the onset of the rise to peak activation levels, or in the magnitude of peak activation levels, between correct and erroneous anti-saccade trials, other than in the putative right DLPFC. In contrast, controls and PD patients on-meds showed enhanced activation in SEF and FEF for correct antisaccade trials, and this effect reached the greatest noticeable difference in the FEF in controls. Note that for both the SEF and FEF in the controls and PD on-meds, peak differences occurred most prominently at the 5^{th} time point (7.7 s) from trial onset, suggesting that the rise to peak began *prior* to the peak of the 'prep' period in Figs. 5.4A and 5.5A. Therefore, repeated measures ANOVAs with the factors of 'Time Point' (4^{th}, 5^{th}, 6^{th}) and 'Performance' (correct and error) were conducted to assess the statistical significance of this enhanced activation. The results revealed that in control subjects only, FEF activation for correct antisaccades was significantly greater across these three time points compared to erroneous antisaccades, $F(1,12) = 4.98$, $P < 0.05$ (Fig. 5.6). No other tests reached significance, $F(1,12) < 2.68$, $P > 0.1$, other than in the right DLPFC in PD off-meds, $F(1,12) = 4.89$, $P < 0.05$. Supplementary Fig. 5.S2 shows similar overall results derived from the ROIs identified by the antisaccade activation maps (Supplementary Fig. 5.S1), in which an early rise in activation on correct antisaccade trials was observed most prominently in the FEF in controls.

5.4 Discussion

Here, we propose that reduced brain activation in oculomotor regions of the frontal cortex corresponds to ineffective pre-setting of networks important to voluntary movement initiation in Parkinson's disease (PD). Specifically, reduced preparatory activation for antisaccades in PD patients off their medication resulted most prominently in the motor structures sub-serving antisaccade generation (FEF, SEF), and also in DLPFC and PEF (Fig. 5.4A, Fig. 5.5A). Secondly, a reduced enhancement of an early rise in preparatory activation in FEF on correct antisaccade trials compared to incorrect antisaccade trials was also observed in PD compared to the controls (Fig. 5.6, Supplementary Fig 5.S2), providing for a correlate of impaired performance.

Fig 5.6

From these findings, we propose that PD patients were less *efficient* at configuring neural networks into the appropriate, voluntary task set. Our findings, as well as our proposals, are consistent with a general view that decreased cortical functioning occurs in PD, as the result of increased inhibitory output from the BG (Mink, 1996; Dagher and Nagano-Saito, 2007), which interferes with the *dis*-inhibitory mechanisms of the BG's direct pathway (Nambu, 2005).

There were two main observations from our results that permit us to make the inference that PD patients have impaired dis-inhibitory mechanisms. First, throughout the oculomotor network, controls typically showed the highest levels of preparatory activation on both pro and anti trials (Fig. 5.4A), suggesting that they were better able to utilize instruction-related information to prepare for an appropriate future behavior. The motor, premotor (FEF and SEF) and prefrontal (DLPFC) cortices are all influenced by BG output (Alexander et al., 1986), suggesting that failed dis-inhibitory signals might result in impaired frontal lobe function. Second, in controls the measures of preparatory activation for correctly executed antisaccades were greater in magnitude compared to those for erroneous antisaccades (in FEF), and anti prep trial activation was greater, in general, than pro prep trial activation in controls and PD patients on medication, suggesting that controls, overall, were better able to *utilize* the instruction-related information to configure the oculomotor network to the appropriate task set. It has been shown consistently that antisaccade activation in these five ROIs is greater than prosaccade activation (Sweeney et al., 1996; Luna et al., 1998; Curtis and D'Esposito, 2003; DeSouza et al., 2003; Connolly et al., 2005; Ford et al., 2005; Brown et al., 2006; Brown et al., 2007; Curtis and Connolly, 2008), and this greater activation is presumed to reflect the additional neural processes necessary for generating an antisaccade compared to generating a prosaccade (Munoz and Everling, 2004). Thus, a reduction in cortical excitation of frontal areas important in establishing a voluntary antisaccade task set should lead to impaired performance, as observed.

To understand what antisaccade task set may be at the neural level, our knowledge of the oculomotor control network from monkey neurophysiology provides us with a sensible interpretation, based on how neurons in a motor region (FEF) are configured to appropriate levels of activity prior to the generation of a desired behavior. FEF has a specialized role in generating

voluntary saccade commands (Hanes and Schall, 1996), and it also contains mechanisms to suppress automatic saccades, via enhanced activity in a distinct population of cells entitled 'fixation neurons', along with reduced activity in saccade neurons, during the antisaccade instruction period (Everling and Munoz, 2000; Munoz and Everling, 2004). Therefore, execution of a successful antisaccade requires that firing rates of fixation and saccade neurons in FEF are configured to appropriate levels of activity, and as such, represents antisaccade 'task set'. Note that while similar preparatory activation patterns to controls were observed in anti and pro prep trials in PD patients *on* medication, their behavioral performance (Fig. 5.1) was not improved to the level of the control subjects, and, correspondingly, they did not show the same magnitudes of antisaccade preparatory processes in FEF (Fig. 5.4A, Fig. 5.6, Supplementary Fig. 5.S2), suggesting that task set was not as effectively configured. How this task set is configured is not clear, however our understanding of the nature of the BOLD signal does follow the idea that some signal that is inputted to FEF that results in enhanced fixation neuron activity, and reduced saccade neuron activity, might correspondingly result in increased BOLD activation.

Specifically, it has been proposed that the BOLD signal correlates with the synaptic activity (input), as well as (and perhaps more than), the spiking activity (output) of a region (Logothetis et al., 2001; Logothetis and Wandell, 2004), and from this, one could predict that the proper setting of the states of FEF saccade and fixation neurons could be the result of incoming neural signals, possibly from DLPFC or via BG-mediated dis-inhibition (Munoz and Everling, 2004; Hikosaka and Isoda, 2010). Thus, reduced BOLD activation in FEF could correspond with reduced input signals critical to establishing the correct preparatory levels of saccade and fixation neurons. Along with FEF, SEF has also been shown to be important in antisaccade programming, in particular, as a region mediating voluntary saccade generation when alternative or conflicting responses are possible (Schlag-Rey et al., 1997; Coe et al., 2002; Parton et al., 2007). Moreover, SEF neurons show enhanced firing rates prior to antisaccade generation compared to prosaccade generation (Schlag-Rey et al., 1997), suggesting that inappropriate presetting of SEF in PD may also contribute to impaired antisaccade behavior.

The DLPFC, PEF and CN showed activation patterns that were more difficult to interpret based on BG models and our current knowledge from neurophysiology. Nevertheless, there are sensible explanations that can be derived from previous studies of PD behavior and our fMRI results. First, enhanced DLPFC activation for anti prep trials compared to pro prep trials was not observed in PD off-meds (Fig. 5.5A), suggesting that the *resolution* of the instruction into the establishment of an appropriate task set was less efficient in PD off their medication. While the motor, premotor (FEF and SEF) and prefrontal (DLPFC) cortices are all influenced by BG output (Alexander et al., 1986), the latter (DLPFC) is associated with general executive control mechanisms (Miller and Cohen, 2001; Gazzaley and D'Esposito, 2007). The DLPFC is believed to be a crucial brain region involved in establishing an antisaccade task set, because patients with DLPFC lesions make more reflexive direction errors on antisaccade trials (Guitton et al., 1985), demonstrating that they are less capable of suppressing the more pre-potent automatic prosaccade to a visual stimulus. Patients with PD also display a variety of deficits in executive control, which mirror those of prefrontal cortical dysfunction (Monchi et al., 2004; Owen, 2004; Williams-Gray et al., 2006).

Second, PEF showed greater activation in general in controls than in PD patients, suggesting the possibility that it too may be related to antisaccade performance in PD, or at least to changes in processing in the oculomotor network. Enhanced PEF BOLD activation on antisaccades has been observed previously, and is thought to reflect modulation of attention in fronto-parietal networks (Desimone and Duncan, 1995; Miller and Cohen, 2001; Curtis et al., 2005; Bisley and Goldberg, 2010), such that this ‘top-down’ modulation might be required to generate a saccade to the opposite side of space from the target stimulus. Tasks that require top-down attentional deployment typically result in decreased cortical activation in PD (Dagher and Nagano-Saito, 2007).

Finally, one of the most interesting findings in this study was that PD off-meds showed significantly greater activation for anti prep compared to pro prep in the CN (Fig. 5.5A). If the BOLD signal does reflect a significant component of synaptic processes (input), this strongly suggests that the depleted dopamine levels in PD off-meds do not result in decreased CN BOLD

activation. It is possible, however, that the CN is being activated in PD off-meds by converging inputs from many cortical regions, perhaps as compensation for a known difficult task. What appears to be important is whether the BG can operate functionally at the output level, which as explained previously, is impaired in PD.

Following this, what still remains to be understood is whether the looped architecture of cortical-BG networks can have differential activation in PD in, for example, in the prefrontal loop including DLPFC, compared to the oculomotor loop, including FEF (Alexander et al., 1986). Degeneration in PD typically occurs in the motor-loop first (Cools, 2006). Thus, networks involving DLPFC that are normally involved in setting up the frontal cortical eye fields via assistance from BG output (Hikosaka and Isoda, 2010), could still show increased DLPFC and CN activation in PD patients off medication. However, if the appropriate preparatory state of neurons in motor regions (FEF and SEF) is what is critical, this could explain why PD patients can show greater antisaccade activation in CN (PD off-meds) or DLPFC (PD on-meds) related to compensatory strategies, but that were not effective at translating into appropriate preparatory setting of FEF or SEF neurons, perhaps because of the relatively greater pathology in the (oculo)motor loop. To make this conclusion, however, more work is needed to understand the influence of DA medication on PFC and striatal function, as it has been shown that exogenous DA can exert beneficial, as well as detrimental effects on behavior based on its relation to intrinsic levels in these areas (Cools, 2006; Cools et al., 2010). Nevertheless, it can be concluded in this study that the degree to which *motor* areas can be properly configured prior to response initiation dictates subsequent performance accuracy, and might be the major reason why PD patients display deficits in the voluntary control over behavior.

5.5 Methods

Twenty-eight patients with mild to moderate PD were recruited from the movement disorders clinic at the Kingston General Hospital by co-author GP. Patients underwent an evaluation of motor function (Unified Parkinson's Disease Rating Scale), cognitive capacity (Mini-Mental State Examination) and depression (Beck Depression Inventory). Of this, 13 patients were used in the current study based on the following exclusion criteria: patients could not score less

than 26/30 on the MMSE (0 patients excluded), could not score higher than 15 on the BDI (1 patient excluded), were required to participate in two sessions of the experiment (on and off their regular dopaminergic medication: 5 patients excluded), were able to successfully perform the task and provide online eye-tracking data (5 patients excluded), did not posses any visual abnormalities (e.g., macular degeneration: 2 patients excluded) or structural abnormalities other than diffuse white matter bodies not affecting oculomotor regions (1 patient excluded), and did not move more than 2 mm from starting position in the fMRI scans (1 patient excluded). In the end, the 13 remaining patients consisted of 7 males, with a mean age of 64.7 years, range of 52-74, and a mean maximum movement in any direction of 1.03 mm (off-meds), and 1.04 mm (on-meds) in the fMRI scans. Each patient was age-matched to a control subject that did not possess PD or any other neurological/psychiatric disorders as assessed by experimenter questioning and the use of the MMSE or MoCA exam, and fit the criteria for exclusion as described with the patients. The control subjects (13) consisted of 7 males, with a mean age of 64.8 years, range of 51-74, and a mean maximum movement in any direction of 0.96 mm in the functional runs.

5.5.1 Experimental design

A rapid event-related design was employed, allowing for the presentation of 64 trials in a given run (totaling approximately 5 min), each no longer than 4.5 s in length (Fig. 5.1A). Each run contained a pseudorandom presentation of 16 ‘prosaccade’ trials, 16 ‘antisaccade’ trials, 8 pro ‘prep’ trials (preparation instruction only), 8 anti ‘prep’ trials, and 16 ‘fixation’ only trials. Prosaccade and antisaccade trials began with 1000 ms of fixation on a neutral fixation stimulus at center, subtending approximately 2 degrees of visual angle. The neutral fixation stimulus was a hollow gold coin (Fig. 5.1A). The pro or anti instruction was then presented for 1300 ms, and was either a bluish/green stimulus (a turtle), or a reddish/orange stimulus (a lobster), of the same size. (These stimuli were chosen based on the conduction of this identical experiment for comparison across other neurological disorders, such as Attention Deficit Hyperactivity Disorder, which included child-age participants). A gap of 200 ms in the central stimulus subsequently occurred prior to the presentation of the peripheral, ‘target’ stimulus (another gold coin) for 100 ms at 6 or 7 degrees to the left or right of fixation. The gap was employed to push the subjects towards

automatic responding, and to increase the occurrence of short latency, highly automatic ('express') prosaccades in both the pro and antisaccade task (Dorris et al., 1997; Fischer and Weber, 1997). Following the presentation of the target, 1400 ms of darkness occurred, in which subjects were required to hold their gaze at the location of the target on a prosaccade trial, or at its mirror location on an antisaccade trial. If they executed the incorrect response (a direction error), they were instructed to correct themselves. A period of 500 ms of neutral fixation was then included to return the subjects' fixation to center. (Subjects were encouraged to wait for this stimulus before returning their gaze, but were not required for the purpose of analysis). 'Prep' trials were identical, however did not include the presentation of the target, and thus contained a period of 1700 ms of darkness (200 + 100 + 1400) following the pro or anti instruction, and subjects were required to remain fixated at center. Under this design, saccade and prep trials were 4500 ms (3 TRs, described below) in length. Trials containing only the neutral fixation point were also included, such that 8 of these trials were 3 TRs in length, 4 were 2 TRs and 4 were 1 TR in length. The inclusion of prep trials, as well as fixation trials of varying length were necessary for the deconvolution analysis of the rapid event related design, explained in the following paragraphs (Dale, 1999; Ollinger et al., 2001). All runs began with an additional period of fixation for 3 s (to account for the BOLD signal to reach stead-state longitudinal magnetization), and ended with a period of fixation for 16.5 s, to allow for the return of the hemodynamic response signal to the baseline level of activation. Each subject performed between 6-8 runs.

Functional images during the experimental runs were acquired with 24 horizontal slices (3.3 mm thick) covering the brain from the top and including the frontal/prefrontal, parietal, visual areas, and BG to the level of the ventral striatum. Each functional volume consists of a T2*-weighted echo-planar image (EPI) sensitive to BOLD contrast (Ogawa et al., 1990; Kwong et al., 1992) acquired in an interleaved fashion (repetition time, TR =1500 ms; echo time, TE = 30 ms; flip angle, FA = 72º, field-of-view, FOV = 211 x 211 mm, matrix size 64 x 64, 3.3 mm isovoxel resolution, 185 volumes). High-resolution MP-RAGE 3D T1-weighted scans were acquired for anatomical localization (TE = 2.2 ms, TR = 1760 ms, FA = 9º; 176 slices, 1 mm thick). Each run was 277.5 s and was composed of 64 trials consisting of the trial types described above.

5.5.2 Data analysis

Behavioral data were analyzed with custom MATLAB v7.04 programs (The MathWorks Inc., Natick, MA) and imaging data was analyzed using the Brain Voyager QX v2.1 software package (Brain Innovation, Maastricht, The Netherlands). Correct trials were separated from incorrect trials, which consisted of: direction errors on saccade trials, trials that included failure to initiate a saccade, uncorrected correct trials, multiple saccades during any trial, and breaks in fixation during prep trials and neutral fixation periods. Pre-processing of imaging data was performed, utilizing rigid-body 3D motion correction to the first volume in each run, slice scan-time correction with a cubic-spline interpolation, temporal filtering (high-pass filter with cut-off of 3 cycles/run and linear trend removal), and 3D spatial smoothing with a 4 mm FWHM Gaussian kernel. Functional data were then superimposed on the 3D anatomical data transformed into Talairach coordinate space, and generated by an average of all subjects Talairached anatomical scans. With a rapid event-related fMRI design, time-locked hemodynamic responses to behavioral evoking events overlap significantly (Dale, 1999; Ollinger et al., 2001). Therefore, a deconvolution analysis was utilized such that the hemodynamic response was modeled as separate stick predictors for the closest approximation of 20s/TR, corresponding to a 13-point time series with a temporal resolution of approximately 1.5 s that is locked to the start of each trial (actual times displayed in seconds in Figs. 5.2B, 5.6 and Supplementary Fig. 5.S2). This process is used so as to model the hemodynamic response for each event and cover the temporal extent of a typical hemodynamic response, of approximately 20s. The 'events' of interests pertained to following trial types: correct anti prep, correct pro prep, correct anti saccade, and correct pro saccade. Correctly performed fixation trials were not modeled explicitly in the design matrix, so as to provide a baseline measure (Ollinger et al., 2001). All other trials (e.g., erroneously executed saccade trials, breaks in fixation, loss of eye-tracking data, uncorrected correct trial) were pooled together and incorporated into the design matrix as a separate event of no interest, such that they would not contaminate the estimation of the BOLD signal for neighboring correctly performed trials (Brown et al., 2007). A random-effects multi-subject general linear model (GLM) with a Z-normalization was run using the 5^{th} to 7^{th} time points (at 7.7, 9.3 and 10.8 s, Fig. 5.3B) from the onset of a saccade trial, to account for a reliable measure surrounding peak activation from trial

onset as determined by preliminary examination, in order to generate group-level statistical maps at a threshold of $P < 0.01$ (T value = 3.06), corrected for multiple comparisons across the voxel population at $P < 0.01$ (8 contiguous voxels). Region of interests (ROI) analyses were conducted using a random-effects GLM in order to extract Beta-weight values (parameter estimate from the GLM) for subsequent post-hoc analyses of BOLD signal change (Fig. 5.4). ROIs were selected as the 125 contiguous voxels (5 X 5 X 5) within a cubic cluster centered around the point of peak activation in the DLPFC, FEF, SEF, PEF and CN as defined by anatomical landmarks, and known locations in Talairach space. For the analysis of preparatory effects in both the ROI analysis (Fig. 5.4A) and the prep only contrast maps (Fig. 5.5A), the mean beta values from the 5^{th} and 6^{th} time points relative to the onset of saccade or prep trials was used to account for a measure of the peak activation. For the analysis of processes from the saccade execution period, the time points were shifted by 1.5 s to include only the 6^{th} and 7^{th} time points (Figs. 5.4B, 5.5B), as the onset of the peripheral target occurs 1.5 s (one time point) after the appearance of the instruction (Brown et al., 2007). For the comparison of BOLD signal time courses on correct and erroneously executed antisaccade trials (Fig. 5.6, Supplementary Fig. 5.S2), both pro and anti direction errors were incorporated as distinct events into the GLM (i.e., were not placed in events of no interest).

Chapter 6: General Discussion

To summarize the main findings, I show throughout this thesis that environmental stimuli that evoke a particular behavior automatically can lead to detrimental effects when subjects must perform an alternative behavior. Starting with Chapter 2, I explored the ability of subjects to plan for a given behavior, and then rapidly change it upon the switch of an instruction. We proposed in this Chapter that the *switch costs* (increased error rates and response times) that resulted came from the switching of a response program, rather than from the switching of task set signals alone. However, instruction probability modulated switch costs (Figs. 2.5, 2.6), suggesting that 'top-down' signals are able to establish some degree of a voluntary task set appropriate for a given environmental situation; however the presence of explicit external information affects behavior in such a way that responses can be evoked automatically, and cannot always be overridden by top-down control. While we did not explore the difference between pro and antisaccades in depth in Chapter 2, it can be seen in Figs. 2.3, 2.6 and 2.8 that the general asymmetry in response automaticity between pro and antisaccades results in greater antisaccade error rates overall, which also demonstrates the influences that more automatic behaviors can have on voluntary behaviors. This theme of response automaticity is translated throughout the remaining chapters, such that Chapter 3 shows that the basal ganglia (BG) are important for overriding the *biases* towards more automatic behaviors, in particular that the input of the BG (the CN) carries fMRI signals related to the generation of more difficult behaviour. Importantly, so does the FEF, a motor region affected by BG output. Following this, Chapters 4 and 5 show that pathology of the BG results, correspondingly, in an enhanced bias towards more automatic behavior, and further suggest that the signals related to overcoming a behavioral bias are likely those that are common to executive control signals mediated by networks involving the prefrontal cortex (PFC) and basal ganglia (BG). The PFC and motor regions important for voluntary behavior are known to be affected by BG output (Alexander et al., 1986; Mink, 1996), and with BOLD fMRI, enhanced activation in these areas appears to correspond to task set signals carried through to pre-motor and motor regions. The functional significance of these results in the context of the role of the BG in executive control is explained in this Discussion section.

6.1: Basal Ganglia Architecture and Executive Control

A critical finding that would best help our conclusions in these chapters would be neuronal evidence of anti and pro task set signals in BG circuits. Indeed, this evidence has been very recently discovered in our laboratory, such that activity in CN neurons is shown to be greater prior to target stimulus presentation on antisaccade trials than on prosaccade trials (Watanabe and Munoz, 2010). This enhancement in CN neural activity is driven only by the central fixation instruction, and is found only in the CN neurons that show saccade related activity for volitional (anti)saccades (Watanabe and Munoz, 2009) thus providing the first physiological evidence of antisaccade task set signals in the input nucleus of the BG. A distinctly different pattern of activity was seen in the CN neurons related to prosaccade programming, and a third population of neurons was identified that appeared to carry signals related to response inhibition. Based on this, it was suggested that the different populations of CN neurons may carry signals through the direct, and indirect pathways of the BG, related to the dis-inhibition of the voluntary antisaccade, while at the same time, enabling the suppression of the automatic saccade commands (Watanabe and Munoz, 2009; Watanabe and Munoz, 2010). While this hypothesis provides for a means for the BG *itself* to resolve conflicting commands and produce a desired behavior, the looped architecture of the BG and cortex also provides for an enhancement and suppression of signals in cortex that might be the source of executive control signals regulating the generation of behavior. I favor this explanation based on the evidence from Chapters 3 and 5 (i.e., that cortical regions showed enhanced activation related to the more difficult behavior), and due to the fact that the subjects in the current experiments were naïve humans. This is important, because it suggests a possible interpretation of BG signals related to mechanisms following the initial stages of *learning*, as will be discussed in Section 6.2. Nevertheless, physiological evidence of task set signals in the BG is important for building conclusions about a role of the BG in executive control.

The first important, but somewhat puzzling, piece of evidence for cortical executive signals modulated by BG output comes from the observation in Chapter 5 that PD patients off medication showed enhanced preparatory activation for antisaccades in the CN that was not observed to the same extent in PD patients on medication, or in the control participants. These

latter groups, instead, showed greater task set activation in cortical regions affected by BG output (e.g., Fig. 5.5A). It is possible that fMRI may be too insensitive to detect changes in pre-target activity in a sub-population of CN neurons on anti compared to pro trials, as shown by Watanabe and colleagues, 2010. This could be because signals measured with fMRI are more closely correlated with signals incoming to a brain region (which would not be identified with single cell recordings of CN neurons projecting out of that region) (Logothetis et al., 2001; Logothetis and Wandell, 2004), or that elevated pre-target activity in distinct CN neurons coupled to a particular behavior occurs after a long period of training, as shown in other monkey neurophysiological experiments (Graybiel, 1998). Both these explanations are sensible, and are addressed in Section 6.2. However, one alternative explanation that is perhaps the most unifying across this thesis, is that enhanced fMRI signals in the CN only appear when there is a significantly large requirement for top-down voluntary control.

This proposal reconciles the observations from Chapter 5 that enhanced CN activation for anti preparation compared to pro only resulted in the PD off-meds group (the group for which establishing an antisaccade might be the most difficult), but did not arise on the less demanding non-switch antisaccade trials compared to pro in Chapter 3. Note however that enhanced CN activation did arise for pro2anti trials in Chapter 3, and which while not explored extensively, also showed a greater enhancement of pro2anti FEF activation than non-switch anti FEF activation. Therefore, it appears that a correlate of the degree of executive control required can be observed in fronto-striatal circuits mediating antisaccade generation. In the case of PD, these findings also suggest that incoming executive signals to the BG may result in increased CN activation, however, if the BG provides ineffectual functional output to cortical networks, increased activation in cortex may not be observed, and may predict deficits in voluntary behavioral control.

6.1.1 Evidence from Previous Studies

The proposal that the BG influences cortical signals to produce voluntary behavior efficiently is in line with our knowledge of BG anatomy and physiology. First, the parallel looped architecture of cortico-BG channels provides researchers studying BG anatomy with the ability to subdivide striatal regions into their relationship to *channels* sub-serving distinct functions, such as

limbic, executive, motor and oculomotor (Alexander et al., 1986; Cui et al., 2003). However, the parallel loops are not completely independent, as there is convergence of cortical signals in the striatum and STN (Mink, 1996; Graybiel, 1998; Gerardin et al., 2003) as well as in the SNpc, the source of dopaminergic (DA) inputs that modulate striatal processing. The majority of inputs to the SNpc originate from the striatum, and return to striatal locations in a looped architecture as well (Haber and Knutson, 2010). However, *these* loops are also not independent, and it has been identified that a directional axis exists within the striatal-SNpc loops, such that outputs to the SNpc from ventromedial prefrontal cortex and orbitofrontal (limbic) striatal regions influence those of the DLPFC (executive) striatal regions, of which a subset of SNpc outputs project to motor striatal regions (Haber and Knutson, 2010). Thus, the BG are structured in such a way that 'higher' limbic and executive regions can influence 'lower' motor regions, which would be important if BG has a role in the regulation of voluntary motor behavior.

Consideration of this anatomical evidence of a hierarchy of BG channels provides reconciliation of many theories revolving around the roles of the BG in executive control, learning as well as response initiation. For instance, it has been suggested by some groups that deficits in PD relate to difficulties in performing 'automatic' behavior (Wu and Hallett, 2005; Doyon, 2008). How can it be that PD patients show deficits in 'automatic*'* behavior, when the present thesis proposes they are not impaired in initiating the more *automatic* prosaccade? If one considers that during the learning of a voluntary, difficult task, the BG are modulating cortical signals related to a given behavior (via dis-inhibition in positive feedback loops through the thalamus), an eventual outcome over *learning* how to behave in a given environmental context would be to execute a behavior in a more automatic fashion (Doyon, 2008). A role of the BG in both recurrent excitation of given inputs, say in the executive channels, but also the transfer of excitation to the motor channels via divergence from the looped architecture as described in the previous paragraph, is a sensible explanation, and BG dysfunction in dis-inhibition in PD would predict difficulty in achieving this (Fig. 1.2B). Following this, it may very well be that the BG itself can reconcile conflicting signals between pro and antisaccade responses in highly trained subjects (Watanabe and Munoz, 2009; Watanabe and Munoz, 2010).

Direct physiological evidence for a rostral-to-caudal axis in voluntary-to-automatic behavior from the human and animal functional studies are in-line with the anatomy described above. In PET studies, it has been shown that during the learning of a pattern of novel movement sequences, prefrontal regions typically associated with executive control (e.g., ACC and DLPFC) were activated along with the CN, whereas posterior striatal regions and motor cortical regions were not (Jueptner et al., 1997a; Jueptner et al., 1997b). Conversely, the posterior putamen along with motor cortex was more active when subjects made repetitive, pre-learned movements, and the CN was not. (Note that unlike in the oculomotor system, the putamen, and not the CN, is the motor input nucleus (Alexander et al., 1986)). In another study that involved lesions to only a specific striatal region (dorsolateral or dorsomedial), rats, who had previously responded to a stimulus regardless of reward value (indicating that the response to a given stimulus had become automatic) became sensitive to reward value, decreasing their likelihood to respond when the reward lost value (Yin et al., 2004). Hence, the automatic nature of responding had been lost due to a lesion to the dorsolateral striatum. However, this did not happen if the lesion was given to the dorsomedial striatum; in this case, the rats responded as if the stimulus evoked an automatic response. The dorsomedial and dorsolateral striatum roughly map on to anatomical regions sub-serving more cognitive and more motor functions, respectively (Graybiel, 1998; Haber and Knutson, 2010). Hence, the BG can both assist in performing novel, voluntary behavior, as well be involved in automatization. These two distinct functions produced by similar architecture could result from the differential input signals related more to executive (task set) or motor function. However, the interdependence of the cortico-BG loops, as well as cortico-cortico connections between the PFC and motor cortical regions suggests multiple ways in which modulated executive signals by the BG can, in turn, modulate motor signals. One possible way in which this transfer from executive to motor output might occur via BG mechanisms, comes from our knowledge of the role of the BG in reward learning.

6.2: Learning, Reward and their Implications

Traditional models of BG function and physiology have often focused on trial-by-trial learning made possible by trial-by-trial rewards. Given that experiments are often conducted in

animal populations, it is likely a necessity to use trial-based rewards, as the 'subjects' may not perform the task otherwise. However, with human research, rewards are not often, nor necessary to be delivered on a trial-by-trial basis. The intrinsic value of performing a given task is sufficient to motivate human participants (especially in the presence of experimenter observation), to the point that it can lead to participants adjusting their performance strategy in a so called 'Hawthorne effect' (Macefield, 2007). Regardless, however, of how a 'reward' is delivered, the BG have an important role in learning, and these learning mechanisms are made possible in part by phasic dopaminergic (DA) modulation of cortico-striatal synapses (Mink, 1996; Graybiel, 1998; Horvitz et al., 2007). Via modulation of these synapses through long-term potentiation (LTP) and long-term depression (LTD), DA signalling introduces plasticity into the systems, which is a critical parameter to learning, as it allows for effective or desired signals to strengthened, and ineffective or undesirable signals to be weakened (Frank, 2005). DA neurons in the SNpc will fire in response not only to rewarding stimuli, but also to highly salient or novel stimuli, and to conditioned stimuli that were previously associated with a reward (Schultz et al., 1997; Schultz, 2001; Horvitz et al., 2007). This DA signalling modifies the strength of cortical-striatal synapses, and the looped architecture of the striatal-SNpc and cortical-striatal systems suggests DA modulation changes activity in neural networks related to a specific behavior (known as 'modules') (Wise et al., 1996). Moreover, the projections to SNpc dopamine cells from the anterior regions of the striatum are greater than they are for the motor regions (Graybiel, 1998; Haber and Knutson, 2010), highlighting, perhaps, the greater importance of DA modulation to limbic (especially) and executive control circuits rather than motor circuits, which makes sense given the relationship of 'rewarding' stimuli to DA firing. Once the executive circuits related to a given behavior are strengthened, they could potentially modulate signals in motor and sensory regions operating through cortical-cortical top-down fashion (Norman and Shallice, 2000; Miller and Cohen, 2001; Gazzaley and D'Esposito, 2007). In the oculomotor system, this might correspond to the presetting of neurons in the SEF and FEF (as well as DLPFC) which individually have been shown to code for pro or antisaccade behaviors (Everling and Munoz, 2000; Munoz, 2002; Munoz and Everling, 2004; Everling and DeSouza, 2005; Johnston and Everling, 2006).

6.1.1 Relationship to Parkinson's disease

Based on this evidence from learning, do the anatomical and functional properties of BG circuits fit with the behavior of PD patients in Chapters 4 and 5? Anatomically speaking, the results are in line with findings that the loss of DA in early stages of PD occurs in the cells projection to the dorsal, rather than ventral striatum, and therefore affects primarily the circuits that involve the DLPFC, primary and pre-motor cortices – the ones that are critical to voluntary motor behavior (Frank, 2005; Cools, 2006). However, it has been suggested that the tonic DA levels are more affected than phasic DA in PD (Schultz, 2001), suggesting that PD patients, in theory, should be *unimpaired* in learning novel associations between stimuli and behavior that are supported by phasic DA signals. Of course, ample evidence points to the contrary, because PD patients do show performance deficits in many cognitive tasks. This might be partially reconciled by the facts that changes in tonic DA levels influences phasic release (Cools, 2006), and that degeneration of SNpc cells (typically > 75% in PD) would also affect those mediating phasic DA signals because of the sheer volume of neurons that are lost (Frank, 2005). However, their deficits might be best explained by the baseline imbalance between the direct and indirect pathways (Owen, 2004; Dagher and Nagano-Saito, 2007; Leh et al., 2010), that would depend on the interactions of tonic as well as phasic DA as explained in the following paragraph.

Phasic DA is thought to have greater effects on the D2 receptors (predominant in the indirect pathway), than on the D1 receptors (predominant in the direct pathway) (Cools, 2006; Surmeier et al., 2007), meaning that if the balance between the direct and indirect pathways is already shifted 'against' the direct pathway due to reduced levels of tonic DA, the weaker effect of phasic D1 stimulation on the direct pathway in PD may produce impaired voluntary behavior, due to reduced focused BG dis-inhibition on the desired task set or motor signals. Pathologically, a heightened influence from the indirect pathway may also contribute to a greater propensity to execute alternative behaviors in error, as it is now more difficult to dis-inhibit thalamo-cortical signals (Mink, 1996; Nambu, 2005). It has been proposed that one of the reasons PD patients have difficulty executing voluntary behavior (and suppressing competing behaviors) is that there is increased inhibition which slows responding, but also a weakened dis-inhibitory direct pathway which results in failure to overcome the competition from other signals; thus erroneous

responding in cognitive tasks, as well as motor rigidity, may result from a reduced signal-to-noise ratio related to focally selecting signals related to one behavior out of competing signals (Mink, 1996). Thus, it does appear that the balance between the direct and indirect pathways on cortico-BG-thalamo-cortical networks can explain many of the deficits observed in these experiments. However, the PFC-cortical networks themselves can operate in a top-down modulatory fashion (Gazzaley and D'Esposito, 2007), and some behavioral deficits in PD can be explained by changes in PFC function directly (Owen, 2004; Cools, 2006). Therefore, more work is needed to examine PFC processing in PD and the role of DA in PFC function, which is indeed a focus of many current research programs in other laboratories, but was not addressed in this thesis.

It is also difficult to conclude, based solely on our understanding of DA and BG circuitry, why PD patients on their normal medication regimens still showed impairments in the given experiments. However, it has been shown by other groups that medicated PD patients display deficits in antisaccade generation (Hood et al., 2007) and it has also been shown that PD patients display *enhanced* switch costs for switching between two non-dominant Stroop responses, but *reduced* costs when switching between two automatic responses in comparison to control subjects (Pollux and Robertson, 2002), pointing to similar findings to those in Chapter 4. Also, as PD patients on medications were seldom observed to exhibit normal motor function (see demographics of UPDRS ON medication scores in Table 4.1), DA medications may not be able to completely restore function in many tasks of executive control either. Evidence does suggest that DA medications can affect the delicate balance between tonic and phasic dopamine levels in the striatum as well as PFC directly, such that an ‘overdose’ of PFC DA can result in impairments in many tasks of executive function (Cools, 2006; Cools et al., 2010; Leh et al., 2010). It has been suggested that DA in PFC circuits optimizes performance on tasks where maintenance of a behavior or working memory process is required, whereas DA in the striatum mediates cognitive flexibility (Cools, 2006). Thus there are two hypotheses related to the relative effects of DA on PFC and BG circuits that could be considered to explain the deficits while taking medication: first, under a PFC-focused hypothesis, DA medications may have a detrimental overdosing effect on task set maintenance, leading to the intrusion of the more automatic behavior (prosaccade) when

stable antisaccade task set maintenance is required to be in place; alternatively, under a BG-focused hypothesis, it has been suggested that increasing tonic levels of DA in the striatum by L-DOPA impairs the DA 'dips' which need to occur in order for 'no-go' behavior to be produced via the indirect pathway (Frank et al., 2004; Frank, 2005). Impaired 'no-go' behavior is that which results following negative feedback (in other words, to not repeat the previous behavior), which while not provided explicitly in the current experiments, was nonetheless observed as participants corrected their errors on erroneous antisaccade trials, implying some sort of internal evaluation on performance. Thus impaired DA dips would predict impairments in learning *not* to perform a given response. While both explanations related to the effects of DA on PFC and BG function are possible, I will suggest, at least, that an explanation that favors impairments in '*no-go* learning' in medicated PD is less likely based on the current experimental data in this thesis. This is because it implicates an important role of the *indirect* pathway in response suppression, which as described in the following section, is less likely to be the major contributor to the observed behavior throughout Chapters 2-5.

6.3: Boosting or Suppression

Throughout this thesis, I have alluded to the role of BG output as being important to 'boosting' cortical signals. As introduced above, an equally important role of the BG is in suppressing behavior, via the indirect pathway, and both processes are certainly involved in voluntary response generation, and very likely in task switching (Mink, 1996; Camalier et al., 2007; Hikosaka and Isoda, 2010). However, to explain the behavior in Chapters 2-5, as well as the fMRI BOLD signal activations measured in Chapters 3 and 5, the enhancement by thalamo-cortical excitation (boosting) of a desired behavioral program is a more favorable explanation for the following reasons:

1) The fact that the CN contains medium spiny neurons (MSNs) projecting to both the direct (SNr) and indirect (GPe) pathways makes the ability to differentiate whether CN BOLD activation corresponds to net inhibition or net excitation difficult to dissociate. However, it is known that the fastest pathway (in terms of conduction time) through the BG does not include the striatum, and as such has been named the 'hyperdirect' pathway, consisting of convergent

cortical excitement of STN, which results in the global increase in BG output (SNr and GPi) activity, and thus to widespread thalamic inhibition (Mink, 1996). The hyperdirect pathway has also been referred to as the 'stop' or 'no-go' pathway, and is thought to be important to suppressing ongoing responses as well as globally inhibiting competing responses (Mink, 1996; Hikosaka et al., 2000; Aron and Poldrack, 2006; Aron et al., 2007; Hikosaka and Isoda, 2010). Noting that the stopping network is fast, has widespread effects, and does not directly require the signals from the striatum, I suggest that fMRI signals measured in the CN are related to the boosting mechanism, corresponding to the dis-inhibition of the desired task set or voluntary motor program signals. Other studies (including our own in Chapter 3) have shown that striatal activation occurs more in switching between higher cognitive processes, and STN activation occurs more in stopping a pre-potent response (Hikosaka and Isoda, 2010). However, the striatal mediated dis-inhibitory mechanisms might *utilize* inhibitory processes from the hyperdirect and indirect pathway (slowest), to *focus* the dis-inhibition of the desired thalamo-cortical signals, or by *sequentially* activating a desired program after the response system is globally suppressed (Mink, 1996; Hikosaka et al., 2000). Thus, signals measured in the CN likely correspond primarily to 'boosting', as activation of the indirect pathway originating in the striatum may be representative of a supportive role in the same processes.

2) The basic nature of our understanding of the BOLD signal also supports the hypothesis of a cortical boosting mechanism. Undoubtedly, fMRI is related to activity in populations of neurons as well as vascular processes in a voxel (on the order of millimeters), rather than the spiking of a single neuron (Ogawa et al., 1990; Kwong et al., 1992). Thus, while the exact nature of the BOLD signal is still debatable, whatever results in an enhancement of metabolic processes in and surrounding a population of neurons, would result in increased BOLD signal in a given region. Conceptually, one can consider that what causes increased 'use' of a brain region results in increased BOLD signal. If one also takes the proposal that BOLD signal reflects more of the inputs to a given region and synaptic processing (Logothetis et al., 2001; Logothetis and Wandell, 2004), then one would predict that signals related to a desired behavior are inputted to the striatum as corollary signals to those in cortex, and this results in increased

BOLD signal relative to a baseline state. In Chapters 3 (Figs. 3.2 and 3.3, for example) and 5 (Supplementary Fig. 5.S1), for either a pro or antisaccade response, enhanced BOLD signal activation in the CN occurred relative to baseline. Should these neural signals be even greater in terms of firing rate, or in the integration of signals from a large number of neurons carrying an increase in firing rate, the BOLD signal would rises to a greater magnitude. Given the looped architecture of executive as well as motor channels, I also suggest this should coincide with the increased activity of DLPFC neurons and to the presetting of fixation and saccade neurons in FEF towards the appropriate task described in Chapter 5 (Everling and Munoz, 2000; Munoz and Everling, 2004). Therefore, the same mechanisms that result in increased BOLD activation in the CN likely apply to cortical regions as well. Indeed, it has been shown that PD patients display reduced PFC activation (in regions including DLPFC) that are activated along with the striatum in controls (Monchi et al., 2004; Monchi et al., 2007), and it has been shown recently that when subjects are told to respond faster, rather than more accurately, both the CN and pre-SMA showed increased activation related to the degree in which subjects adjusted their threshold in favor of responding, suggesting a mechanism favoring dis-inhibition of a desired behavior via cortical-striatal signaling (Forstmann et al., 2008).

3) Finally, as described in Chapter 3, a boosting mechanism is sensible to describe anything that results in increased BOLD activation, when the demands to overcome any bias against eliciting a particular response is required. We utilized this explanation in Chapter 3 to explain the results on erroneous switch trials, in which enhanced CN activation was seen when subjects erroneously executed an antisaccade before switching to a prosaccade (i.e., the response system was initially inhibited against a prosaccade). It also fits with the findings of Chapter 5, in which successful antisaccade performance corresponded with increased preparatory activation, particularly in FEF, which could be explained by enhanced excitation from thalamic dis-inhibition. However, what is perhaps one of the most difficult challenges to overcome in our understanding of the relationship between BG and cortical signaling, is to determine which signals are the originators of a given neural network process in a feedback loop. This is particularly problematic when the fMRI BOLD signal is used as a measure of brain function, and

so one of the greatest hurdles in the next generation of fMRI studies will be to dry to develop better methods for assessing the directional neuronal interactions using BOLD activation signals.

6.4 Future Directions

As the boosting mechanisms described in Section 6.3 fall under the BG-looped architecture (Alexander et al., 1986) it is not clear if a region, say preSMA in the study by Forstmann and colleagues (2008), or the DLPFC in studies by that of Monchi and colleagues (2004, 2007), is showing increased BOLD activation due to these areas being the originators of a given signal, or due to them being boosted by the BG. The temporal resolution of fMRI cannot reliably dissociate these alternatives, and likely both processes may contribute to the enhanced BOLD activation. However, from our knowledge of PD, a lower boosting signal would predict decreased cortical activation in areas receiving BG output (Dagher and Nagano-Saito, 2007), but not necessarily reduced CN activation, if the inputs that the CN receives are derived from brain regions that are not directly impaired by decreased cortical excitation, or, at least are not completely dependent on only excitation from thalamus, such as the PFC which is extensively connected with virtually the rest of cortex (Miller and Cohen, 2001). Following this, Chapter 5 showed that while cortical areas were hypoactive in terms of enhanced anti activation in PD patients off medication, one area that consistently showed greater activation for antisaccades in the PD off-meds group was the CN. Indeed, it was observed in the task switching study by Monchi and colleagues (2007) that in some experimental conditions, PD patients displayed increased CN activation and *not* increased cortical activation, while control subjects showed it in both regions. Thus, it is possible that these patterns of decreased cortical activation, but increased CN activation in PD patients off medication reflect, in a sense, the ‘halting’ of functional signals at the input of the CN. I refer to ‘halting’ to represent the signals related to unimpaired, or compensatory mechanisms from areas of cortex that are functionally spared from decreased thalamo-excitation in PD, and can result in increased BOLD activation upon convergence in the CN; however, the functional benefit of these signals ends at the input stage of the BG, with areas normally driven by the net excitation at the output stage not showing corresponding increases in BOLD activation. From this suggestion, it can be seen that one of the most important advances

required in functional neuroimaging is to try to understand the directional 'flow' of information in a looped system, using a technique with limited temporal resolution. However, this is indeed something that is being attempted through multivariate techniques in many laboratories, and as an exploratory component of the following experiments currently planned or underway.

The activation patterns in Chapter 3 provide for interesting predictions about what fMRI signals might be expected in PD if they performed the fMRI version of the task switching experiment. The simplest prediction from their prosaccade bias (Chapters 4 and 5) would be that CN signals on correct 'pro2anti' trials might reach greater magnitudes compared to 'pro' trials in PD patients than in control subjects, reflecting the even greater difficulty for patients to switch to an antisaccade. Following this logic, 'anti2pro' trial signal magnitude would be even less in the patients. However, it is entirely possible that PD patients would show the opposite patterns. During the prosaccade instruction, it is possible that a significant amount of *response-system inhibition* is imposed in control subjects, preventing the execution of the more automatic repsonse (as described in Chapter 3). This would constitute, in effect, a voluntary task set *against* responding (a 'no-go' signal). PD patients might be expected to have more difficulty imposing this, and therefore, would not be expected to show enhanced 'pro2anti' activation, since there was less inhibition to overcome. Indeed, it has been shown that PD patients show significantly greater stop-signal reaction times (the difference between response time and when a stop signal was delivered) in a go/no-go task (Gauggel et al., 2003), highlighting the bias towards 'go' behavior. In any case, these two hypotheses can only be tested by experimentation, and the results would contribute to our understanding of what BOLD signal might mean at the input stage of the BG.

A second valuable experiment, which is currently in progress, is a whole brain imaging study following the design of Chapter 3, in order to identify other brain regions besides the CN and FEF that are involved in some of the switching processes described previously. For instance, one would expect the DLPFC to be active in switching from a pro to an antisaccade, as it is an integral component of the executive BG-loop. Also, the anterior cingulate cortex (ACC), which has not been considered in the current experiments, is thought to have a significant role in error monitoring, feedback learning, conflict processing, and general behavioral control (Dehaene et

al., 1998; Miller and Cohen, 2001; Johnston et al., 2007). As such, the ACC may show important signals related to successful as well as failed switch trials. Finally, the thalamus itself should be examined, as the ventroanterior, ventrolateral and mediodorsal (MD) nuclei are involved in aspects of saccade generation (Schlag and Schlag-Rey, 1984; Schlag-Rey and Schlag, 1984; Lynch and Tian, 2005; Kunimatsu and Tanaka, 2010), with the MD also being associated with the executive loops through the BG (Alexander et al., 1986; Haber and Knutson, 2010) and PFC (Gazzaley and D'Esposito, 2007). Recent evidence suggests the thalamus may play a *functional* role in antisaccade preparation (Kunimatsu and Tanaka, 2010).

Preliminary experiments in the whole brain switching task (N=7 subjects) are revealing the following promising findings: First, non-switch 'anti' trials compared to 'pro' trials reveals greater anti activation in FEF and PEF as expected, and switch trials compared to non-switch trials reveals greater switch trial activation in the DLPFC, ACC, medial PFC, and the CN (ventrally). When comparing 'pro2anti' to pro trials, the FEF, SEF, PEF, DLPFC, right inferior frontal cortex, right CN, ventral striatum and dorsomedial cerebellum show greater pro2anti activation. Additional analysis exploring the correlation in BOLD signal time courses (functional connectivity) between these regions do show sensible connectivity maps (Fig. 6.1), in particular, with the left DLPFC being functionally connected with FEF seed regions, and the DLPFC, FEF, and PEF being functionally connected with the CN seed region. In contrast to these findings for switching from pro to anti, no significant increase is occurring on 'anti2pro' trials relative to anti trials in the DLPFC, CN or FEF. Instead, the lateral cerebellum and primary visual cortex are two regions showing the greatest increase in activation for 'anti2pro' compared to anti trials. Together, these findings do suggest that cortical connections to the BG, in particular, the oculomotor regions and those of the executive loop are showing patterns of activation reflecting the switch from an automatic to a more difficult behavior. The role of the cerebellar regions is also something that warrants further investigation, and most importantly, further steps to attempt to establish directional neuronal interactions, using methods such as Granger causality mapping, are also underway (Roebroeck et al., 2005).

Fig 6.1

Finally, one additional problem to consider is the role of *preparatory* processes. These processes may be able to be dissociated from processes associated with an external cue to switch task. While attempts in this thesis were made to control the *experimentally*- delivered preparation effects as much as possible (e.g., the peripheral stimulus always appeared at a fixed time following initial instruction onset in Chapters 2 and 4, and trials were aligned for fMRI comparisons based on preparatory instruction periods in Chapter 3), it must be acknowledged that this does not necessarily mean that subjects *were* in the same degree of preparation based on the initial task instruction. This is important, as switch costs, or benefits, could depend on the level of preparation (i.e., task set establishment) that the subjects were in. For instance, if PD patients in Chapter 4 never really established an antisaccade task in the first place, then the larger anti2pro switch costs at +100 ms compared to -200 ms depends mainly on the fact that they had less time to configure a prosaccade task set. Alternatively (and not completely exclusive from the former possibility), switch costs could be greater at +100 ms because subjects were actually prepared initially prepared to execute an antisaccade. The methodological designs in Chapters 2-4 cannot dissociate these alternatives reliably, but overall I do suggest that subjects do prepare the initially instructed task set to some degree (see Section 2.6). It is also evident that reaction times and error rates increased on experimentally identical non-switch trials as subjects moved from the blocked to the interleaved design (Figs. 4.2, 4.3), suggesting, perhaps, that in the blocked design, subjects were more prepared to execute the initial behavior than they were in the interleaved design where a switch of task was possible. Note that this does not exclude an alternative possibility related to *interference* from the alternate task set in the interleaved design (Allport et al., 1994). Thus, the best way to test the effects of these preparatory processes would be to conduct experiments whereby the initial instruction period varied, but parameters related to peripheral stimulus onset and instruction change were constant. Differential switch costs across these conditions might suggest different degrees of preparation based on the initial instruction.

6.5 Conclusions

In the analogy of a global ‘workspace’ described in Chapter 1, executive control operates in a top-down fashion to bias the activity in lower processing regions (Dehaene et al., 1998). This

top-down control is necessary to enable goal-directed behavior to be produced, when the lower processing regions are biased towards evoking an alternative behavior. While this 'workspace', and for that matter, executive control, cannot be thought of as being isolated from the these lower motor regions, it is clear from years of investigation that the prefrontal cortex (PFC) is a critical brain region to the implementation of top-down executive control (Miller and Cohen, 2001; Gazzaley and D'Esposito, 2007). However, throughout this thesis, I have suggested that in situations in which a human, or other animal, is biased towards executing very automatic behaviors, an efficient top-down overriding mechanism is necessary, and this mechanism requires the BG. Importantly, this can occur when an inappropriate behavior is imminent (e.g., Chapters 2 and 3) (Hikosaka and Isoda, 2010), but also in advance of response execution – at a more cognitive stage when an appropriate voluntary task set is required to be in place (Chapters 4 and 5).

It can also be concluded that there is in fact a critical component of cognitive 'effort', that is likely the source of much of the enhanced BOLD activation observed in Chapters 3 and 5. The patients with PD showed impairments in the establishment of the more difficult task set, and this dysfunction mapped on to cortical regions affected by BG output. While not directly explored in this thesis, the structure of a fast-acting hyperdirect pathway provides a means to rapidly arrest or inhibit response, until a more focused voluntary choice of behavior is selected. Thus, at the very least the BG contain the plausible response-stopping mechanisms allowing for novel, cognitively demanding behavior, to be implemented for the first time, and this implementation appears to depend on the direct pathway of the BG to result in an increase in activity in cortical regions critical to generating difficult, or novel voluntary behavior.

To further explore these findings, we will need to draw on many of the recent advances in technology to dissociate subcomponents of these very large executive control mechanisms that span the frontal portion of the brain. The idea of a rapid, reconfiguration mechanism, or one that can result in the correct execution of a behavior upon first exposure is something that would be difficult to study in animal models that require extensive trial-by-trial reward learning; even if the single-cell recording method is one of the best ways to study neuronal computations. Instead, it is

evident that improvements to methods that can capture some measure of human behavior instantaneously, like fMRI, will play a critical role, at the very least, in image-guided exploration of the critical processing hubs. Our understanding of what fMRI can do will need to be pushed continually towards utilizing this technique to examine correlations between signals in separate regions, to attempt to map a directional flow of signaling. Combining fMRI with more fine-grained approaches, such as single-cell recordings, and cause-effect manipulations in human subjects (like transcranial magnetic stimulation) will afford scientists with the necessary tools to manipulate subcomponents of executive control and then observe downstream effects on behavior and underlying neuronal processes. This will be critical to understand the processing in networks that display both properties of segregated, positive feedback loops, but also, lateral interactions, such as those that involve the BG.

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Appendix: Supplementary Analysis, Tables and Figures

Supplementary Table 2.S1
Response time and direction error switch costs for Experiment 1

a) Blocked Pro-Antisaccade Task (Day 1)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	-6	1.63	0.131	-0.6	-1.34	0.500	-8	1.24	0.243	1.4	-0.14	0.945
-400	-3	0.72	0.488	-0.2	0.00	1.000	-6	1.53	0.154	0.6	-0.36	0.770
-200	4	-0.61	0.551	-0.7	-0.73	0.625	0	-0.11	0.914	-2.0	-0.89	0.426
0	7	-1.94	0.079	0.6	-1.10	0.375	**12**	-2.91	0.014	-0.2	0.00	1.000
+200	5	-0.52	0.619	-0.3	-1.00	1.000	**21**	-2.59	0.027	-1.3	-0.40	0.813

b) Interleaved Pro-Antisaccade Task (Day 2)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	**-21**	3.78	0.003	-0.2	0.00	1.000	-10	1.10	0.296	2.0	-1.60	0.110
-400	-8	0.67	0.516	-0.6	-0.66	0.508	-17	1.58	0.144	**-6.7**	-2.93	0.003
-200	3	-0.32	0.759	-0.6	-0.27	0.790	-17	1.57	0.145	5.1	-1.78	0.075
0	15	-1.18	0.262	**6.8**	-3.06	0.002	1	-0.10	0.923	3.1	-0.63	0.530
+200	**94**	-5.33	0.000	**13.9**	-2.98	0.003	**88**	-2.96	0.013	**16.1**	-2.85	0.004

c) Blocked Pro-Antisaccade Task (Day 3)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	2	-0.37	0.721	-0.3	-0.45	0.655	**-9**	2.24	0.047	-3.3	-1.21	0.225
-400	3	-0.74	0.475	-0.3	-1.00	0.317	**-11**	2.39	0.036	-1.9	-0.31	0.753
-200	1	-0.16	0.874	-0.2	-1.00	0.317	-6	1.13	0.285	2.8	-1.69	0.090
0	**5**	-2.40	0.035	0.0	----	1.000	6	-1.55	0.148	-0.9	-0.31	0.753
+200	6	-0.65	0.526	0.0	----	1.000	1	0.08	0.937	-0.5	-1.00	0.317

Switch costs = mean(switch) - mean(non-switch), N = 12 participants. t-test = Paired t-test,
WSR = Wilcoxon Signed Rank test. (**Bold** cells indicate significant switch costs or switch benefits)

Supplementary Table 2.S2
Response time and direction error switch costs for Experiment 2

a) 25% Switch Probability (Interleaved Pro-Antisaccade Task)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	**-27**	3.34	0.007	0.9	-0.31	0.753	**-16**	3.08	0.011	-0.4	-0.53	0.594
-400	-20	2.04	0.066	0.5	-0.85	0.398	-7	1.61	0.137	-2.2	-1.24	0.213
-200	**17**	-2.71	0.020	1.7	-0.98	0.327	-3	-0.48	0.642	-1.3	-1.07	0.284
0	**46**	-4.79	0.001	1.3	-0.42	0.674	**45**	-4.17	0.002	7.6	-1.87	0.062
+200	**145**	-9.07	0.000	**24.1**	-2.67	0.008	**105**	-6.70	0.000	**20.8**	-2.82	0.005

b) 50% Switch Probability (Interleaved Pro-Antisaccade Task)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	**-35**	2.89	0.015	-0.3	-0.05	0.959	**-30**	3.60	0.004	-1.9	-0.62	0.534
-400	**-27**	3.70	0.004	0.0	-0.28	0.779	**-17**	2.34	0.039	1.7	-0.76	0.445
-200	1	-0.27	0.793	1.5	-0.84	0.401	-10	0.89	0.393	0.0	-0.46	0.647
0	**38**	-4.19	0.002	-0.5	-0.36	0.721	**19**	-3.42	0.006	0.2	-0.18	0.859
+200	**99**	-13.1	0.000	**15.4**	-2.93	0.003	**77**	-7.65	0.000	**14.6**	-2.76	0.006

c) 75% Switch Probability (Interleaved Pro-Antisaccade Task)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	**-28**	2.53	0.028	-0.2	-0.17	0.866	**-35**	3.63	0.004	-1.6	-1.26	0.208
-400	-6	1.19	0.258	-1.6	-0.17	0.866	-24	2.20	0.050	0.7	-0.89	0.374
-200	-3	0.25	0.809	1.6	-1.27	0.202	**-24**	2.38	0.037	-2.0	-0.51	0.610
0	**23**	-2.37	0.037	2.6	-1.60	0.109	-11	1.13	0.283	-0.5	-0.30	0.767
+200	**70**	-6.85	0.000	**11.3**	-2.93	0.003	**41**	-4.86	0.001	**3.9**	-2.04	0.041

Switch costs = mean(switch) - mean(non-switch), N = 12 participants. t-test = Paired t-test,
WSR = Wilcoxon Signed Rank test. (**Bold** cells indicate significant switch costs or switch benefits)

Supplementary Table 2.S3
Response time and direction error switch costs for Experiment 3

a) 25% Stimulus Probability (Interleaved Pro-Antisaccade Task)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	**-53**	3.81	0.003	-2.3	-1.34	0.180	**-47**	3.60	0.004	-0.5	-0.53	0.594
-400	-11	1.00	0.338	0.0	----	1.000	-11	0.87	0.401	-4.3	-0.76	0.445
-200	12	-0.83	0.427	2.4	-1.63	0.103	2	-0.14	0.892	-7.9	-1.35	0.176
0	**39**	-2.46	0.032	2.3	-0.74	0.462	-31	1.61	0.139	-1.2	0.00	1.000
+200	**121**	-4.58	0.001	6.5	-1.33	0.182	**94**	-3.22	0.008	12.2	-1.89	0.059

b) 50% Stimulus Probability (Interleaved Pro-Antisaccade Task)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	-14	1.51	0.159	0.4	-0.95	0.343	-14	1.63	0.132	-5.0	-1.96	0.051
-400	-11	1.67	0.124	-0.7	-0.63	0.528	-8	1.60	0.138	-1.7	-0.71	0.477
-200	6	-0.56	0.587	0.6	-0.13	0.893	-9	1.09	0.297	-0.1	-0.25	0.799
0	**31**	-3.18	0.009	3.5	-1.90	0.058	15	-1.70	0.118	-2.8	-0.80	0.424
+200	**102**	-4.47	0.001	4.8	-1.89	0.059	**93**	-5.00	0.000	**16.2**	-2.67	0.008

c) 75% Stimulus Probability (Interleaved Pro-Antisaccade Task)

	Prosaccades						Antisaccades					
	Response time			Direction errors			Response time			Direction errors		
Switch Time	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value	switch cost (ms)	t-test (t)	*P* value	switch cost (%)	WSR (Z)	*P* value
-800	**-30**	2.48	0.030	-0.1	-0.13	0.893	-20	1.73	0.111	0.3	-0.49	0.625
-400	-14	1.65	0.127	0.8	-0.85	0.398	**-29**	2.42	0.034	-1.0	-0.73	0.463
-200	-3	0.34	0.744	0.7	0.00	1.000	-10	1.72	0.113	-2.9	-0.98	0.327
0	33	-1.89	0.085	1.5	-0.73	0.465	8	-0.45	0.660	0.1	-0.36	0.722
+200	**123**	-6.04	0.000	**9.1**	-1.99	0.047	**78**	-3.84	0.003	**14.0**	-2.67	0.008

Switch costs = mean(switch) - mean(non-switch), N = 12 participants. t-test = Paired t-test,
WSR = Wilcoxon Signed Rank test. (**Bold** cells indicate significant switch costs or switch benefits)

Table 3.S1

Fig 3.S1

Fig 3.S2

Fig 3.S3

Fig 3.S4

4.A1 Supplementary Analysis of Task Switching for Chapter 4

An omnibus ANOVA of Group X Switch Time X Response (prosaccade or antisaccade) was conducted to examine task switching under the conditions whereby identical responses were performed despite task differences (e.g., non-switch antisaccade trials compared to 'pro2anti' switch trials). Under this method, switch costs correspond to increased SRT and direction errors on switch trials, because the alternative task set was initially established but then reconfigured to the new task set, with less time to do this compared to non-switch trials of the same response type. For clarity, we will refer to these switch costs as 'reconfiguration costs'. Under this analysis, there was no significant 3-way interaction for direction errors $F(4,19) = 0.74$, $P = 0.57$, or for SRT, $F(4,19) = 0.46$, $P = 0.76$. Two-way ANOVA's were subsequently conducted, below, for trials constituting a prosaccade response separately from trials constituting an anti-saccade response.

4.A1.1 Anti and Pro2Anti trials

For direction errors, there was not a significant Group X Switch Time interaction, $F(4,19) = 1.77$, $P = 0.18$, but was there was a main effect of Switch Time, $F(4, 88) = 31.12$, $P < 0.01$. There was no main effect of Group $F(1,22) = 1.81$, $P = 0.19$. (Post-hoc Mann-Whitney U tests between the Groups for responses at individual switch times are identical to those in the main Results section, and will not be reported here).

For SRT, there was not a significant Group X Switch Time interaction, $F(4,19) = 0.39$, $P = 0.81$. However, there was a main effect of Switch Time, $F(4,88) = 36.79$, $P < 0.01$, and there was a marginally significant main effect of Group, $F(1,22) = 4.02$, $P = 0.06$, illustrating that PD patients were slower to respond overall.

Supplementary Fig. 4.S1A illustrates the direction error reconfiguration costs whereby non-switch antisaccades were subtracted from pro2anti trials. Both groups produced reconfiguration costs in error rates for pro2anti trials (Y axis > 0), with a Group by Switch Time interaction that approached significance, $F(3,20) = 2.42$, $P = 0.096$. There was no main effect of Group, $F(1,22) = 0.31$, $P = 0.58$, nor were there any differences in reconfiguration costs at any switch time $t < 1.46$, $P > 0.16$. For SRT reconfiguration costs (Supplementary Fig. 4.S2A), there was no significant Group X Switch Time interaction, $F(3,20) = 0.142$, $P = 0.93$, no main effect of

Group, $F(1,22) = 0.33$, $P = 0.57$, nor were there any differences in reconfiguration costs at any switch times $t < 0.55$, $P > 0.59$.

One sample t-tests were conducted separately for each group in order to examine the time course in which the reconfiguration costs evolved. For direction errors, both groups showed significant costs at all switch times, $t > 3.06$, $P < 0.05$, (Supplementary Fig. 4.S1A). For SRT reconfiguration costs, neither group showed significant reconfiguration costs (or benefits) at the -200 ms or -100 ms, $t < 1.75$, $P > 0.11$, but both groups did show costs at the 0 ms and +100 ms switch times $t > 4.15$, $P < 0.01$. Thus, both groups had greater errors on all pro-to-antisaccade switch trials whereby a prosaccade task set was initially instructed, and then had to be reconfigured to the antisaccade task set. However, at switch times prior to target onset neither group was significantly slower at reconfiguring to the antisaccade on trials that were performed correctly.

4.A1.2 Pro and Anti2Pro trials

There was no significant Group X Switch Time interaction for percentage direction errors, $F(4,19) = 2.16$, $P = 0.11$, but there was a main effect of Switch Time, $F(2.04, 44.81) = 24.03$, $P < 0.01$. There was no main effect of Group $F(1,22) = 2.45$, $P = 0.13$. For SRT, there was no significant Group X Switch Time interaction, $F(4,19) = 1.56$, $P = 0.23$, but there was a main effect of Switch Time, $F(2.17,47.73) = 33.61$, $P < 0.01$, and the main effect of Group approached significance, $F(1,22) = 3.32$, $P = 0.08$.

Analysis of these reconfiguration costs for direction errors produced a Group X Switch Time interaction that was marginally significant, $F(3,20) = 2.94$, $P = 0.06$, but there was no main effect of Group $F(1,22) = 0.47$, $P = 0.50$ (Supplementary Fig. 4.S1B). At +100 ms, the reduction in reconfiguration costs in PD was not significant, $t = 1.66$, $P = 0.11$. For SRT, there was not a significant Group X Switch Time interaction, $F(3,20) = 0.45$, $P = 0.72$, and the main effect of Group approached significance, $F(1,22) = 3.13$, $P = 0.09$ (Supplementary Fig. 4.S2B). There were not, however any significant differences between the Groups at any switch time $t < 1.54$, $P > 0.14$. One sample t-tests showed that both groups did not have direction error reconfiguration costs at -200 ms, $t< 1.29$, $P > 0.22$, but did at all other switch times $t > 2.36$, $P < 0.05$

(Supplementary Fig. 4.S1B). For SRT, no significant reconfiguration costs or benefits occurred in either group at -200 ms, $t < 1.23$, $P > 0.24$, (nor at -100 ms in controls, $t = 1.23$, $P = 0.23$), but significant costs did occur at the 0 and +100 ms in controls, and at the -100 ms, 0 ms, and +100 ms switch times in PD, $t > 4.31$, $P < 0.01$ (Supplementary Fig. 4.S2B).

4.A1.3 Summary and Implications

As with the analysis conducted in the Result section, PD patients were slower to respond. However, there were no significant differences between the two groups with respect to reconfiguration costs, other than trends for PD patients to have reduced anti-to-prosaccade direction error costs, but at the same time, a greater SRT costs. These trends might indicate a speed-accuracy trade-off in order to compensate for their know difficulty in performing an antisaccade (because, anti-to-prosaccade trials begin with an initial instruction to prepare an antisaccade task set). Interestingly, the one sample t-tests revealed that at -200 ms for both groups, only reconfiguration costs for direction errors on pro-to-antisaccade switch trials occurred. This highlights the fact that it was difficult for both groups to consistently reconfigure to the antisaccades task set when instructed to prepare for a prosaccade initially. However, 200 ms appears to be enough time to accomplish this on correct trials (i.e., no SRT reconfiguration cost), suggesting that on a subset of trials, the automatic nature of the prosaccade task set may have prevented the successful reconfiguration to the antisaccade task set. Following this, the greater percentage direction errors on both non-switch antisaccade trials in PD, and on pro-to-antisaccade switch trials at -200 ms, suggests that their deficit is really related to the underlying prosaccade bias. Consider that in almost all of the plots in Supplementary Figs. 4.S1 and 4.S2, reconfiguration costs increased with switch time, as increasing switch time makes the reconfiguration process more difficult to accomplish in time. This does not occur for PD patients on pro-to-antisaccade direction error trials, suggesting an inherent underlying difficulty in establishing an antisaccade task set.

Fig 4.S1

Fig 4.S2

Table 5.S1

Table 5.S2

Table 5.S3

Fig 5.S1

Fig 5.S2