Effects of Unilateral vs. Bilateral Subthalamic Nucleus Deep Brain Stimulation on Eye Movements

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Thesis

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This thesis is dedicated to Roy Minnich, AKA "Uncle Butch".

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ACC	Anterior Cingulate Cortex
AS	Anti-saccade
CN	Caudate Nucleus
DBS	Deep Brain Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
FEF	Frontal Eye Field
GPe	Globus Pallidus Externus
GPi	Globus Pallidus Internus
LFP	Local Field Potentials
LIP	Lateral Intraparietal Area
MDS-UPDRS	Movement Disorder Society- Unified Parkinson's Disease Rating Scale
MGS	Memory-guided Saccades
PD	Parkinson's Disease
PEF	Parietal Eye Fields
pre-SMA	Pre-Supplementary Area
PS	Prosaccades
rCBF	Regional Cerebral Blood Flow
SC	Superior Colliculus
SEF	Supplementary Eye Field
SMA	Supplementary Motor Area
SNr	Substantia Nigra Pars Reticulata
STN	Subthalamic Nucleus
STN DBS	Subthalamic Nucleus Deep Brain Stimulation
UPDRS	Unified Parkinson's Disease Rating Scale
VGS	Visually-guided Saccades
VIM	Ventral Intermediate Nucleus of the Thalamus

SUMMARY

High frequency deep brain stimulation of the subthalamic nucleus (STN DBS) dramatically ameliorates most but not all symptoms of Parkinson's disease. Despite the fact that STN DBS improves the motor signs of Parkinson's, there is mounting evidence that STN DBS can impair performance of tasks using cognitive resources that require frontostriatal circuits. The purpose of this study was to determine the differential effects of unilateral and bilateral STN DBS on motor and cognitive aspects of eye movements. We studied 10 right-handed patients with Parkinson's disease with bilateral STN stimulators and 10 sex- and age-matched healthy controls. The patients were tested after a 12-hour overnight withdrawal from their anti-parkinsonian medication under 4 conditions on 4 separate days. The conditions were OFF stimulation, RIGHT stimulator on, LEFT stimulator on, and BOTH stimulators on. For each condition, the patients were rated on a Parkinson's disease clinical rating scale, the MDS-UPDRS part III, and they performed 2 eye movement tasks: a prosaccade task and an anti-saccade task. The order of stimulation conditions and eye movement tasks were randomized.

We were the first to compare the effects of unilateral vs. bilateral STN DBS on clinical motor function using the MDS-UPDRS. We found that unilateral STN DBS improved clinical ratings, yet bilateral STN DBS had a significantly greater effect than unilateral stimulation. These findings were consistent with reports of unilateral vs. bilateral STN DBS on UPDRS part III scores. This was also the first study to look at the effects of unilateral STN DBS on eye movements. In contrast to the abundance of studies reporting the beneficial effects on limb movements, we found that unilateral stimulation did not improve saccadic eye movements. When BOTH stimulators were on, velocity and gain were significantly improved for the prosaccade and anti-saccade task, yet saccadic latency was not improved. Latency for the prosaccade task was significantly reduced when BOTH stimulators were on, but this reduction

SUMMARY (CONTINUED)

moved the average latency further from the average latency of the control subjects. There was

no change in latency during the anti-saccade task when BOTH stimulators were on.

Additionally, the amount of erroneous prosaccades in the anti-saccade task increased when

BOTH stimulators were on but did not increase when only one stimulator was on. Erroneous

prosaccades occur when subjects fail to inhibit a prosaccade to the target during the anti-saccade

task. The increase in erroneous prosaccades when BOTH stimulators were on indicates that

bilateral STN DBS impairs saccadic inhibition.

It is possible that bilateral STN DBS improves measures of saccadic velocity and gain by

reducing the excessive inhibitory output of the substantia nigra pars reticulata thereby allowing

the superior colliculus to more effectively activate brain stem saccade generators. Unilateral

STN DBS may be unable to improve these measures as bilateral stimulation does due to the

bilateral nature of oculomotor control. The finding that bilateral stimulation further reduced

latency in the prosaccade task and had no effect on the anti-saccade task suggests that bilateral

STN DBS may alter the activity of the posterior parietal cortex, which is responsible for

triggering visually guided reflexive responses, and may not alter the activity of the frontal eye

fields, which are responsible for triggering internally-guided saccades. Further, the increase in

erroneous prosaccades during bilateral STN DBS may be due to a disruption in prefrontal

cortical processing. Specifically, the dorsolateral prefrontal cortex has been shown to play a

critical role in saccadic inhibition. It is possible that STN stimulation produces an informational

lesion in the dorsolateral prefrontal cortex. The fact that bilateral, and not unilateral, STN DBS

resulted in an increase in erroneous prosaccades could be that during unilateral stimulation, the

non-stimulated side can compensate for the disrupted stimulated side.

In summary, unilateral STN DBS does not improve eye movements as it does limb movements. Although bilateral STN DBS improves certain aspects of eye movement control, it also appears to abnormally increase the reflexive response to visual stimuli and deleteriously affect the processes underlying saccadic inhibition.

Chapter 1: Introduction

1.1 Organization of the dissertation

The overall purpose of this dissertation is to understand how deep brain stimulation of the subthalamic nucleus alters the control of two different types of eye movements, prosaccades and anti-saccades, in patients with Parkinson's disease. Chapter 1 will first outline some general motor and cognitive characteristics of Parkinson's disease. It will then outline the main treatments that are used for patients with Parkinson's disease. Chapter 2 will provide an in depth overview of the control of saccadic eye movements and the effects of STN DBS in Parkinson's disease. Chapter 3 will present the results of a study in which we compare the effects of bilateral stimulation of the subthalamic nucleus with unilateral left side stimulation, unilateral right side stimulation, and no stimulation. Chapter four outlines a series of potential future studies that build on the current experiment.

1.2 Parkinson's disease

1.2.1 Incidence & etiology

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimers disease (Schapira, 2006). The number of people with Parkinson's disease over the age of 50 years in Western Europe's 5 most and the world's 10 most populous nations is estimated to be between 4.1 and 4.6 million in 2005, and this number is expected to double to between 8.7 and 9.3 million by 2030 (Dorsey et al., 2007).   In the United States, it is estimated that at least 500,000 to 1,000,000 people suffer from Parkinson's disease, and approximately 50,000-60,000 new cases are reported annually (http://www.pdf.org/en/understanding_pd; http://www.parkinsonshealth.com/About-Parkinson-s-Disease.aspx). These numbers do not

reflect the thousands of cases that presumably go undetected. The annualized age- and gender-adjusted incidence rate has been estimated to be 13.4 per 100,000 person years (Van Den Eeden et al., 2003). This rate rises steeply with age. The incidence rate increases to 17.4 in 100,000 person years between 50 and 59 years of age and further increases to 93.1 in 100,000 person years between 70 and 79 years of age (Bower, Maraganore, McDonnell, & Rocca, 1999; de Rijk et al., 1995). Only 4 percent of cases are under the age of 50 years (Van Den Eeden et al., 2003). Studies have shown men to be 1.5 times more likely than women to develop PD (Twelves, Perkins, & Counsell, 2003; Wooten, Currie, Bovbjerg, Lee, & Patrie, 2004). The incidence rate of PD has also been shown to vary by race. Age- and gender-adjusted rate per 100,000 has been estimated to be highest among Hispanics (16.6) followed by non-hispanic whites (13.6), Asians (11.3) and blacks (10.2) (Van Den Eeden et al., 2003). The mean duration of the disease is 15 years from diagnosis to death with pneumonia being the most documented cause (de Rijk et al., 1995).

Despite years of investigative study, the exact cause of PD is unknown. The disease is characterized by a substantial loss of dopaminergic cells of the substantia nigra pars compacta (Hornykiewicz, 2006) and an accumulation of lewy bodies in several brain areas including the substantia nigra and other subcortical nuclei (Wakabayashi & Takahashi, 2000). Lewy bodies are mainly composed of alpha-synuclein and ubiquitin (Murakami et al., 2004) and are thought to arise from the peripheral portion of inclusions called pale bodies located in the substantia nigra and locus ceruleus (Wakabayashi & Takahashi, 2000). By the time clinical symptoms of PD emerge, approximately 60 percent of neurons in the substantia nigra pars compacta have been lost (Hornykiewicz, 2006). The cellular mechanisms underlying nigral cell loss and lewy body accumulation have not been fully elucidated, yet mitochondrial dysfunction, oxidative

stress, and altered protein handling have all been shown to be associated with PD pathology. Both genetic and environmental factors have been implicated as probable causes for this pathology.

Genetic studies have found several mutations in 10 genes associated with PD: Alpha-synuclein, Parkin, PINK1, DJ-1, ATP13A2, LRRK-2, Omi/Htr A2, UCH-L1, PLA2CG, and FBXO7 (Lees, Hardy, & Revesz, 2009; Saiki, Sato, & Hattori, 2012; Schapira, 2006). Mutations of these genes have been linked with dysfunction of protein handling, oxidative stress, and mitchondrial function. Mutations in the alpha-synuclein gene cause misfolding of the alpha-synuclein protein and self-aggregation resulting in an insoluble form of alpha-synuclein (Feany, 2004), which is a main component of Lewy bodies. The formation of these mutated alpha-synuclein proteins interfere with molecular mechanisms in the presynaptic terminal of the central nervous system leading to cell death (Eriksen, Wszolek, & Petrucelli, 2005; Saiki et al., 2012). PINK 1, parkin, Omi/HtrA2, and DJ-1 have been linked to mitochondrial maintenance; parkin, PINK1, and LRRK2 have been associated with micotubule dynamics; and alpha-synuclein, parkin, PINK1, and omi/HtrA2 have been associated with the autophagy-lysosome pathway (Saiki et al., 2012). Additional support for a genetic contribution to PD pathology comes from several studies reporting an increased prevalence of PD in relatives of patients (Bonifati, Fabrizio, Vanacore, De Mari, & Meco, 1995; Marder et al., 1996; Payami, Larsen, Bernard, & Nutt, 1994). One large case-controlled study found that first-degree relatives of patients with PD are 2.3 times as likely to have PD as first-degree relative of controls (Marder et al., 1996).

In addition to genetic factors, environmental factors have been shown to interfere with mitochondrial mechanisms and protein handling related to PD pathology as well. 1-Methyl 4-phenyl 1,2,3,6 tetra-hydropyridine (MPTP) is known to cause parkinsonism by inhibiting

mitochondrial NADH CoQ reductase (complex I) in the nigrostriatal pathway (Tipton & Singer, 1993). Similarly, the Rotenone pesticide and Paraquat herbicide have been shown to damage the nigrostriatal pathway by inducing alpha-synuclein aggregates and nigral cell loss (Betarbet et al., 2000; Manning-Bog et al., 2002). Further, rural living, drinking well water, and an association with the agricultural industry have all been found to increase the incidence of PD (Barbeau, Roy, Cloutier, Plasse, & Paris, 1987; Noyce et al., 2012). Interestingly, smoking tobacco and drinking coffee are 2 environmental factors that have been found to decrease the risk for PD (Liu et al., 2012; Noyce et al., 2012; Quik, 2004; Wirdefeldt, Gatz, Pawitan, & Pedersen, 2005). Physical activity and exercise have also been shown to be associated with a lower risk for developing PD (Chen, Zhang, Schwarzschild, Hernán, & Ascherio, 2005; Logroscino, Sesso, Paffenbarger, & Lee, 2006).

Although the cause of PD is unknown, genetic and environmental factors have been shown to be associated with PD pathology- specifically, mitochondrial dysfunction and protein mishandling. It is likely that the cause is multi-factorial involving a complex interaction between genetics and environment.

1.2.2 Pathophysiology: dysfunction of the basal ganglia

The basal ganglia integrate input from several areas of cortical and subcortical structures and are involved with coordinated movement, attention, implicit learning, reward-related behaviors, and emotions (Hikosaka, Nakamura, Sakai, & Nakahara, 2002; Yin & Knowlton, 2006). The basal ganglia include the 1) striatum, 2) globus pallidus, 3) substantia nigra (consisting of the pars compacta and pars reticulata), and 4) subthalamic nucleus and are functionally subdivided into 5 circuits: motor, oculomotor, dorsolateral prefrontal, lateral

orbitofrontal, and anterior cingulate (Alexander, DeLong, & Strick, 1986). Dopamine depletion due to loss of dopaminergic neurons of the substantia nigra pars compacta results in impaired motor control and cognition as well as emotional disturbances.

The striatum, consisting of the putamen, caudate, and ventral striatum (Hikosaka, Takikawa, & Kawagoe, 2000), serves as the input station for the basal ganglia (Alexander & Crutcher, 1990). The striatal neurons, mostly medium spiny GABAergic (inhibitory) neurons, receive tens of thousands of glutamatergic (excitatory) inputs from the cortex and thalamus in addition to dopaminergic, cholinergic, and GABAergic inputs (Wilson, 2004). The globus pallidus internus and substantia nigra pars reticulata, serve as inhibitory, GABAergic output stations of the basal ganglia (Weinberger & Dostrovsky, 2011). Transient inhibitory projections from the striatum to the pallidum determine the amount of inhibitory output from the basal ganglia nuclei. Approximately 100 medium spiny neurons project to one pallidal neuron (Purves, 2008). Dopamine modulates the glutamatergic input to the striatum , both pre- and post-synaptically, and therefore is involved in the massive convergence of input by the medium spiny neurons before projecting to the pallidum (Obeso et al., 2008).

Medium spiny neurons of the striatum express either D1 or D2 dopamine receptors. The neurons expressing the D1 receptors project mainly to the globus pallidus internus (GPi) and substantia nigra pars reticulata (SNr) and are considered to be part of the "direct pathway" (Onn, West, & Grace, 2000). Dopamine excites striatal neurons that express D1 receptors leading to an overall effect of disinhibition of the pallidum (West & Grace, 2002). The striatal neurons expressing the D2 receptors project to the globus pallidus externus (GPe) and are considered to be part of the "indirect pathway" (Onn et al., 2000). Dopamine inhibits striatal neurons that express D2 receptors leading to reduced excitation of the pallidum (West & Grace, 2002). Thus,

through its excitatory effects on D1 receptor neurons and its inhibitory effects on D2 receptor neurons, dopamine reduces the inhibitory output from the pallidum. In PD, the reduced levels of striatal dopamine results in decreased excitation of striatal neurons expressing D1 receptors (direct pathway) and decreased inhibition of striatal neurons expressing D2 receptors (indirect pathway) (Obeso et al., 2008) with an overall effect of excessive inhibitory output from the basal ganglia.

In addition to the direct and indirect pathways through the striatum, a cortico-subthalamo-pallidal "hyperdirect" pathway exists which bypasses the striatum and conveys strong excitatory signals from the motor cortex to GPi and SNr with shorter conduction times than the direct and indirect pathways (Nambu, Tokuno, & Takada, 2002). Because the cortico-subthalamic projections of the hyperdirect pathway bypass the striatum, some consider the subthalamic nucleus (STN) to be an additional input station of the basal ganglia (Mink & Thach, 1993; Nambu et al., 2000). STN sends glutamatergic, excitatory projections to the pallidum, therefore activation of the hyperdirect pathway results in increased inhibitory pallidal output. In PD, the STN is overactive leading to excessive inhibitory activity of the GPi and SNr (Obeso et al., 2008). It was shown, that when dopamine terminals directed to the STN are blocked, the firing rate of the STN increases (Kreiss, Anderson, & Walters, 1996).   Blockade or lesioning of the STN in a dopamine-depleted state has been shown to improve basal ganglia and thalamocortical function (Guridi et al., 1996; Trost et al., 2006).

1.3 The motor and cognitive signs of Parkinson's disease

There is no definitive test for the diagnosis of PD. Diagnosis must be made based upon the clinical features exhibited. The recommended diagnostic criteria, as set forth in the UK Parkinson's disease society brain bank clinical diagnostic criteria (Hughes, Daniel, Kilford, &

Lees, 1992), states that a diagnosis of PD can be made if the patient exhibits bradykinesia and exhibits at least one of the following signs: muscular rigidity, 4-6 Hz rest tremor, and/or postural instability not caused by visual, vestibular, cerebellar, or proprioceptive dysfunction. In addition to these 4 cardinal signs of PD- bradykinesia, resting tremor, rigidity (Lees et al., 2009), and postural instability (Jankovic, 2008)- patients may also experience other motor symptoms such as hypomimia, dysarthria, dysphagia, micrographia, gait dysfunction, and dystonia (Jankovic, 2008).   Although once considered to be purely a movement disorder, it is now known that patients with PD exhibit several non-motor symptoms such as executive impairment, apathy, anxiety, depression, and sensory symptoms (eg, pain and tingling) (Rodriguez-Oroz et al., 2009) as well as sleep disorders, hallucinations, and dementia (Chaudhuri, Healy, Schapira, & Excellence, 2006).

1.3.1 Cardinal signs

1.3.1.1 Bradykinesia

Bradykinesia, the hallmark symptom of PD, refers to slowness of movement and leads to difficulty with the planning, initiating, and executing of self-paced movements (Berardelli, Rothwell, Thompson, & Hallett, 2001). It is thought that bradykinesia arises from abnormal motor cortex activity stemming from dysfunctional basal ganglia output due to striatal dopamine depletion (Berardelli et al., 2001; Jankovic, 2008). During simple repetitive movements, speed is reduced, latency between movements in increased, and the amplitude of movement progressively reduces until movement stops completely (Marsden, 1982). Patients tend to perform motor tasks better with an external trigger (eg, audio or visual cues) compared to performing internally

generating movements, thus it has been argued that patients with PD have intact motor programs but are impaired at accessing the programs (Jankovic, 2008; Rodriguez-Oroz et al., 2009). Further, imaging studies have shown that patients performing externally-guided motor tasks exhibit reduced recruitment of cortical and subcortical structures involving movement kinetics and kinematics (Spraker, Prodoehl, Corcos, Comella, & Vaillancourt, 2010; Turner, Grafton, McIntosh, DeLong, & Hoffman, 2003), yet increased activation of cortical structures involving the visuomotor system (Turner et al., 2003).

1.3.1.2 Rigidity

Rigidity is defined as the resistance to passive movement (Baradaran et al., 2013). It is independent of velocity and direction of movement (Delwaide, 2001). It can be constant in nature ("lead pipe") or manifest as jerky resistance to passive movement ("cog-wheel"), and is often associated with pain (Stamey, Davidson, & Jankovic, 2008). The physiological origin is unknown but increased supraspinal facilitation, excessive spinal cord excitability, and disinhibition of brainstem mechanisms have all been suggested as likely factors underlying the pathophysiology of rigidity (Rodriguez-Oroz et al., 2009). Further insight comes from the clinical application of the Froment's maneuver: when patients are asked to make a voluntary movement with the opposite limb, rigidity often increases (or latent rigidity is unmasked) in the tested limb. This finding suggests that the underlying cause of rigidity involves a system-level, distributed brain network mechanism (Baradaran et al., 2013).

1.3.1.3 Tremor

Tremor is defined as involuntary, rhythmic, and alternating movements of one or more

body parts (Abdo, van de Warrenburg, Burn, Quinn, & Bloem, 2010). Only 3 out of 4 patients

with PD present with tremor (Helmich, Hallett, Deuschl, Toni, & Bloem, 2012). Parkinsonian

tremor has an oscillation frequency between 4-9 Hz (Deuschl, Bain, & Brin, 1998). The classic

form (type I) of PD tremor, rest tremor, is frequently seen in the extremities (ie "pill-rolling" of

the hands) but can also involve the lips, chin, jaw, and legs (Jankovic, 2008). Rest tremor

subsides with muscle contraction but may reemerge at the same frequency while the patient is

holding a posture. Some patients also present with a second type of postural and kinetic tremor

(type II) which by definition oscillate at > 1.5 Hz relative to the rest tremor frequency and are

considered to be under a separate classification than re-emergent tremor (Deuschl et al., 1998).

Less than 10% of patients with PD present with type II postural and kinetic tremors (Helmich et

al., 2012). It has been suggested that tremor arises from 2 separate circuits: the basal ganglia

which triggers the tremor episodes, and the cerebello-thalamo-cortical circuit which produces the

tremor (Helmich et al., 2012). It has also been shown that patients with prominent tremor have

degeneration of a subgroup of midbrain (A8) neurons. This degeneration is not evident in

patients who do not have tremor (Jankovic, 2008).

1.3.1.4 Postural instability

Loss of postural reflexes typically occurs in the later stages of PD (Jankovic, 2008).

Ninety-six percent of patients with PD experience postural instability (Klawans & Topel, 1974).

One study showed that 38% of patients fall; 13% of those patients fall on a weekly basis, 13%

experience fractures, 18% are hospitalized, and 3% are wheelchair-bound (Koller, Glatt, Vetere-Overfield, & Hassanein, 1989). It has been shown that patients with PD have difficulties adapting to altered support conditions (Horak, Nutt, & Nashner, 1992). Lack of postural stability may be due partially to impaired somatosensory feedback mechanisms (Demirci, Grill, McShane, & Hallett, 1997) and partially to motor dysfunction (Bronte-Stewart, Minn, Rodrigues, Buckley, & Nashner, 2002). Sensory organization issues related to postural instability may be due to incoherent firing patterns of the GPi, and motor impairment underlying instability may be due to the increased firing rate of Gpi (Bronte-Stewart et al., 2002).

1.3.2 Cognitive symptoms

Cognitive impairment in PD ranges from mild impairment in the early stages of the disease to dementia in the advanced stages (Hely, Morris, Reid, & Trafficante, 2005; Jankovic, 2008; Rodriguez-Oroz et al., 2009). A longitudinal population-based study found that 30% of newly diagnosed patients with PD (n=88) had deficits in cognitive function (Elgh et al., 2009). Patients with PD have almost a sixfold increased risk for dementia (Aarsland et al., 2001). It has been shown that patients with PD have impaired performance on tasks that require planning and problem solving (Owen et al., 1992; Taylor, Saint-Cyr, & Lang, 1986), shifting attentional set (Cools, Barker, Sahakian, & Robbins, 2001; Owen et al., 1992), suppression of prepotent or habitual responses (Dirnberger, Frith, & Jahanshahi, 2005; Taylor et al., 1986), visuospatial processing (Levin et al., 1991), and dual-task processing (Brown & Marsden, 1991). Studies investigating whether side and type of initial motor symptoms are related to cognitive symptoms have found conflicting results. One study found that patients who initially presented with tremor

on the right-side have been shown to be cognitively spared (Katzen, Levin, & Weiner, 2006).

However, another study found that there was no relation of cognition to side and symptom

presentation yet patients who initially presented with tremor on the right side had a lower risk for

developing depressive symptoms (Dewey et al., 2012).

There is a correlation between the loss of dopaminergic neurons in the caudate and the

degree of dementia in patients with PD (Rinne, Rummukainen, Paljärvi, & Rinne, 1989).

Disrupted frontostriatal processes, secondary to striatal dopamine depletion, is a likely

mechanism responsible for cognitive impairment and dementia in PD (Owen, 2004). Compared

to healthy controls, it has been shown that patients show underactivation in the caudate,

putamen, and globus pallidus during execution of a working memory task (Marklund et al.,

2009). Further, patients with executive deficit reveal underactivation in the striatum and frontal

cortex during a working memory task compared to patients without executive deficit (Lewis,

Dove, Robbins, Barker, & Owen, 2003). In addition to frontostriatal dysfunction, dopamine

depletion of the mesocortical pathway may be a cause of cognitive deficit as well. It has been

shown that L-dopa modulates activity in the prefrontal cortex during working memory tasks and

does not change the activity of the basal ganglia nuclei (Cools, Stefanova, Barker, Robbins, &

Owen, 2002; Mattay et al., 2002). However, a study investigating synaptic dopamine levels

during a spatial working memory task showed significantly attenuated dopamine release in the

dorsal caudate in PD, but preserved levels of medial prefrontal dopamine release suggesting that

the mesocortical pathway was in tact in PD (Sawamoto et al., 2008).

1.4 Medication and DBS as treatments for Parkinson's disease

Parkinson's disease is a chronic, neurodegenerative disease with no known cure. Drug treatments and surgical procedures are aimed at reducing the symptoms and improving quality of life by increasing dopamine stimulation, or reducing cholinergic or glutamatergic stimulation (Rascol, Goetz, Koller, Poewe, & Sampaio, 2002). Initially, PD symptoms are managed with medication, but prolonged drug therapy leads to disabling motor side effects and wearing off periods. When medication is no longer effective at managing symptoms, deep brain surgical procedures may be implemented.

1.4.1 Medication

Levodopa, in combination with carbidopa, is considered the gold standard for PD treatment (Clarke & Guttman, 2002; Lees et al., 2009). Levodopa is an amino acid precursor of dopamine that is converted to dopamine by DOPA decarboxylase. Carbidopa is a peripheral dopa decarboxylase inhibitor that prevents the conversion of levodopa in peripheral tissues and enhances the delivery of dopamine to central nervous tissues. Individual patients have a variable response to levodopa, but motor symptoms initially improve by 20-70% (Lees et al., 2009). Levodopa reduces fatigue, bradykinesia, and rigidity, and it improves gait (Fahn et al., 2004). Speech, swallowing, and postural instability are also improved by levodopa initially (Hely, Reid, Adena, Halliday, & Morris, 2008), yet tremor can be more difficult to treat (Lees et al., 2009). There has been some evidence to suggest that levodopa may be toxic to dopaminergic neurons, but this is debatable and may be due to misinterpreted findings from imaging studies (Clarke & Guttman, 2002) and/or experimental procedures (Mytilineou, Walker, JnoBaptiste, & Olanow,

2003). It is clear that long-term use of levodopa leads to response fluctuations (end-of-dose deterioration and unpredictable on/off fluctuations) and dyskinesias (involuntary choreoathetoid and dystonic movements). Dopamine agonists (apomorphine, cabergoline, pergolide, pramipexole, and ropinirole), although not as efficacious as levodopa, improve motor symptoms and delay the onset of dyskinesias, and are therefore frequently used in early PD to delay the need for levodopa (Clarke & Guttman, 2002). However, dopamine agonists may also cause negative side effects such as gastrointestinal and psychiatric problems, ankle edema, sleep attacks, and impulse-control disorders (Lees et al., 2009). Dopamine transmission enhancers (monoamineoxidase-B (MAO-B) and catechol-O-methyltransferase (COMT) inhibitors) are effective at reducing PD symptoms when prescribed as monotherapy and are also used in conjunction with levodopa to enhance and extend the therapeutic effect allowing for a reduction in levodopa dosage (Kaakkola, 2000; Mínguez-Mínguez, Solís-García Del Pozo, & Jordán, 2013). Amantadine, an antiglutamatergic, is an effective adjuvant to levodopa and markedly reduces levodopa-induced motor complications (Verhagen Metman et al., 1998). Anticholinergics (benzhexal, orphenadrine, benztropine, bornaprine, benzapryzine, and methixine) are useful for managing tremor but frequently have adverse psychiatric and cognitive effects (Katzenschlager, Sampaio, Costa, & Lees, 2003). Levodopa also has been shown to have adverse cognitive effects, yet it improves certain aspects of cognition as well: it impairs cognitive functions that require facilitating or suppressing actions (Frank, 2005; Growdon, Kieburtz, McDermott, Panisset, & Friedman, 1998; Morrison, Borod, Brin, Hälbig, & Olanow, 2004), yet it improves cognitive deficits involved with implicit learning (Frank, Seeberger, & O'reilly, 2004). Further, levodopa has been shown to have no adverse or beneficial effects on attention, language, visuospatial processing, or memory (Morrison et al., 2004).

1.4.2 Surgery

Surgical options for treating PD symptoms include lesioning, grafting, and stimulation. Although rarely used today, thalamotomy may be performed unilaterally to reduce contralateral tremor in tremor-predominant PD, and pallidotomy may be performed either unilaterally or bilaterally (Favre, Burchiel, Taha, & Hammerstad, 2000) to the GPi to reduce tremor, bradykinesia, rigidity, and levodopa-induced dyskinesias (Uitti, 2000). Although lesioning can be effective at reducing PD symptoms, the procedure involves permanent destruction of neural tissue and has become less popular with the advent of stimulation techniques. Grafting involves transplantation of dopaminergic neurons derived from human embryonic tissue into the striatum of PD patients. There has been some evidence that suggests this may be an effective surgical procedure in the future, but the technique needs refinement before it can successfully be performed on a large series of patients (Brundin, Barker, & Parmar, 2010). High frequency stimulation of specific basal ganglia nuclei is currently the most sought after surgical procedure for managing PD symptoms. Stimulators may be implanted in the ventral intermediate nucleus of the thalamus (VIM), the GPi, or the subthalamic nucleus (STN). VIM stimulation is effective at reducing tremor, but has no effect on bradykinesia or rigidity and is therefore mainly performed on patients with essential tremor rather than PD patients (Lozano, 2000). Both GPi and STN deep brain stimulation (DBS) have been shown to be effective at improving all cardinal signs of PD (Follett et al., 2010; Moro et al., 2010). In two patients, it was found that GPi DBS was not as effective as STN DBS in the long-term (Houeto et al., 2000). Additionally, STN DBS has been shown to have more beneficial effects on symptoms and quality of life than GPi DBS (Odekerken et al., 2013), and patients with STN DBS require less dopaminergic medication than patients with GPi DBS (Follett et al., 2010; Moro et al., 2010). Although STN DBS is a

common surgical procedure being performed for PD (Kleiner-Fisman et al., 2006), there is evidence that STN DBS may negatively affect certain aspects of cognition (Okun et al., 2009; Zahodne et al., 2009) and mood (Follett et al., 2010; Okun et al., 2003). The debate is ongoing whether STN or GPi is the better target, and some have suggested that the decision should be made on an individual basis based upon specific patient symptoms (Follett et al., 2010). The remainder of this summary will focus on the effects STN DBS on motor function and cognition.

1.4.2.1 Effects of STN DBS on motor control

STN DBS dramatically improves bradykinesia, rigidity, and tremor. It was shown that STN DBS improves scores on the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) by 60% in the off-medication state one year after surgery (Limousin et al., 1998) and by 54% 5 years after surgery (Krack et al., 2003). On average, patients are able to reduce their levodopa requirements by 55.9% and show marked reduction in levodopa-induced dyskinesias after surgery (Kleiner-Fisman et al., 2006). Additionally, STN DBS reduces the average duration of "off" periods and increases the duration of "on" periods without dyskinesias (Pinter et al., 1999). Although some measures of gait (Limousin et al., 1998) and postural instability (Shivitz, Koop, Fahimi, Heit, & Bronte-Stewart, 2006) are improved with STN DBS, STN DBS does not improve postural instability and gait as consistently as it does bradykinesia, rigidity, and tremor (St George, Nutt, Burchiel, & Horak, 2010). Whereas STN DBS improves movement amplitude during gait (Johnsen, 2011), it may impair anticipatory postural preparation for step initiation (Rocchi et al., 2012). Furthermore, it was shown that there is a slight loss of the initial stimulation-induced motor improvement 10 years after surgery, and most of the decline is related to a progressive loss of benefit of axial symptoms (Castrioto et al., 2011).

There is some evidence to suggest that chronic stimulation may have neuroprotective benefits. In one study, ankle strength was tested while patients were off treatment (off medication and stimulation) after 5 years of chronic stimulation, and it was found that peak velocity and peak torque were both improved compared to baseline measurements (Sturman, Vaillancourt, Metman, Bakay, & Corcos, 2010). Another study showed that untreated PD UPDRS motor scores did not change for up to 5 years after surgery, suggesting that there was no progression of motor severity (Tagliati, Martin, & Alterman, 2010).

1.4.2.2 Effects of STN DBS on cognition

STN DBS offers improvements as well as detrimental effects. It has been shown to result in deterioration in speech intelligibility (Tripoliti et al., 2011), emotional disturbances (ie. depression, apathy, manic episodes)(Witt, Daniels, & Volkmann, 2012), and impairment in certain cognitive domains. This section will expand upon the known effects of STN DBS on aspects of cognition.

Although STN DBS is implemented to balance the activity of the motor circuit by altering basal ganglia output from the Gpi, STN projections to the substantia nigra pars reticulata (SNr) are likely affected as well (Jahanshahi et al., 2000; Limousin et al., 1997). The dorsolateral prefrontal cortex (DLPFC), which is known to be involved in executive functions and working memory, is a target of the thalamic projection from the SNr (Barbas, Henion, & Dermon, 1991). It is thought that STN DBS may affect cognition via its direct effect on basal ganglia output as well as its indirect effect on cortical areas such as the DLPFC (Jahanshahi et al., 2000). Indeed it has been shown that STN DBS alters executive function and working memory processes, but findings across studies have been somewhat inconsistent showing both

beneficial and detrimental effects (Alegret et al., 2001; Daniele et al., 2003; Pillon et al., 2000; Witt et al., 2004). The most common and consistently reported cognitive effect of STN DBS is impairment in verbal fluency (Halpern, Rick, Danish, Grossman, & Baltuch, 2009; Massano & Garrett, 2012; Schroeder et al., 2003). Additionally, studies have consistently shown STN DBS to impair response inhibition (Campbell et al., 2008; Frank, 2006; Ray et al., 2009; Witt et al., 2004). Interestingly, impaired performance on a working memory task during STN DBS has been shown to be accompanied by an *increase* in regional cerebral blood flow to the DLPFC (Campbell et al., 2008); impaired performance on a verbal fluency task during STN stimulation has been shown to be accompanied by *decreased* regional cerebral blood flow to the right orbitofrontal cortex, the left inferior temporal gyrus, and the left inferior frontal/insular cortex (Schroeder et al., 2003); and impaired performance on a response inhibition task has been shown to be accompanied by an *increase* in blood flow to the anterior cingulate cortex (ACC)(Campbell et al., 2008). Thus, it appears that STN DBS increases blood flow to some cortical areas and reduces it to others, and this variable effect on cerebral blood flow gives rise to its differential effects on various cognitive functions.

1.4.2.3 Unilateral vs. bilateral STN stimulation

Bilateral STN stimulation improves motor function considerably more than unilateral stimulation and therefore is considered the "gold standard" treatment for medically intractable PD symptoms (Kumar, Lozano, Sime, Halket, & Lang, 1999; Park et al., 2012). Frequently, patients begin with unilateral STN DBS, and then opt to undergo surgery for the second stimulator at a later time. The most common reason patients with unilateral STN DBS undergo surgery for a second stimulator is the inadequacy of unilateral STN DBS to address motor

symptoms (Taba et al., 2010). One study followed highly asymmetric PD patients with unilateral STN DBS for 2 years and found that although unilateral stimulation effectively improved contralateral motor function, ipsilateral motor function progressively worsened to the point that all subjects (n=8) were considering bilateral STN DBS at the end of the two years (Kim et al., 2009).

In a study assessing the effects of bilateral and unilateral STN DBS 6-18 months after surgery (n=19), bilateral STN DBS improved the mean total Unified Parkinson's Disease Rating Scale motor score by more than 54%, and unilateral STN DBS only improved the motor scores by 23% (Kumar et al., 1999). The additive effects of bilateral stimulation are not seen for all measures of motor control. Whereas bilateral STN DBS improves walking speed and stride length to a greater degree than unilateral STN DBS, it has been shown that bilateral STN DBS does not afford additional improvements in speed during reaching to a target compared to unilateral STN DBS (Bastian, Kelly, Revilla, Perlmutter, & Mink, 2003). Due to these findings, the authors speculated that the basal ganglia may influence walking through bilateral projections to pedunculopontine nuclei and reaching through ipsilateral thalmocortical projections (Bastian et al., 2003).

Although bilateral STN DBS offers greater benefits to overall motor function than unilateral STN DBS, it appears that unilateral may be more beneficial during certain cognitive tasks. While performing a cognitive test (n-back task) and a motor task (upper extremity force-tracking) simultaneously under complex conditions, it was shown that patients performed significantly better under unilateral STN DBS (stimulation to more affected side of the brain) compared to bilateral STN DBS in both the cognitive and force tasks (Alberts et al., 2008). However, another study compared the effects of unilateral to bilateral stimulation during

performance of a working memory task. It found that unilateral stimulation of the more affected

side of the brain induced impaired performance in working memory function and that there was

no difference of effects on working memory between unilateral STN DBS and bilateral STN

DBS (Hershey et al., 2008). It is currently unclear whether unilateral stimulation is more

beneficial than bilateral stimulation for cognitive performance. More comparative studies are

necessary to understand these effects.

1.5 STN and Parkinson's disease

Studies have shown that the firing pattern of STN in people with Parkinson's disease is

hyperactive and is described as having increased oscillatory and synchronized activity (Hamani,

Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004; Magill, Bolam, & Bevan, 2001; Magnin, Morel, &

Jeanmonod, 2000). Results of single-unit analyses suggest that the mean firing rate of the STN

in PD is elevated (Bergman, Wichmann, Karmon, & DeLong, 1994; Magnin et al., 2000; Parr-

Brownlie et al., 2007). Additionally, several studies investigating local field potentials (LFP) of

the STN show abnormal oscillatory patterns in PD. The parkinsonian STN exhibits

characteristic oscillatory activity in the 2-7 Hz (Giannicola et al., 2013; Priori et al., 2004), 4-10

Hz (2001), and 13-30 Hz (Brown et al., 2001; Marceglia et al., 2006; Priori et al., 2004)

frequency bands. The 2-7 Hz band has been shown to be correlated with clinical status, as

measured by the motor subsection of Unified Parkinson's Disease Rating Scale (UPDRS III)

(Giannicola et al., 2013); the 4-10 Hz firing rate is thought to be related to tremor, which

oscillates at 4-7 Hz in PD (Bergman et al., 1998; Brown et al., 2001; Hamani et al., 2004); and

the 13-30 Hz (peak ~ 20 Hz) band, commonly referred to as the beta band, has been suggested as

a possible contributor to bradykinetic movement in PD (Brown et al., 2001; Burgess et al., 2010; Eusebio, Cagnan, & Brown, 2012; Little, Pogosyan, Kuhn, & Brown, 2012).

1.5.1 Effect of dopaminergic medication on firing rate and oscillatory activity of the STN

It has been proposed that dopaminergic medication suppresses pathological STN activity. The effect of dopaminergic medication on firing rate is less clear than the effect on oscillatory patterns. It has been shown that dopaminergic medication reduces the firing rate of STN neurons in PD patients undergoing DBS surgery (Levy et al., 2002); yet experiments with hemiparkinsonian rhesus monkeys revealed that dopamine had no effect on firing rate (Gilmour et al., 2011). The administration of levodopa medication results in an increase in power in the 2-7 Hz frequency band, and this increase is correlated with clinical improvement (Giannicola et al., 2013; Priori et al., 2004). It was postulated that the increased power in this band following levodopa intake is due to an increase in synchrony between single STN neurons and their projections (Priori et al., 2004). In contrast to these findings, Brown and colleagues found that levodopa treatment induced a reduction in power for all frequencies less than 30 Hz, including the very low frequencies, and an increase in power for the 60-90 Hz band (Brown et al., 2001). It has also been shown that dopaminergic medication induces an increase in power in the 150-200 Hz (Kane, Hutchison, Hodaie, Lozano, & Dostrovsky, 2009) and 300-400 Hz bands (Litvak et al., 2012). Power in the 60-90 Hz and 300-400 Hz bands is associated with voluntary movement (Litvak et al., 2012). Litvak et al. found that an increase in power in these bands after ingestion of levodopa was correlated with improvement of bradykinesia and rigidity. Therefore,

these findings support the idea that levodopa may improve bradykinesia by dampening pathological beta activity and amplifying higher frequency activity necessary for voluntary movement.

Interestingly, when the beta band is divided into low- (13-20 Hz) and high- (20-35 Hz) beta bands, it has been shown that levodopa reduces activity in the low- but not high-beta band (Priori et al., 2004). It was also discovered that the low- and high-beta bands are abnormally correlated in a non-linear manner- that is, they are abnormally "synchronized". After dopaminergic treatment, the non-linear correlation between the low and high bands is significantly reduced (Marceglia et al., 2006). It was concluded that, in the absence of medication, the low-beta band harmonically distorts the high-beta band. Levodopa removes this distortion and restores segregation of the signals and/or segregation of the functional units generating these rhythms (Marceglia et al., 2006).

Thus, there is evidence to suggest that levodopa may help to improve parkinsonian symptoms by modifying oscillatory output of the STN- specifically, increasing power in the 2-7 Hz band and attenuating beta frequency oscillations. The question then emerges- does STN DBS work via similar mechanisms?

1.5.2 STN stimulation

1.5.2.1 Effect of high-frequency stimulation on firing rate and oscillatory activity of the STN

Studies have shown that high-frequency STN DBS reduces the mean firing rate and alters oscillatory patterns recorded from the STN. Welter et al. (2004) recorded single-unit STN

activity and showed that the mean firing rate of cells in PD patients was reduced by 77% during stimulation of the (ipsilateral) STN at a frequency greater than 40 Hz. Further, it was shown that ipsilateral as well as contralateral high-frequency STN DBS suppressed STN firing rate (Toleikis et al., 2012). One explanation for why STN DBS reduces STN neuronal activity is that neuron stimulation depolarizes the cell membrane and inactivates sodium channels (Beurrier, Bioulac, Audin, & Hammond, 2001). It has also been proposed that DBS may activate inhibitory afferents of the stimulated nucleus which would then result in reduced neuronal activity (Dostrovsky et al., 2000). Whereas DBS appears to inhibit neuronal cell body activity- either directly by inactivating sodium channels or indirectly by activating inhibitory afferents- it simultaneously stimulates the output of local STN neurons by initiating action potentials in the efferent axons (Grill, Snyder, & Miocinovic, 2004). It has been shown that nuclei receiving STN efferents exhibit increased activity during stimulation (Hashimoto, Elder, Okun, Patrick, & Vitek, 2003). This finding does not explain why DBS improves motor function, for the increased activity of the basal ganglia output structures (ie. GPi, SNr) would indicate increased inhibitory output. It follows that single unit analysis provides some useful information about the mechanisms underlying DBS, yet it does not explain the effects of DBS on motor function. The mechanisms underlying the efficacy of DBS are likely more complex than simple neuronal activations/inhibitions (Rosa et al., 2012).

As an alternative to single unit analysis, local field potential (LFP) recordings allow investigators to study the changes in network rhythms due to DBS. Several LFP studies have shown that STN DBS alters oscillatory patterns. Similar to levodopa, stimulation of the STN at 130 Hz results in an increase in activity in the 2-7 Hz band that is correlated with improved motor control (Giannicola et al., 2012). The functional significance of this effect is unclear. As

mentioned in the above medication discussion, the increased power may be indicative of augmented synchrony between STN neurons and those to which they project. Although levodopa and stimulation have similar effects on oscillations in the 2-7 Hz band, levodopa appears to have a more drastic effect than STN DBS in modifying power in the 8-20 Hz frequency range (alpha and beta oscillations). In a study of 9 PD patients with bilateral STN DBS, levodopa abolished the 8-20 Hz oscillatory power while in the off-stimulation condition in all patients tested (Giannicola et al., 2010). In contrast, DBS in the off-medication condition attenuated, but did not abolish, power in this band in only 5 of the 9 patients. Perplexingly, in 1 of the 9 patients DBS evoked an increase in power in the 8-20 Hz band. Despite the heterogeneous oscillatory results of DBS, all patients showed clinical improvement during testing after STN DBS was turned on. Improved clinical status after STN DBS, therefore, is not achieved by the attenuation of low-frequency (alpha/beta) oscillations alone. The results from this study suggest it is not even a requisite for improving clinical symptoms.

1.5.2.2 Effect of low-frequency STN stimulation on motor behavior

The finding that a reduction in STN neuronal beta activity is not imperative for motor improvement is interesting since studies have found that the pathological synchronous activity recorded from the STN in patients with DBS occurs at 20Hz (Brown et al., 2001; Cassidy et al., 2002; Priori et al., 2004). Several additional experiments were conducted to test the effects of STN stimulation at 20Hz. The studies were designed on the premise that if impaired motor output was due to excessive synchrony at low-frequencies, in particular 20 Hz, it should follow that stimulating the STN at 20 Hz would result in reduced motor output. Indeed, it was

discovered that STN stimulation in patients with PD at 5 and 20 Hz is related to increased

movement time in a tapping task relative to no stimulation, and STN stimulation at 5 and 10 Hz

increases the variability of tap intervals (Eusebio & Brown, 2007; Fogelson et al., 2005).

Additionally, stimulation at 10 and 25 Hz has also been shown to increase movement time in a

tapping task (Fogelson et al., 2005). When the STN in non-parkinsonian rodents and primates is

stimulated at 23 Hz (the frequency at which parkinsonian monkeys have exhibited altered STN

output), motor control is unaffected (Syed et al., 2012). An explanation for this finding may be

that excessive synchrony at 23 Hz is processed differently by the non-parkinsonian basal ganglia

compared to basal ganglia with dopamine depletion. It follows that excessive low-frequency

synchronous activity does not appear to be the sole mechanism underlying impaired basal

ganglia function. Rather it is more probable that the excessive beta activity is just one factor in a

complex pathophysiology.

1.5.2.3 Deep brain stimulation may create an informational lesion

Another theory to explain the mechanisms underlying the efficacy of STN DBS is that

high-frequency stimulation creates an informational lesion in the output signal of the STN (Grill

et al., 2004). Grill et al. showed that DBS produced frequency-dependent modulation of the

variability of neuronal output. Lower-frequency stimulation resulted in a superposed signal of

the external stimulation and the intrinsic activity of the neuron resulting in an increased

coefficient of variation of the output signal. In contrast, stimulation at frequencies that were

higher than the intrinsic activity of the neurons masked the intrinsic activity of the neurons and

decreased the coefficient of variation to zero. Information content of the output signal is related

to the variability of the signal. Abolishing the variation of the signal eliminates the information content of the signal. Therefore, there is evidence to support that high-frequency STN DBS helps to regulate basal ganglia function by eliminating the pathological information generated by the STN.

1.5.2.4 Effect of STN DBS on cortical activity

It has been shown that STN DBS induces metabolic changes in subcortical and cortical areas. Whether the effect on cortical areas is due to altered thalamic activity via the pallidal-thalamic-cortical pathway or directly via antidromic activation of STN afferents from the cortex is not known. Many cortical areas are hyperactive in the resting state in patients with PD. STN DBS has been shown to reduce regional cerebral blood flow (rCBF) in frontal (Ceballos-Baumann et al., 1999; Hershey et al., 2003; Payoux et al., 2004; Trost et al., 2006) and temporal (Hershey et al., 2003) cortices during rest indicating that STN DBS helps to normalize resting cortical activity (Ceballos-Baumann et al., 1999; Hershey et al., 2003). Further, it has been shown that unilateral STN DBS reduces rCBF in ipsilateral primary sensorimotor cortex and lateral premotor cortex during rest (Payoux et al., 2004). In contrast, STN DBS has also been shown to increase metabolic activity in certain cortical areas. Sestini et. al (2002) showed that bilateral STN DBS increases rCBF in the dorsolateral prefrontal cortex (DLPFC), pre-supplementary area (pre-SMA), and the anterior cingulate cortex (ACC). Interestingly, Hershey et. al (2003) studied patients with bilateral STN DBS and found that blood flow decreased in the parietal cortex bilaterally when both stimulators were on, but Trost et. al (2006) studied patients with unilateral STN DBS and found that ipsilateral parietal metabolism increased. The reported

findings regarding the effects of STN DBS on parietal metabolism suggest that further investigation is warranted to distinguish between the effects of unilateral versus bilateral STN DBS.

In addition to changes in cortical metabolism during rest, STN DBS has also been shown to alter metabolism during movement. Ceballos-Baumann et al. (1999) investigated the effects of STN DBS while patients moved a joystick with their contralateral hand and found that unilateral stimulation increased rCBF in the ipsilateral supplementary motor area (SMA) and premotor cortex. Similarly, Payoux et. al (2004) found that unilateral stimulation increased metabolism in the anterior cingulate cortex and primary sensorimotor cortex during hand movements. The authors posited that the increase was actually secondary to the reduction of abnormal resting overactivity induced by STN DBS - that the reduction in overactivity of the motor system elicited by STN DBS allows for selective cortical activation during movement. In a study directly comparing unilateral STN DBS during contralateral joy stick movements to bilateral STN DBS during the same movement, it was shown than bilateral STN DBS increased rCBF in the ACC and SMA to a greater extent than unilateral STN DBS (Strafella, Dagher, & Sadikot, 2003).

Chapter 2: Control of saccadic eye movements and therapeutic efficacy

In this Chapter, we first outline the neural circuitry of saccadic eye movements and the role of the basal ganglia in initiating and inhibiting saccadic eye movements. Second, we will review the role of the STN in saccadic control. We will then outline saccadic performance in Parkinson's disease and conclude with a review of the findings of the efficacy of DBS on saccades in patients with Parkinson's disease.

2.1 Neural circuitry of saccadic eye movements

Saccadic eye movements are critical for sampling the visual world. Saccades align the fovea of the retina with targets of interest. The fovea is a central area of the retina (1.2 mm diameter) that is most densely populated with cone photoreceptors (Purves, 2008). It serves the central 1° of visual field and provides the greatest visual acuity (Perry & Cowey, 1985). Six extra-ocular eye muscles control the movement of the eye: superior rectus, inferior rectus, medial rectus, lateral rectus, superior oblique, and inferior oblique. These muscles are innervated by cranial nerves III, IV and VI which arise from the midbrain and pons (Purves, 2008). The motor neurons in these cranial nerve nuclei discharge a burst of action potentials to the agonist muscles to generate a saccade while at the same time silencing action potential bursts to the antagonist muscles of that saccade. These agonist/antagonist motor neuron pulses are coordinated by excitatory and inhibitory premotor burst neurons located in the gaze centers in the brainstem. The excitatory and inhibitory burst neurons for horizontal eye movements are located in the paramedian pontine reticular formation. For vertical eye movements, the burst neurons are located in the rostral interstitial nucleus of medial longitudinal fasciculus. The gaze centers are

activated by the superior colliculus (SC) located in the midbrain. The superior colliculi consist

of several layers and are responsible for processing and integrating sensory and motor

information. The superficial layers of the SC have visual receptive fields for the contralateral

visual hemifield (Goldberg & Wurtz, 1972) and receive visual input from the retina and other

visual areas (Robinson & McClurkin, 1989). The intermediate layers of the SC contain saccade

and fixation neurons arranged in a two-dimensional motor-map which code for saccades directed

to the contralateral visual field (Mohler & Wurtz, 1976). The deep layers of the SC consist of

fibers which project to the premotor neurons of the gaze centers and are directly involved with

generating motor signals (Sparks & Hartwich-Young, 1989). The SC receives afferents directly

from the retina as well as several cortical areas including the visual cortex, lateral intraparietal

area (LIP), frontal eye field (FEF), supplementary eye field (SEM), and dorsolateral prefrontal

cortex (DLPFC) (Munoz & Wurtz, 1992). Additionally, the basal ganglia send inhibitory

GABAergic efferents to the SC via the substantia nigra pars reticulata (SNr). The convergence

of these multiple projections from cortical and subcortical areas onto the SC suggests that the SC

may be the "final common pathway" for purposive saccades (Hikosaka et al., 2000; Terao et al.,

2011).

The basal ganglia, in conjunction with cortical and brainstem structures, play an integral

role in initiating and inhibiting saccades.   Whereas cortical areas such as the frontal eye fields

(FEF), supplementary eye fields (SEF), and lateral intraparietal cortex (LIP) send excitatory

signals to the oculomotor neurons of the superior colliculus (SC), it is the direct and indirect

pathways of the basal ganglia that are responsible for selecting the appropriate cortical signals to

process (Hikosaka et al., 2000). In the absence of saccades, the substantia nigra pars reticulata

(SNr) tonically inhibits the saccadic burst neurons of the intermediate layer of the SC (Hikosaka

et al., 2000). When the direct pathway is engaged via the activation of D1 striatal dopamine receptors (Gerfen et al., 1990), the caudate nucleus conveys a transient inhibitory signal to the SNr. This results in disinhibition of the burst neurons of the SC. Once disinhibited, the SC is allowed to activate the appropriate saccadic premotor neurons in the brainstem (Sparks, 2002).

In contrast, there also exists an indirect pathway in which the output of the caudate nucleus (CN) is modified by the globus pallidus externus (GPe) and subthalamic nucleus (STN) with the overall result being *enhanced* inhibition of unwanted saccades (Hikosaka et al., 2000). GPe tonically inhibits the excitatory projections from the STN to the SNr. It is thought that when the indirect pathway is active, the caudate conveys an inhibitory signal to the Gpe that results in disinhibition of the STN. The disinhibited STN then excites the SNr, and the inhibition of saccades is enhanced. Direct connections from the GPe to the SNr have been found and are implicated in the indirect pathway as well (Smith & Bolam, 1991). It is unclear whether the direct and indirect paths work together or sequentially to control saccades. Working together, the direct and indirect pathways could suppress inappropriate movements and only allow select movements to occur (also referred to as lateral/surround inhibition). Working sequentially, the indirect pathway may inhibit movements during the preparation for a movement until the direct pathway selects and triggers the planned movement (Hikosaka et al., 2000).

2.2 The role of STN in saccadic control

There is strong evidence to support that the STN has an oculomotor role. In non-human primates, neurons related to fixation and saccade activity were located in the ventral STN (Matsumura, Kojima, Gardiner, & Hikosaka, 1992). The neurons exhibiting activity related to fixation were active during fixation at the target light and became silent when the target light

disappeared. The activity of saccade-related neurons was time-locked to saccade onset, yet the

greatest increase in spike frequency actually occurred after saccade onset (Matsumura et al.,

1992). Oculomotor-related neurons were located in the ventral portion of the human STN as

well (Fawcett et al., 2007; Fawcett, Dostrovsky, Lozano, & Hutchison, 2005). The oculomotor

neurons fired at 33 +/- 15 Hz, mostly responded to just one movement direction, and similar to

the primate findings, activity increased in these neurons mainly after saccade onset (Fawcett et

al., 2005). The finding that STN oculomotor neurons in both human and non-human primates

are active after saccade onset could suggest that the STN may be involved in sensory feedback or

modification of SNr activity and not necessarily responsible for saccade generation. However,

the same group later uncovered evidence supporting a role of STN in motor preparation (Fawcett

et al., 2007). Premovement potentials, analogous to the Bereitschafts/Readiness Potentials

recorded before limb movement, were recorded before both visually-guided and self-paced

saccades. Interestingly, the onset of the premovement potential for self-paced saccades was no

different than the potentials recorded before self-paced wrist extensions. The authors concluded

that the STN may be involved in motor preparation of both the eyes and limbs in a common

manner.

2.3 Saccade performance and Parkinson's disease

Saccades can be classified into 2 general groups: externally-guided and internally-

guided. In PD, externally-guided saccade generation is thought to be relatively preserved yet

internally-guided saccade generation is markedly impaired. The externally-guided saccade is

typically visually guided and is thought to be primarily reflexive. During a visually-guided

saccade task, the subject is simply required to look from a central visual fixation point to a peripheral visual target. Tasks involving internally-guided saccades include memory-guided saccades (MGS), anti-saccades (AS), and predictive saccades. Unlike externally-guided saccades, internally-guided saccades are considered to be more cognitively challenging. Both memory-guided and anti-saccades require the subject to inhibit a saccade to a visual stimulus and then make a saccade to a location using an internal spatial coordinate system rather than an external cue. During a predictive saccade task, subjects are required to use spatial and temporal memory to generate saccades to visual stimuli that are presented in two alternating locations at regular time intervals. Neurophysiological and lesion studies have revealed specific brain regions involved with the performance of these different tasks. Therefore, the deficits exhibited by patients with PD during these different tasks can lend further insight into how Parkinson's disease affects different brain regions.

2.3.1 Externally-guided saccades (Visually-guided saccades)

Visually-guided saccades are generated by the superior colliculus (SC) and rely on critical inputs to the SC from the parietal eye fields (PEF) of the posterior parietal cortex (Pierrot-Deseilligny, Milea, & Müri, 2004). During visually-guided saccade (VGS) tasks participants are asked to fixate on a central light until a target light is presented at which time they are instructed to make a saccade to the target. When the fixation light disappears at the same time as the target light comes on, it is referred to as a "Step" paradigm. When the fixation light is extinguished before the appearance of the target light, the paradigm is referred to as a "Gap" paradigm. And, if the fixation light remains illuminated while the target light comes on,

the paradigm is termed "Overlap". The type of task –step, gap, or overlap- presents different challenges to the oculomotor system.

The dynamics of fixation and saccade generation are processed in the SC which is modulated by several cortical inputs as well as basal ganglia activity via the SNr-SC pathway (Jiang, Stein, & McHaffie, 2003) and via projections from the SNr to the thalamus to the FEF (Hikosaka et al., 2000). Fixation-related cells in the superior colliculus (SC) are active during fixation and become silent when a saccade is generated (Munoz & Wurtz, 1992). Conversely, saccade- related cells of the SC are silent during fixation and become active during a saccade (Dorris, Paré, & Munoz, 1997). A saccade cannot be initiated until fixation activity is sufficiently diminished (Chambers & Prescott, 2010). Thus, altering the timing of the onset and offset of fixation and peripheral target stimuli in the different tasks (step, gap, and overlap) presents distinctive challenges to the oculomotor system.

Compared to saccades performed during the step and overlap tasks, saccades performed during a gap task have reduced latencies (time between the onset of the peripheral target and the onset of the saccade) (Reuter-Lorenz, Hughes, & Fendrich, 1991). This latency reduction is termed the "gap effect". It has been hypothesized that the time gap releases ocular fixation and facilitates premotor processes leading to the observed reduction in latency (Dorris et al., 1997). In support of this hypothesis, Dorris et. al showed that fixation-related cells reduce their activity and saccade-related cells show preparatory activity during the gap period (Dorris et al., 1997). Whereas an average saccade typically has latencies above 200 ms, the gap effect can elicit fast saccades with latencies below 200 ms (Roll, Wierzbicka, & Wolf, 1996) or even "express saccades" with latencies between 90-120 ms (Gezeck, Fischer, & Timmer, 1997). Express saccades are considered to be reflexive eye movements that depend on decreased activity of

collicular fixation cells and occur in a disengaged state of attention. The removal of the fixation

target in the gap task serves to reduce the activity of the fixation cells and exogenously

disengages attention (Sereno & Holzman, 1993). Although express saccades depend upon

reduced activity of collicular fixation cells, frontal areas such as the FEF influence the activity of

the fixation cells of the SC and therefore can influence the occurrence of express saccades. It has

been shown that lesions to the FEF result in increased frequency of reflex saccades with latencies

in the range of express saccades (Guitton, Buchtel, & Douglas, 1985).

2.3.1.1 Visually-guided saccade latency

It has been reported that people with Parkinson's disease have shorter (Briand, Strallow,

Hening, Poizner, & Sereno, 1999; Kingstone et al., 2002), longer (DeJong & Jones, 1971;

Müller, Wenger, Fertl, & Auff, 1994; Terao et al., 2011), and the same (Briand et al., 1999;

Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Gibson, Pimlott, & Kennard, 1987; Gurvich,

Georgiou-Karistianis, Fitzgerald, Millist, & White, 2007; Rivaud-Péchoux, Vidailhet, Brandel, &

Gaymard, 2007; van Koningsbruggen, Pender, Machado, & Rafal, 2009; van Stockum,

MacAskill, Anderson, & Dalrymple-Alford, 2008; van Stockum, MacAskill, & Anderson, 2012)

visually-guided saccade (VGS) latencies as non-PD controls. The contradictory findings may be

due to a variety of confounds including different experimental procedures and medication status.

A meta-analysis of 47 VGS studies showed that people with Parkinson's disease overall

have longer saccadic latencies (Chambers & Prescott, 2010). A sub-group analysis of these

studies further showed that this effect was strongest for experiments that utilized the Step

paradigm. The effect was less prominent for the Gap paradigm and nearly negligible for the

Overlap paradigm. Additionally, they proposed that target eccentricity has an effect on saccadic latency. Targets that were presented at smaller distances ($< 5°$) evoked a "hyperreflexive" response resulting in participants with PD having shorter latencies than controls. Targets with larger eccentricities ($> 20°$) resulted in longer latencies for patients relative to controls. Importantly, many of the included studies did not control for levodopa medication, and the effect of medication was not considered in their analysis.

Studies that tested PD patients in their off medication state showed that there was no significant difference between PD and control VGS latency (Briand et al., 1999; Gibson et al., 1987). Further, studies comparing VGS latency during off- versus on-medication states showed that levodopa *increased* VGS latency (Hood et al., 2007; Michell et al., 2006). It follows that the results of the meta-analysis (Chambers & Prescott, 2010), which suggest that patients have reduced VGS latencies compared to controls, may be confounded by the slowing effect of levodopa on VGS latency.

On the other hand, some studies have also shown that even when patients are on their anti-parkinsonian medication, patients make more express saccades (latencies between 90-120 ms) than healthy controls (Armstrong, Chan, Riopelle, & Munoz, 2002; Chan et al., 2005; van Stockum et al., 2008). The increased rate of express saccades may be due to an imbalance of the inhibitory basal ganglia outputs onto the SNr or due to changes in cortical processing involving suppression of reflexive saccades (van Stockum et al., 2008). Further, it has been shown that movements, such as walking (Morris, Iansek, Matyas, & Summers, 1996) and arm reaching (Majsak, Kaminski, Gentile, & Flanagan, 1998), are significantly improved when patients are provided visual cues. It has also been shown that patients react earlier and are more strongly influenced by visual stimuli than healthy controls (Praamstra, Stegeman, Cools, & Horstink,

1998). It has been speculated that the exaggerated motor response to visual stimuli in PD may be due to a compensatory mechanism whereby the parietal cortex exhibits increased activity as a result of the overactive inhibitory activity of the basal ganglia (McDowell, Dyckman, Austin, & Clementz, 2008; Samuel et al., 1997).

2.3.1.2 Visually-guided saccade gain

Similar to the apparently contradicting findings on VGS latency, the effects of Parkinson's disease on saccadic gain (ie. saccadic amplitude relative to the target) in visually-guided tasks is somewhat inconclusive as well. The amplitude of saccades relative to the target amplitude is referred to as saccadic gain and has been shown to be unaffected by Parkinson's disease in some studies (Briand et al 1999, Kingstone et al 2002) and hypometric in others (Chan et al., 2005; Gibson et al., 1987; Hood et al., 2007). The discrepancy in gain findings in the above studies is not easily explained by differences in experimental paradigm or target eccentricity- for even when the same paradigm (ie Gap) and similar eccentricities were implemented (Briand et al 1999 and Hood et al), results differed. If in fact patients with PD have deficits in performing visually-guided saccades, the impairment appears to be milder than the deficits reported for the performance of internally-guided saccades.

2.3.2 Internally-guided saccades

Similar to visually-guided saccades, internally-guided saccades require the oculomotor system to balance fixation and saccade activity of the SC, and this balance is achieved via basal

ganglia output and cortical input to the SC. Whereas the initiation of visually-guided saccades is mediated primarily by the parietal eye fields (PEF), internally generated saccades are triggered by the frontal eye fields (FEF) (Pierrot-Deseilligny et al., 2004). Further, certain tasks, such as the anti-saccade and memory-guided saccade tasks, also require inhibition of a reflexive saccade to a visual target before the internal generation of a saccade. The inhibition of a saccade to a visual target has been shown to be mediated by the DLPFC (Condy, Rivaud-Péchoux, Ostendorf, Ploner, & Gaymard, 2004). In general, the saccade areas recruited to generate visually-guided saccades are more active and additional prefrontal areas are recruited during internally-generated saccades (McDowell et al., 2008).

2.3.2.1 Anti-saccades (AS)

The anti-saccade task requires the participant to fixate on a central target until a peripheral target is illuminated at which time the participant performs a saccade in the opposite direction of the displayed target- to the displayed target's mirror image. The correct execution of this task involves two mechanisms: the inhibition of a reflexive saccade to the displayed target followed by the internal generation of a saccade to the opposite direction. Both of these mechanisms appear to be dysfunctional in Parkinson's disease. Patients have difficulty inhibiting reflexive saccades as is evident by an increased rate of erroneous prosaccades to target (Briand et al 1999, Chan et al 2005, Hood et al 2007, Ridder 1997, Crevits and DeRidder 1997, Amador 2006, Armstrong 2002). Patients also exhibit slower AS latencies (Briand et al., 1999; Chan et al., 2005; Hood et al., 2007) and reduced gain (Armstrong et al., 2002; Briand et al., 1999; Hood et al., 2007); (van Stockum et al., 2012) revealing a dysfunction in the internal

generation of saccades. Levodopa has been shown to reduce the rate of erroneous prosaccades to target but also to reduce gain in AS tasks (Hood et al 2007).

The increased rate of erroneous prosaccades to target is most likely due to an impairment in suppressing saccade-related SC neurons (Terao et al., 2011). Along with most other areas involved with saccade generation, the SC receives direct input from the FEF and DLPFC (Selemon & Goldman-Rakic, 1988). Although it has been shown that the FEF is active before the execution of an anti-saccade, studies have shown that lesions of the FEF do not affect the percentage of erroneous prosaccades (Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Rivaud, Müri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994). In contrast, it has been shown that unilateral lesions of the DLPFC result in a bilateral increase in the percentage of erroneous prosaccades (Pierrot-Deseilligny et al., 2003). Furthermore, it is known that the basal ganglia is also intricately involved with the inhibition of saccade-related cells of the SC (Hikosaka et al., 2000). To determine whether inhibition of reflexive saccades was related to basal ganglia activity, Condy et. al 2004 investigated the effects of basal ganglia, thalamus, and DLPFC lesions on the rate of erroneous prosaccades. They found that the DLPFC, and not the basal ganglia or thalamus, was critical for suppressing unwanted saccades to a visual stimulus. Therefore, it is probable that the increase in erroneous prosaccades exhibited by patients in the anti-saccade task indicates that the DLPFC processes are dysfunctional in Parkinson's disease.

Although the FEF may not be the source of saccadic disinhibition underlying the increased rate of erroneous prosaccades, it is a likely source of increased latency of anti-saccades in PD. The FEF are crucial for triggering intentional saccades (Pierrot-Deseilligny et al., 2004). In an fMRI study comparing FEF activity during a prosaccade task and an anti-saccade task in healthy subjects, it was found that FEF activation was larger for anti-saccades, and that activity

of the contralateral FEF-SC pathway was responsible for generating the anti-saccade (de Weijer et al., 2010). Patients with PD exhibit remarkable hypoactivation of the FEF compared to healthy controls before the execution of a saccade (Rieger et al., 2008). It has been shown that lesions of the FEF increase the latency of correct anti-saccades (Rivaud et al., 1994).

Whereas saccadic latency is known to reflect the time-course of neural processes of the SC and the cortical and subcortical areas that project to it (Dorris et al., 1997; van Stockum et al., 2012), saccadic gain (ie. amplitude relative to target) is controlled in the reticular formation of the brainstem by excitatory burst neurons which project directly to the motor neurons (Sparks, 2002). It is possible that impaired gain in PD is due to the excessive inhibition of the SC by the dopamine-deficient basal ganglia. The SC projects to the brainstem burst neurons, and therefore excessive inhibition of the SC would lead to reduced activation of the saccadic burst neurons resulting in hypometric saccades.

2.3.2.2 Memory-guided saccades (MGS)

Memory-guided saccade tasks require the participant to inhibit saccades to a target, maintain spatial information in memory, and generate saccades by internal guidance. The participant begins by fixating on a central target and continues to fixate when a peripheral target is displayed and then extinguished. After a delay period, the central fixation light disappears and the participant makes a saccade to the remembered target location. The correct execution of the task involves the inhibition of a reflexive saccade to the peripheral cue and the internal generation of a saccade to a location that is held in memory. Patients with Parkinson's disease have shown impairment in these processes: they have a higher rate of erroneous saccades to cue

(Chan et al., 2005; Crevits & De Ridder, 1997; Gurvich et al., 2007; Terao et al., 2011), increased latency (Terao et al., 2011), and reduced spatial accuracy (Chan et al., 2005; Crevits & De Ridder, 1997; Terao et al., 2011) relative to non-Parkinsonian controls. In a study investigating dopaminergic effects on saccadic latency, it was found that medication increased latency (Müller et al., 1994).

Similar to the increased rate of erroneous prosaccades in the AS task, the increased rate of erroneous saccades to cue in the MGS task also reveals impairment in reflexive saccade inhibition and therefore might be an indication that impaired DLPFC processing is the underlying cause (Crevits & De Ridder, 1997). Additionally, it is probable that the hypometria exhibited in anti-saccades shares a common mechanism underlying the hypometria in memory-guided saccades- both types of saccades are generated using an internal spatial coordinate system rather than an external, visual target. Thus, excessive inhibition of the SC due to overactive basal ganglia output might be the reason MGS saccades are hypometric in PD. Further, the DLPFC has been shown to be critically involved with short-term spatial memory (Pierrot-Deseilligny et al., 2004). It is probable that the reduction in spatial accuracy exhibited by patients with PD could be caused by dysfunctional DLPFC processing as well.

2.3.2.3 Predictive saccades

For a predictive saccade task, the participant is instructed to makes saccades between 2 targets which are alternately displayed at a regular frequency between 2 fixed locations on either side of midline. When participants begin the task, they react to the target light and begin their saccade after the onset of the light, and the saccades are visually-guided. As they continue the

task, participants begin to anticipate the timing of the target lights and make saccades prior to the

target light turning on, and the saccades are internally-guided. Healthy controls adopt this

predictive strategy during the task earlier than patients (T. Crawford, Goodrich, Henderson, &

Kennard, 1989). When patients do begin to make these predictive saccades, their saccades

become hypometric (T. Crawford et al., 1989; Ventre, Zee, Papageorgiou, & Reich, 1992).

Further, comparing self-paced alternating saccades to externally-cued alternating saccades,

patients showed a reduction in saccadic gain when performing the externally-cued relative to the

self-paced saccades (Winograd-Gurvich, Georgiou-Karistianis, Fitzgerald, Millist, & White,

2006).

In addition to saccadic inhibition and short-term spatial memory, the DLPFC is also

critically involved with prediction (Pierrot-Deseilligny et al., 2004). Although patients with PD

take longer than healthy controls to start predicting during a predictive saccade task, they are

eventually able to make predictive saccades. This may imply that the learning of a regular

timing pattern is impaired in PD, but once they have learned the pattern patients are able to

predict the onset of targets.

2.4 Effects of STN DBS on saccade performance

2.4.1 STN DBS and externally-guided saccades

2.4.1.1 STN DBS and VGS latency

Most studies have shown that high-frequency STN DBS reduces visually-guided saccadic

latency in patients with PD both on (Antoniades, Carpenter, & Temel, 2012; Temel, Visser-

Vandewalle, & Carpenter, 2008; Yugeta et al., 2010) and off (Fawcett et al., 2010; Sauleau et al.,

2008; Temel, Visser-Vandewalle, & Carpenter, 2009) dopaminergic medication. In contrast, one

study, which involved testing patients in the on medication state, found that STN DBS has no

effect on VGS latency (Rivaud-Péchoux et al., 2000). The lack of effect on VGS latency in this

study could possibly be related to differences in target eccentricity and/or sample size. The

Yugetta et. al 2010 study used a similar paradigm as Rivaud-Pechoux et al. (2000) (gap

paradigm and a variable fixation period), however Yugetta et al. (2010) presented randomized

targets at 5, 10, 20 and 30 degrees and Rivaud-Pechoux et al. presented targets only at 25

degrees. Perhaps the effect of STN DBS is amplitude-specific. Or, more precisely, when

patients are on dopaminergic medication, STN DBS may or may not reduce VGS latency, and

this relationship may be affected by the saccadic amplitude.

2.4.1.2 STN DBS and VGS gain

The effect of STN DBS on VGS gain is inconclusive. Some have reported that STN

DBS increases VGS gain in the on (Yugeta et al., 2010) and off (Sauleau et al., 2008) medicated

states; other reports claim there is no effect of STN DBS on VGS gain in the on (Rivaud-

Péchoux et al., 2000) or off (Fawcett et al., 2010) medicated states. Due to differences in

experimental paradigms and sample size, it could be that the studies that failed to show an effect

on gain were not designed or powered to detect that change. The patients in the Rivaud-Pechoux

et. al 2000 study were already performing the VGS task as well as controls in the off stimulation

condition. In the study ran by Fawcett and colleagues, although not statistically significant, there

was a trend towards increased gain in the on stimulation condition.

2.4.2 STN DBS and internally-guided saccades

2.4.2.1 STN DBS and anti-saccades (AS)

Two of the three studies that have examined the effects of STN DBS on anti-saccades tested patients with PD in their medicated state (Rivaud-Péchoux et al., 2000; Yugeta et al., 2010), and the findings were inconsistent: Yugeta and colleagues found that STN DBS improved saccade latency and gain whereas Rivaud-Pechoux and colleagues found that STN DBS had no effect on either parameter. When patients were tested on STN DBS off medication, they exhibited a significant increase in gain but no effect on latency (Fawcett et al., 2010).

2.4.2.2 STN DBS and memory-guided saccades

The effect of STN DBS on memory-guided saccades is more robust across studies than for VGS and AS tasks. Whether patients are on or off medication, STN DBS improves the gain and accuracy of memory-guided saccades (Fawcett et al., 2010; Rivaud-Péchoux et al., 2000; Yugeta et al., 2010). It has also been shown to reduce erroneous saccades to cue (Yugeta et al., 2010).

Chapter 3: The differential effects of unilateral and bilateral subthalamic nucleus deep brain stimulation on visually-guided prosaccades and anti-saccades

3.1 Introduction

Stimulation of the subthalamic nucleus (STN) is an effective treatment for improving several aspects of motor function in patients with advanced stage Parkinson's disease (PD). Tremor is markedly reduced (Sturman, Vaillancourt, Metman, Bakay, & Corcos, 2004), bradykinesia is improved (Tabbal et al., 2008), rigidity is lessened (Shapiro et al., 2007), and clinical scores on the Unified Parkinson's Disease Rating Scale (UPDRS) are significantly lowered (Castrioto et al., 2011; Krack et al., 2003). Although unilateral stimulation improves bilateral motor function (Alberts et al., 2008; Walker, Watts, Guthrie, Wang, & Guthrie, 2009), it has been shown that bilateral stimulation provides greater improvements in motor function than unilateral stimulation (Bastian et al., 2003; Kumar et al., 1999). However, despite the effectiveness of bilateral STN stimulation on motor control, there is evidence to suggest that bilateral stimulation of the STN- both compared to bilateral stimulation of the globus pallidus internus (GPi) (Follett et al., 2010) and compared to no stimulation (Williams et al., 2011)- has deleterious effects on certain cognitive functions. Furthermore, when comparing the effects of unilateral STN stimulation to bilateral STN stimulation on patient performance on a cognitive-motor dual-task, Alberts and colleagues found motor and cognitive performance was significantly worse with bilateral stimulation compared to unilateral stimulation (Alberts et al., 2008). Participants in their study performed an upper extremity force-tracking task and the n-back test (a working memory task). When performing the motor and cognitive tasks separately, there was no difference between unilateral and bilateral stimulation conditions. In contrast, when performing the motor and cognitive tasks simultaneously, bilateral stimulation resulted in

worse performance than unilateral stimulation and no stimulation (Alberts et al., 2008). No other studies have directly compared the effects of unilateral versus bilateral stimulation on motor tasks with increased cognitive demands. The current study aims to further our understanding of the differential effects of unilateral and bilateral stimulation on motor tasks with increased cognitive demands by comparing the effects of stimulation on oculomotor tasks that differ in their level of cognitive involvement.

Whereas several studies have shown that the execution of visually-guided prosaccades, thought to be primarily reflexive saccades, appears to be fairly preserved in patients with PD (Briand et al., 1999; Chan et al., 2005; T. J. Crawford, Henderson, & Kennard, 1989), impairment is evident when patients perform saccade tasks with a cognitive component, such as the anti-saccade task. The anti-saccade task requires the participant to first inhibit a reflexive saccade to a visual target and then internally generate a saccade in the opposite direction from the target. During execution of the anti-saccade task, patients with PD show 1) an increased rate of erroneous prosaccades, i.e., greater difficulty in suppressing reflexive saccades to the visual target, both on medication (Chan et al., 2005; Crevits & De Ridder, 1997; Hood et al., 2007; van Stockum et al., 2008) and off medication (Briand et al., 1999; Hood et al., 2007), 2) increased saccadic latency, i.e, prolonged reaction times, both on medication (Chan et al., 2005; Hood et al., 2007; van Stockum et al., 2008) and off medication (Briand et al., 1999; Hood et al., 2007), and 3) decreased primary saccade gain, i.e., reduction in the ratio of the primary saccade amplitude to the target amplitude both on medication (Hood et al., 2007; van Stockum et al., 2012) and off medication (Briand et al., 1999; Hood et al., 2007; van Stockum et al., 2012) compared to non-PD controls.

To date, there has been little work that has investigated the effect of STN DBS on visually-guided prosaccade and anti-saccade performance. Fawcett et al. tested the effects of bilateral stimulation on prosaccade and anti-saccade task performance while patients were off their anti-parkinsonian medication and found that bilateral STN stimulation reduced saccadic latency in the visually-guided prosaccade task and increased primary saccade gain in the anti-saccade task (Fawcett et al., 2010). They did not report the rate of erroneous prosaccades to the target in the anti-saccade task. Two other studies have shown that bilateral STN DBS has no effect on the frequency of erroneous prosaccades in the anti-saccade task (Rivaud-Péchoux et al., 2000; Yugeta et al., 2010). A possible reason for this is that participants in both of these studies continued to take their anti-parkinsonian medication throughout the tests. Anti-parkinsonian medication has been shown to improve the ability to suppress reflexive saccades during the anti-saccade task (Hood et al., 2007). Therefore, the effects of stimulation were likely masked by the effects of medication. As such it is unclear how bilateral STN stimulation affects prosaccade error rate in an antisaccade task. It is also unknown how unilateral stimulation affects any of the prosaccade and anti-saccade measures.

In this study we will investigate the effects of unilateral and bilateral STN DBS on visually-guided prosaccades and anti-saccades. Based upon the ample evidence showing that unilateral STN DBS improves limb function but not to the extent that bilateral STN DBS does (Castrioto et al., 2011; Krack et al., 2003), and the fact that medication improves intensive parameters of movement (Schettino et al., 2006), we hypothesize that unilateral stimulation will improve peak velocity and saccade gain, but that bilateral stimulation will improve measures to a greater extent. In contrast, based upon the findings that bilateral STN DBS impairs cognitive processes during motor tasks (Alberts et al., 2008), we hypothesize that bilateral stimulation will

induce a greater percentage of erroneous prosaccades in the anti-saccade task compared to unilateral stimulation. Furthermore, we expect to replicate previous findings and show that bilateral STN stimulation in the off medication state increases primary saccade gain in the AS task and reduces latency in the visually-guided prosaccade task, as previously reported (Fawcett et al., 2010).

3.2 Methods

3.2.1 Subjects

Ten patients (7 male, 3 female; mean age 58 years ± SD 6.8) with advanced Parkinson's disease and bilaterally implanted STN stimulators (Medtronic Inc., Minneapolis, MN, USA) were tested along with 10 healthy, age- and sex-matched controls (57 years ± 8.2). An independent *t* test confirmed there were no statistically significant differences in age between the patient and control groups. All patients and controls recruited for this study were right hand dominant that was confirmed by the Edinburgh Handedness Inventory. Patients were examined by a movement disorders neurologist and included in the study if they: 1) had Parkinson's disease as outlined by the Parkinson's disease Society Brain bank diagnostic criteria (Hughes et al., 1992), 2) had undergone bilateral STN DBS surgery, 3) scored 25 or greater on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975), and 4) exhibited no blepharospams or other eye movement abnormalities. With the exception of Parkinson's disease, both patients and controls had no known other neurological disorders. All subjects gave informed consent to all experimental procedures, which were approved by the Institutional Review Board

at the University of Illinois at Chicago. Table 1 shows patient demographics, stimulator

parameters, and clinical rating scores.

3.2.2 Experimental setup

Patients completed 4 separate testing sessions on 4 consecutive days. Each day, the

patients were tested after a 12-hour over-night withdrawal from PD medication under 1 of 4

stimulator conditions: OFF stimulation (OFF), left unilateral stimulation (LEFT), right unilateral

stimulation (RIGHT), or both stimulators on (BOTH). The order of days, and therefore

conditions, were pseudo-randomized. Each testing session began 3 hours after the appropriate

stimulators were turned off for the condition of that day. Patients were administered the MDS-

UPDRS by a certified rater (LC), followed by a visually-guided prosaccade task (PS) and an

anti-saccade task (AS) each session. The order of the saccade tasks was randomized. One

session lasted approximately 90 minutes. Control subjects completed testing in one session.

One of the 10 patients was unable to perform testing for the OFF stimulation condition due to

extreme discomfort due to excessive rigidity.

3.2.2.1 Instrumentation

The eye movement tasks were performed in a completely darkened room. Patients sat

upright in a height-adjustable chair with arm rests. In order to control for head movement,

patients placed their chin on a stationary chin rest, and head movements were recorded using a 3-

D motion capture system (Optotrak 3020, Northern Digital, Inc.). Horizontal eye movements

were collected using a eye-tracking system consisting of two miniature cameras mounted on a comfortable padded headband (Eyelink II, SR Research Ltd, 2002) which has a spatial resolution (RMS) of $0.01°$ and velocity noise $<0.05°$. Pupil position was sampled at a frequency of 500 Hz. A 5 degrees of freedom robot arm (CRS Robotics Corp., A255) presented green LED visual targets in a plane located 47 cm in front of the subject. Eye and head movement data were synchronized and stored using The Motion Monitor software (Innovative Sports Training, Inc. 2011). Figure 1 illustrates a subject sitting in the experimental set-up.

3.2.3 Eye movement tasks

3.2.3.1 Prosaccade task (PS)

Each trial began with the subject fixating on a central fixation LED ($0°$ visual angle) for 3000 ms. Next, the central fixation disappeared and 200 ms later, a target was presented in one of 2 locations on either side of center for 1500 ms. The 2 locations were horizontally oriented (17.1 cm to the right and left of central fixation; $20°$ visual angle). The subjects were given the following instructions: "When the LED on the stand comes on, please fixate on it. The robot will move to a target location and the LED on the robot will come on. When the target LED comes on, please look at the target location as quickly and accurately as possible. Try to make one eye movement to the target." Targets were presented in a random order. Each of the 2 targets was presented 25 times. The PS task was completed in one block of 50 trials.

3.2.3.1 Anti-saccade task (AS)

The sequence of events and target locations was identical to those used in the PS task. The difference between the PS and AS tasks was the instructions given to subjects: "When the LED on the stand comes on, please fixate on it. The robot will move to a target location and the LED on the robot will come on. When the target LED comes on, please look to the mirror-image location in the opposite direction as quickly and accurately as possible. Try to make one eye movement to the target." Each of the 2 targets was presented 25 times. The AS task was completed in one block of 50 trials.

3.2.4 Data processing

3.2.4.1 Clinical data

The score on the motor section of the MDS-UPDRS was calculated. Given that most previous studies examining the effect of STN DBS used the UPDRS, we also calculated the motor section score on the UPDRS using conversion formulae from the MDS-UPDRS published by Goetz et. al (2012).

3.2.4.2 Eye movement data

The data was analyzed using a custom Matlab script (The MathWorks, Natick, MA). A 20 Hz low-pass 2nd order Butterworth filter was applied to the position data of the right and left eye. Eye velocity was calculated from the filtered eye position data. There were no differences between left and right eye velocities for each of the stimulation conditions for the first 4 subjects

analyzed, therefore, the average of the left and right eye velocities were used to determine

saccade metrics. Saccade onset was determined by an algorithm that first determined peak

velocity and then searched backwards to detect the first time point when velocity went below 5%

of peak velocity; saccade offset was determined as the first time point occurring after peak

velocity when the value decreased below 5% of peak velocity. Every trial was visually inspected

and saccade onsets and offsets were visually marked if needed. Trials were rejected and omitted

from analyses if the subject blinked, failed to perform the task, and/or made an anticipatory

saccade (see 'Saccade latency' below). Eleven percent of PS trials and 7% of AS trials were

rejected and not included in the analyses.   In order to measure saccadic gain in the target plane,

a cyclopean vector that connected the mid-point of both eyes and the binocular gaze focal point

was calculated. The point of intersection of this cyclopean vector with the target plane was

defined as saccade position in two dimensions. Once saccade onset, saccade offset, and saccade

position were determined, the following variables were calculated:

i)   Saccade latency: the time between target LED illumination and saccade onset. If this

        time value was less than 90 ms, it was considered an anticipatory saccade (Braun, Weber,

        Mergner, & Schulte-Mönting, 1992) and was discarded.

ii)   Saccade velocity: peak velocity of the primary saccade in degrees per second.

iii)   Primary saccade gain: the ratio of the primary saccade end point position to target

        position in the horizontal plane. Primary saccade end point was identified as the saccade

        position at offset of the primary saccade. Primary saccade gain was measured by

        dividing primary saccade end point by target position in the horizontal plane.

iv)   Final saccade gain: the ratio of eye position at fixation to target position in the horizontal

        plane.   Saccade fixation was defined to occur when saccade velocity remained lower

than 5% of peak velocity for 200ms. Saccade fixation position was defined as the

saccade position at the beginning of this 200ms interval. Final saccade gain was

calculated by dividing saccade position at fixation by target position in the horizontal

plane.

v)   Percentage of express saccades: the percentage of trials in which the saccades had

latencies that fell in the range of 90-120 ms in the PS task (Gezeck et al., 1997).

vi)   Percentage of erroneous prosaccades: the percentage of trials in which a prosaccade to

target was performed in the AS task.

For the anti-saccade task, trials in which subjects performed prosaccades were not

included in the calculations of latency, velocity, and primary and final saccade gain.

3.2.5 Statistical analysis

To estimate differences in stimulation conditions, planned between group contrasts were

performed using a mixed-effects regression model for the MDS UPDRS,UPDRS, saccade

latency, peak velocity, and primary and final saccade gain. A mixed effect logistic regression

model was used to estimate differences in stimulation conditions for the rate of occurrence of

erroneous prosaccades and express saccades. All p-values were two-sided and were adjusted

using the Bonferroni method.

3.3 Results

3.3.1 Clinical measures: MDS-UPDRS, UPDRS

Figure 2A shows the mean MDS-UPDRS scores measured for all stimulation conditions. There was a main effect of condition for MDS-UPDRS (F= 7.95, P < 0.001). Compared to OFF, LEFT stimulation improved scores by approximately 14 points (mean difference estimate, 13.5; 95% confidence interval, .4 to 26.6; P = 0.02). BOTH improved MDS-UPDRS scores with a reduction of approximately 27 points compared to OFF (26.7; 13.6 to 39.8; P < 0.001). BOTH improved scores more than LEFT (13.2; .5 to 26; P = 0.02) and RIGHT (14.8; 2.1 to 27.5; P = 0.01) stimulation.

As is shown in figure 2B, similar results were found for the UPDRS scores.

3.3.2 Saccade latency

Prosaccades: We observed a main effect of stimulation (F = 24.71, P < 0.001) as well as a main effect of target (F =14.67, P < 0.001). Average latency to the right target was less than average latency to the left target. The condition by target interaction was not significant. As shown in figure 3A, planned comparisons revealed that latency for the BOTH condition was significantly less than for the OFF (33 ms; 18 to 48 ms; P < 0.001), LEFT (42 ms; 28 to 56 ms; P < 0.001), and RIGHT (50 ms; 36 to 64 ms; P < .001) stimulation conditions. RIGHT stimulation increased latency compared to the OFF condition (17 ms; 2 to 32 ms; P = 0.01).

Anti-saccades: We observed a significant condition by target interaction for latency (F = 2.93, P=.03). LEFT stimulation increased latency compared to OFF (48 ms; 10 to 85 ms; P < 0.001) and BOTH (44 ms; 3 to 84 ms; P = 0.003) conditions only for leftward saccades (right target

presentation) (solid line, figure 3B). There were no other effects of stimulation on saccade latency for the anti-saccade task.

3.3.3 Peak velocity

Prosaccades: There was a main effect of stimulation condition on peak velocity (F = 19.17, P < 0.001). The condition by target interaction was not significant. Peak velocity was significantly greater for the BOTH condition compared to the OFF (19 deg/s; 7 to 31 deg/s; P < 0.001), LEFT (34 deg/s; 23 to 46 deg/s; P < 0.001), and RIGHT (33 deg/s; 21 to 45 deg/s; P < 0.001) stimulation conditions (figure 4A). LEFT (15 deg/s; 3 to 28 deg/s; P = 0.005) and RIGHT (14 deg/s; 1 to 26 deg/s; P = 0.01) stimulation significantly reduced peak velocity compared to the OFF condition.

Anti-saccades: There was a significant condition by target interaction for peak velocity (F = 3.23, P = .02). As is depicted in figure 4B, BOTH stimulation increased peak velocity compared to OFF (46 deg/s; 24 to 69 deg/s; P < 0.001), LEFT (45 deg/s; 24 to 67 deg/s; P < 0.001), and RIGHT (46 deg/s; 25 to 68 deg/s; P < 0.001) for saccades away from the left target (dashed line). The BOTH stimulation condition also increased peak velocity compared to OFF (41 deg/s; 17 to 64 deg/s; P < 0.001) and LEFT (24 deg/s; 2 to 47 deg/s; P = 0.002) for saccades away from the right target (solid line, figure 4B). RIGHT stimulation increased velocity compared to the OFF (25 deg/s; 4 to 46 deg/s; P = 0.001) condition for saccades away from the right target.

3.3.4 Primary saccade gain

Prosaccades: There was a significant condition by target interaction for primary saccade gain (F

= 2.67, P = 0.05). Planned comparisons revealed that when saccades were made to the left target

(dashed line, figure 5A), primary saccade gain was greater for the BOTH condition compared to

the OFF (0.0977; 0.04 to 0.15; P < 0.001), LEFT (0.055; 0.004 to 0.1; P = 0.003), and RIGHT

(0.08; 0.03 to 0.13; P < 0.001) conditions. When saccades were made to the right target (solid

line, figure 5A), there were no differences in primary saccade gain between the OFF, LEFT, and

BOTH conditions. RIGHT stimulation showed significantly reduced primary saccade gain

compared to OFF (0.06; 0.01 to 0.11; P = 0.001) and BOTH (0.1; 0.06 to 0.16; P < 0.001).

Anti-saccades: There was a significant condition by target interaction for primary saccade gain

(F = 3.02, P = 0.03). For saccades away from the left target (dashed line, figure 5B), the BOTH

condition increased primary saccade gain compared to the OFF (0.24; 0.14 to 0.34; P < 0.001),

LEFT (0.13; 0.03 to 0.23; P < 0.001), and RIGHT (0.19; 0.10 to 0.29; P < 0.001) conditions.

BOTH stimulation increased primary saccade gain compared to LEFT (0.13; 0.03 to 0.23; P <

0.001) and OFF (0.20; 0.1 to 0.31; P < 0.001) stimulation for saccades away from the right target

(solid line, figure 5B).

3.3.5 Final saccade gain

Prosaccades: There was a significant condition by target interaction for final saccade gain (F =

4.59, P =0.003). As is shown in figure 6A, final saccade gain was greater for the BOTH

condition compared to the OFF (0.09; 0.04 to 0.14; P <0.001), LEFT (0.1; 0.05 to 0.14; P <

0.001), and RIGHT (0.08; 0.04 to 0.12; P <0.001) conditions for saccades to the left target ; and

there was no difference in final saccade gain between OFF, LEFT, and BOTH for saccades to the right target. Final saccade gain of rightward saccades was reduced for the RIGHT stimulation condition compared to BOTH (0.05; 0.01 to 0.1; $P < 0.001$).

Anti-saccades: There was a main effect of condition ($F = 23.11$, $P < 0.001$) and target ($F = 13.05$, $P < 0.001$) for final saccade gain. As shown in figure 6B, saccades to the left (right target presentation) had a greater average gain than saccades to the right. BOTH stimulation increased final saccade gain compared to OFF (0.21; 0.15 to 0.27; $P < 0.001$), LEFT (0.13; 0.08 to 0.19; $P < 0.001$), and RIGHT (0.13; 0.07 to 0.19; $P < 0.001$) stimulation.

3.3.6 Express saccades

There was no effect of stimulation condition ($P = 0.1$) or target ($P = 0.5$) on percentage of express saccades.

3.3.7 Erroneous prosaccades

There was a main effect of stimulation condition ($F = 10.12$, $P < 0.001$) and target ($F = 16.31$, $P < 0.001$) for erroneous prosaccades to target (figure 7). Patients made more erroneous prosaccades to the right target compared to the left target. The condition x target interaction was not significant. BOTH stimulation resulted in a significantly higher percentage of erroneous prosaccades compared to OFF (15.5%; $P < 0.001$), LEFT (12.8%; $P < 0.001$), and RIGHT (14%; $P < 0.001$) stimulation.

3.4 Discussion

Our aim of this study was to investigate the differential effects of unilateral and bilateral STN DBS on the generation of visually-guided prosaccades and anti-saccades. We are the first to compare the effects of unilateral vs. bilateral STN DBS on clinical motor function using the MDS-UPDRS. We found that unilateral STN DBS improved clinical ratings, and bilateral STN DBS had a significantly greater effect than unilateral stimulation. These findings were consistent with reports of unilateral vs. bilateral STN DBS on UPDRS part III scores. This was also the first study to look at the effects of unilateral STN DBS on eye movements. In contrast to the abundance of studies reporting the beneficial effects on limb movements, we found that unilateral stimulation did not improve saccadic eye movements. When BOTH stimulators were on, velocity and gain were significantly improved for the PS and AS task, yet saccadic latency was not improved. Latency for the PS task was significantly reduced when BOTH stimulators were on, but this reduction moved the average latency further from the average latency of the control subjects. There was no change in latency during the AS task when BOTH stimulators were on. Additionally, the amount of erroneous prosaccades in the AS task increased when BOTH stimulators were on but did not increase when only one stimulator was on. It should also be noted that while bilateral stimulation improved measures of velocity and gain, it did not normalize these measures. Patients continued to exhibit velocity and gain impairment relative to the healthy controls (figures 4-6).

3.4.1 Potential mechanisms underlying the efficacy of STN DBS on velocity and gain

The substantia nigra pars reticulatae (SNr) of the basal ganglia tonically inhibit saccade generating cells of the superior colliculus (SC) during rest, and release their inhibitory activity before and during saccade execution (Hikosaka et al., 2000). In PD, dopamine depletion of the basal ganglia results in a weakened direct pathway and an enhanced indirect pathway which leads to excessive inhibitory output of the SNr and impaired activation of saccade cells in the SC (Bergman et al., 1998). The STN, a key structure of the indirect pathway that sends excitatory glutamatergic projections to the SNr, exhibits abnormal firing patterns and enhanced oscillatory and synchronized activity in PD (Hamani et al., 2004; Magill et al., 2001). It is possible that bilateral STN DBS improves measures of saccadic velocity and gain (figures 4-6) by reducing the excessive inhibitory output of the SNr thereby allowing the SC to more effectively activate brain stem saccade generators.

Two models have been proposed to explain the mechanism underlying STN DBS efficacy. One model posits that STN DBS simply reduces the firing rate of the overactive STN which in turn would reduce the activity of the SNr, release the SC from inhibition, and facilitate saccade generation (Yugeta et al., 2010). The second model proposes that stimulation of the STN may alter oscillatory activity in the basal ganglia by normalizing the pathological oscillatory patterns (Hashimoto et al., 2003; Montgomery & Baker, 2000) and restoring the SNr-SC relationship (Yugeta et al., 2010). Our findings showing that bilateral STN DBS improved gain and velocity could support either model. However, if reduced inhibition of the SNr-SC pathway due to STN firing rate reduction was the sole mechanism underlying the effects of STN DBS, we might also expect to see a reduction in latency for both tasks as well as an increase in erroneous prosaccades in the AS task. We did not find a reduction in AS latency (Figure 3B).

On the other hand, if in fact the SNr-SC oscillatory activity was *normalized* during STN DBS, we might expect to see improvements in saccade latency in both tasks as well as improvements in saccade inhibition. Contrary to this, we found that STN DBS was not effective at improving saccade latency (figures 3A and B), and it further impaired saccade inhibition (ie. erroneous prosaccades in the AS task) (figure 6). Regardless of whether bilateral STN DBS induces changes by reducing the firing rate and/or by altering oscillatory patterns of the STN and SNr, our findings suggest that bilateral STN DBS may also be altering activity of saccade-related structures other than those of the basal ganglia.

3.4.2 Bilateral STN DBS and saccade latency

In accordance with previously reported findings (Fawcett et al., 2010), we found that bilateral stimulation significantly reduced latency on the PS task (figure 3A) and had no effect on AS latency (figure 3B). It is known that visually-guided reflexive saccades, such as those in the PS task, are triggered by the posterior parietal cortex (PPC), and internally-guided saccades, such as those in the AS task, are triggered by the frontal eye fields (FEF) (Pierrot-Deseilligny et al., 2004). Since all visual pathways converge on the SC (Hikosaka et al., 2000), modification of SC activity by the nigro-collicular pathway could affect how the SC processes information arriving from the cortex. However, altered SC activity alone does not explain why latency was reduced by bilateral STN DBS in the PS task yet unaffected by bilateral STN DBS in the AS task. It has been postulated that modification of oscillatory activity of the STN by DBS may not only affect patterns in the basal ganglia but may also alter patterns throughout the brain including cortical areas involved with eye movements (Trost et al., 2006). Specifically, it has been shown

that STN DBS alters parietal metabolism (Hershey et al., 2003; Trost et al., 2006). Therefore, it is possible that the altered metabolism of the parietal cortex by STN DBS could evoke hyper-reflexive responses to the visual targets in the PS task. The finding that AS latency was unaffected may indicate that STN DBS does not alter activity in the FEF.

3.4.3 Bilateral STN DBS and saccade inhibition

Imaging studies have shown that changes in neuronal metabolism of the DLPFC occur during STN DBS and that these changes are correlated with changes in cognitive function (Campbell et al., 2008; Kalbe et al., 2009). Lesion studies have shown that the dorsolateral prefrontal cortex (DLPFC) plays a crucial role in saccade inhibition (Condy et al., 2004; Pierrot-Deseilligny et al., 2003). Whereas lesions of the frontal eye fields (FEF), basal ganglia, and thalamus do not affect saccade inhibition, lesions of the DLPFC cause a significant increase in the rate of erroneous prosaccades in an anti-saccade task (Condy et al., 2004; Pierrot-Deseilligny et al., 2003) indicating a disruption in saccadic inhibitory processes. In addition to saccadic inhibition, the DLPFC is known to play a critical role in working memory. Alberts et. al 2008 found that bilateral, and not unilateral, STN DBS impaired working memory function when patients performed a motor task and cognitive task simultaneously. We now show that bilateral, and not unilateral, STN DBS impairs saccadic inhibition when patients perform an oculomotor task with increased cognitive demands (AS task) (figure 6). The findings from the present study along with the findings from the Alberts et. al 2008 study suggest that bilateral STN DBS may negatively affect DLPFC processing. It has been shown with computational models that high-frequency stimulation eliminates the variability of neuronal output (Grill et al., 2004). Since

information content of the output signal is related to the variability of the signal, abolishing the variation of the signal is thought to eliminate the information content of the signal. Thus, it has been proposed that high-frequency STN DBS may normalize basal ganglia function by eliminating the pathological information generated by the STN, but that current spread to other brain regions may alter normal information processing as well (Alberts et al., 2008). The fact that bilateral, and not unilateral, STN DBS resulted in an increase in erroneous prosaccades (figure 6) could be that during unilateral stimulation, the non-stimulated side can compensate for the disrupted stimulated side.

3.4.4 Unilateral STN DBS and saccades

The lack of improvement in the PS task and the unremarkable, target-dependent changes in the AS task show that altering the activity of one STN is not sufficient to improve overall saccadic performance. During unilateral stimulation, patients' performance on the prosaccade task was similar to or even worse than their performance during no stimulation. The minor effects of unilateral stimulation on AS task differed depending upon side of stimulation and direction of target. It is possible that unilateral STN DBS causes an imbalance in the processes underlying saccade generation. This imbalance potentially could be due to the effects of stimulation on the crossed and uncrossed nigro-collicular fibers (Sauleau et al., 2008). Uncrossed nigro-collicular fibers project from the SNr to the ipsilateral SC and facilitate visuomotor activity. Crossed fibers project to the contralateral SC and simultaneously inhibit visuomotor activity. The uncrossed and crossed nigro-collicular cells must work simultaneously and in synchrony to facilitate saccade responses (Jiang et al., 2003). It is possible that unilateral

stimulation disrupts the synchrony between the crossed and uncrossed fibers thereby impairing saccade generation.

3.4.5 Summary

Unilateral STN DBS does not improve eye movements to the same extent and in the same way that it does limb movements. Although bilateral STN DBS improves certain aspects of eye movement control, it also appears to abnormally increase the reflexive response to visual stimuli and deleteriously affect the processes underlying saccadic inhibition. While bilateral STN DBS may improve certain saccadic functions by altering neuronal patterns in the basal ganglia, it may produce detrimental effects on visual reflexes and saccadic inhibition by altering neuronal patterns in cortical areas involved with these processes.

Table 1. Patient characteristics and stimulation parameters

Patient	Sex	Age	Disease Duration	Yrs since Surg.		MDS-UPDRS (0-132)				UPDRS (0-108)				Left Stimulator			Right Stimulator		
				Left	Right	Off	Left	Right	Both	Off	Left	Right	Both	Voltage	Frequency	Pulse Width	Voltage	Frequency	Pulse Width
1	F	50	22	8	8	34	40	36	40	26	31	28	31	2.2 V	185 Hz	120 μs	2.0 V	185 Hz	120 μs
2	M	59	22	7	7	74	48	51	50	60	38	41	40	4.1 V	185 Hz	80 μs	4.5 V	185 Hz	100 μs
3	M	50	16	7	7	55	47	51	31	45	37	42	24	2.9 V	185 Hz	60 μs	2.6 V	185 Hz	60 μs
4	M	58	14	4	4	53	43	49	37	42	34	39	29	2.6 V	185 Hz	90 μs	4.0 V	185 Hz	60 μs
5	M	58	15	2	2	97	45	73	12	81	37	60	8	4.1 V	140 Hz	120 μs	3.5 V	140 Hz	210 μs
6	M	63	11	3	3	38	26	34	13	28	20	28	9	2.3 V	130 Hz	60 μs	2.2 V	130 Hz	450 μs
7	M	59	21	12	13	56	74	36	31	44	60	29	25	3.1 V	160 Hz	60 μs	3.1 V	160 Hz	60 μs
8	M	73	11	6	6	53	27	40	25	42	21	31	19	5.5 V	185 Hz	120 μs	4.0 V	185 Hz	120 μs
9	F	61	14	7	7	X	42	29	30	X	34	22	24	2.9 V	185 Hz	60 μs	3.7 V	125 Hz	80 μs
10	F	53	19	9	11	65	52	61	43	52	41	49	34	2.5 V	130 Hz	60 μs	2.6 V	180 Hz	60 μs
Avg		58	16.5	6.5	6.8	58.3	44.4	46	31.2	46.7	35.3	36.9	24.3						
Std		6.8	4.2	3.0	3.4	18.9	13.4	13.7	12.2	16.6	11.1	11.6	10.2						

Table 2. Solution for fixed effects tests

	Prosaccade Task		
	Stimulation condition	**Target**	**Stimulation x Target**
Latency	F = 24.71, P <.0001	F = 14.67, P =.0001	F = 1.5, P = .21
Peak velocity	F = 19.17, P <.0001	F = 1.05, P = .31	F = 1.86, P = .13
Primary saccade gain	F = 19.49, P<.0001	F = 46.14, P <.0001	F = 2.67, P = .05
Final saccade gain	F = 17.29, P <.0001	F = 109.56, P <.0001	F = 4.59, P = .0033
	Anti-saccade Task		
	Stimulation condition	**Target**	**Stimulation x Target**
Latency	F = 2.76, P = .04	F = .29, P = .59	F = 2.93, P = .03
Peak velocity	F = 20.74, P <.0001	F = .01, P = .94	F = 3.23, P = .02
Primary saccade gain	F = 24.55, P <.0001	F = 2.69, P = .1	F = 3.02, P = .03
Final saccade gain	F = 23.11, P <.0001	F = 13.05, P = .0003	F = 1.16, P = .32

Figure 1. Experimental Set-up

Figure 2. Average scores for MDS-UPDRS (A) and UPDRS (B) part III motor examination.

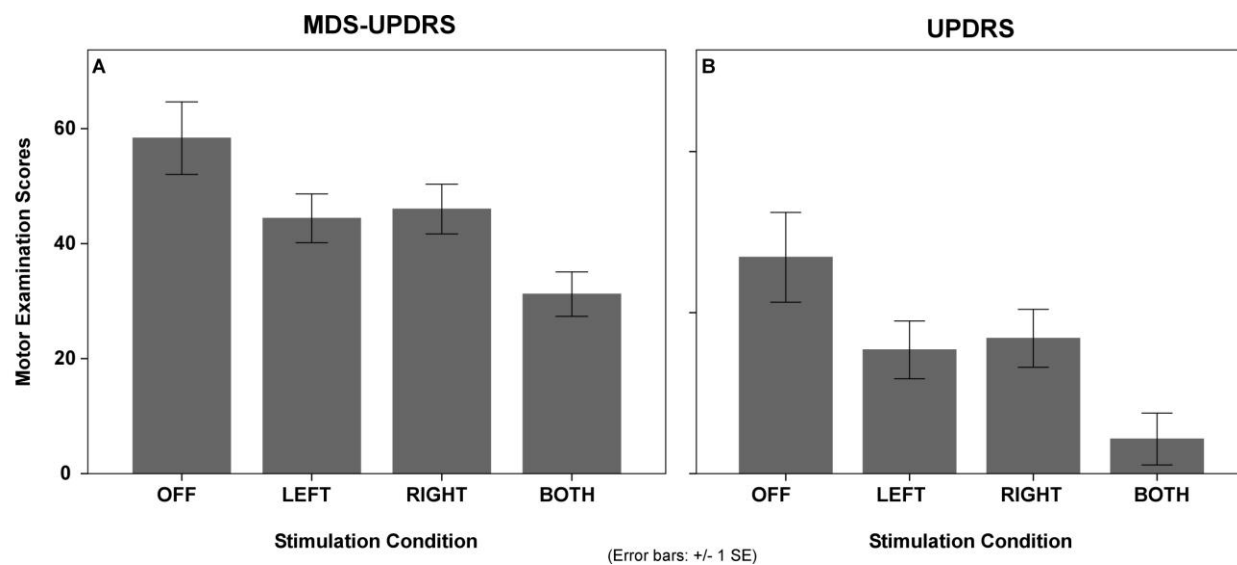**Figure 3.** Average saccade latency for the prosaccade task (A) and anti-saccade task (B) for each stimulation condition (OFF, LEFT, RIGHT, and BOTH) for the left target (dashed black line) and the right target (solid black line). The average saccade latencies for the control subjects are shown for the left target (dashed green line) and the right target (solid green line).

(Error bars: +/- 1 SE)
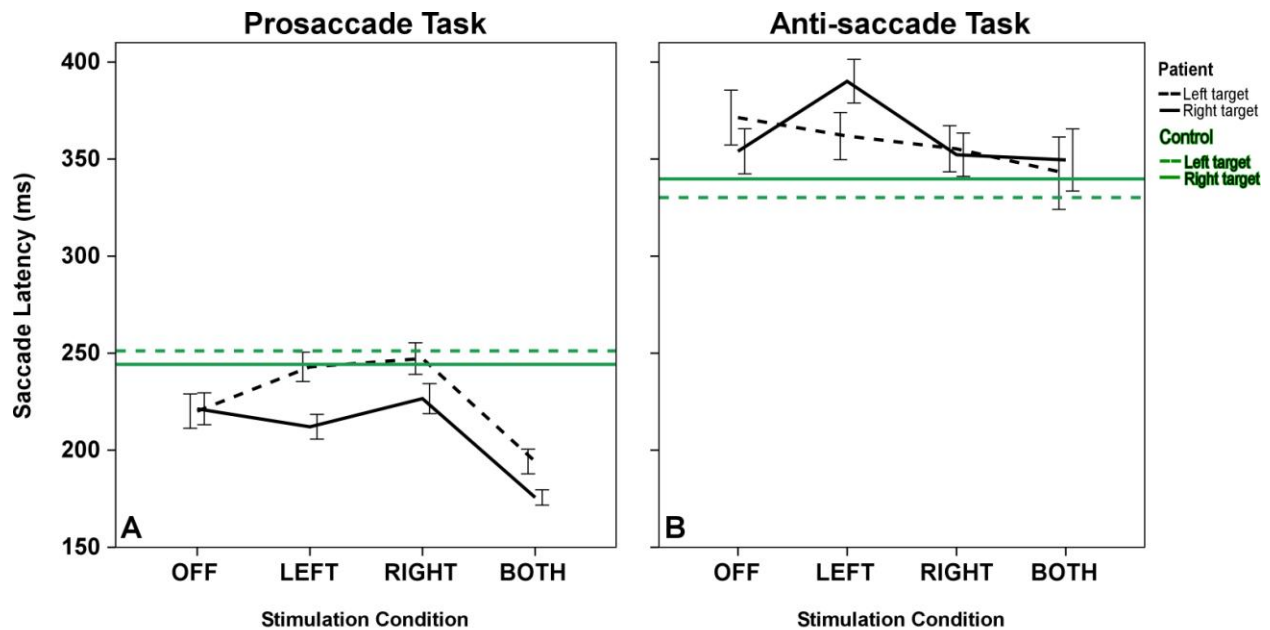
Figure 4. Average peak saccade velocity for the prosaccade task (A) and anti-saccade task (B) for each stimulation condition (OFF, LEFT, RIGHT, and BOTH) for the left target (dashed black line) and the right target (solid black line). The average peak saccade velocities for the control subjects are shown for the left target (dashed green line) and the right target (solid green line).

Figure 5. Average primary saccade gain for the prosaccade task (A) and anti-saccade task (B) for each stimulation condition (OFF, LEFT, RIGHT, and BOTH) for the left target (dashed black line) and the right target (solid black line). The average primary saccade gain for the control subjects are shown for the left target (dashed green line) and the right target (solid green line).

(Error bars: +/- 1 SE)

Figure 6. Average final saccade gain for the prosaccade task (A) and anti-saccade task (B) for each stimulation condition (OFF, LEFT, RIGHT, and BOTH) for the left target (dashed black line) and the right target (solid black line). The average final saccade gain for the control subjects are shown for the left target (dashed green line) and the right target (solid green line).
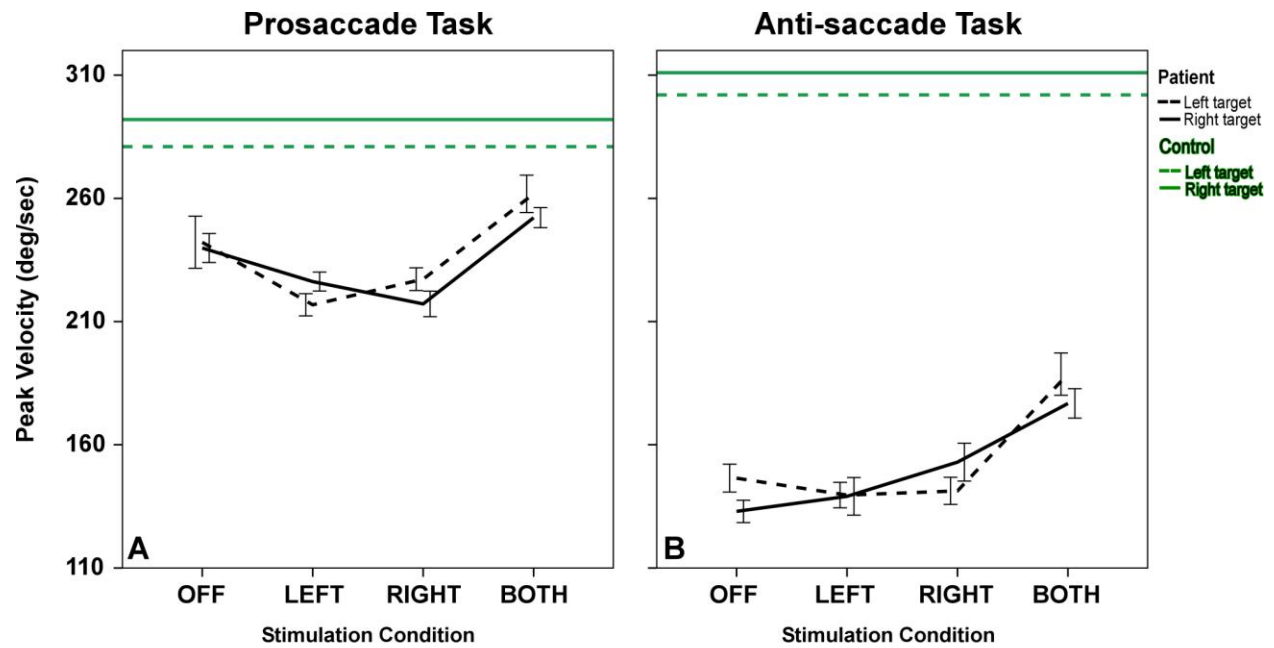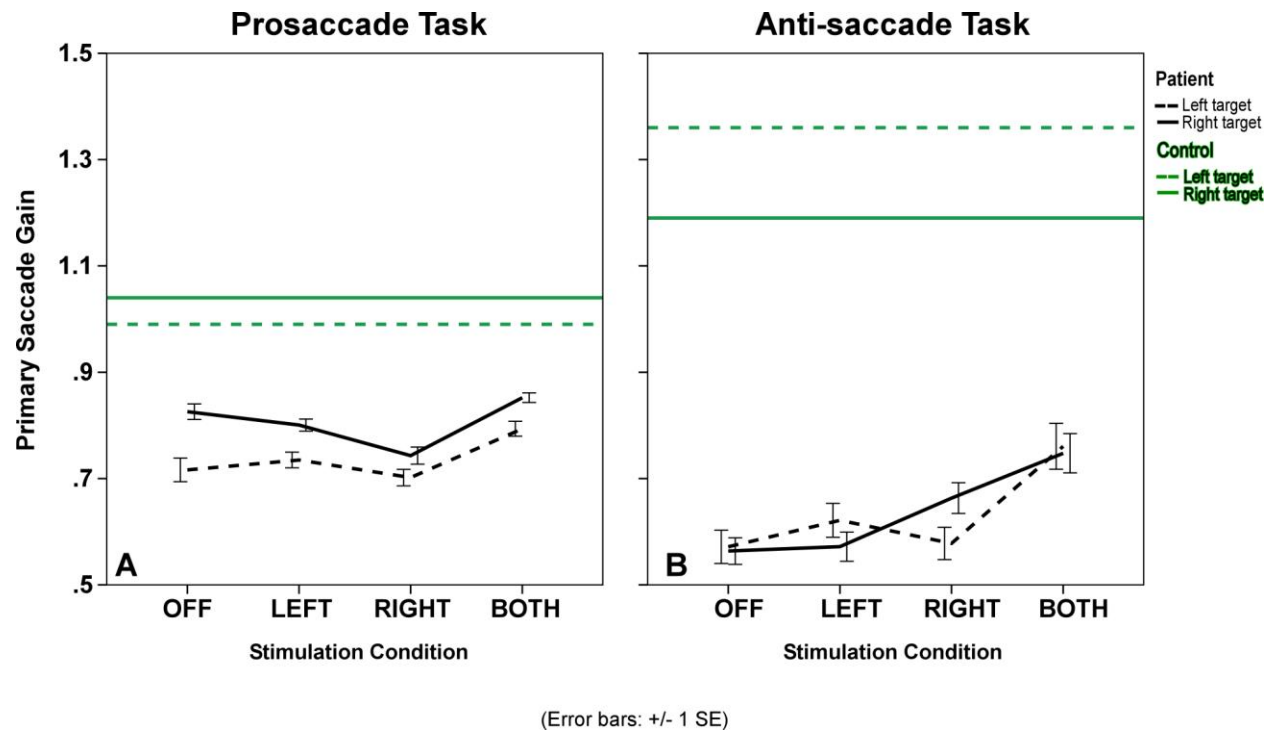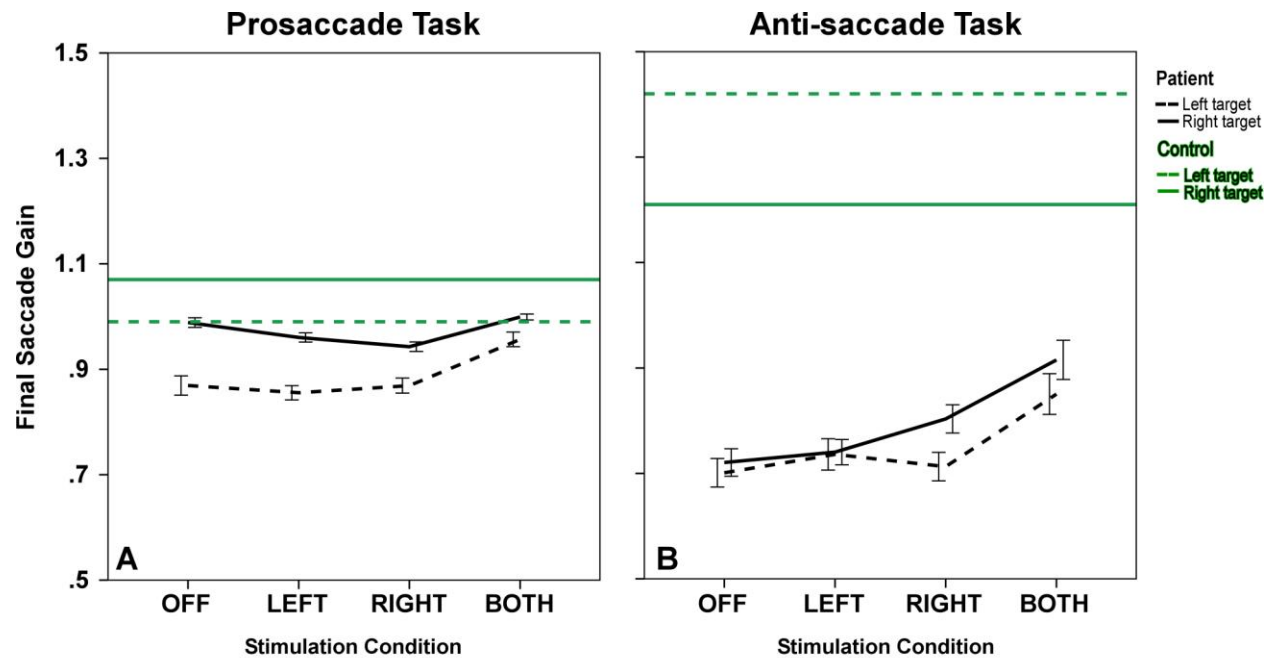
Figure 7. Percentage of erroneous prosaccades to target in the anti-saccade task for each

stimulation condition (OFF, LEFT, RIGHT, and BOTH). Prosaccades made to the right target

are shown by the black bars, and prosaccades made to the left target are shown by the grey bars.

For the control subjects, the percentage of erroneous prosaccades made to the right target are

indicated by the black horizontal line and the percentage of erroneous prosaccades made to the

left target are indicated by the grey horizontal line. A significantly greater amount of erroneous

prosaccades were made when BOTH stimulators were on, and this effect was more salient for

right target presentation.
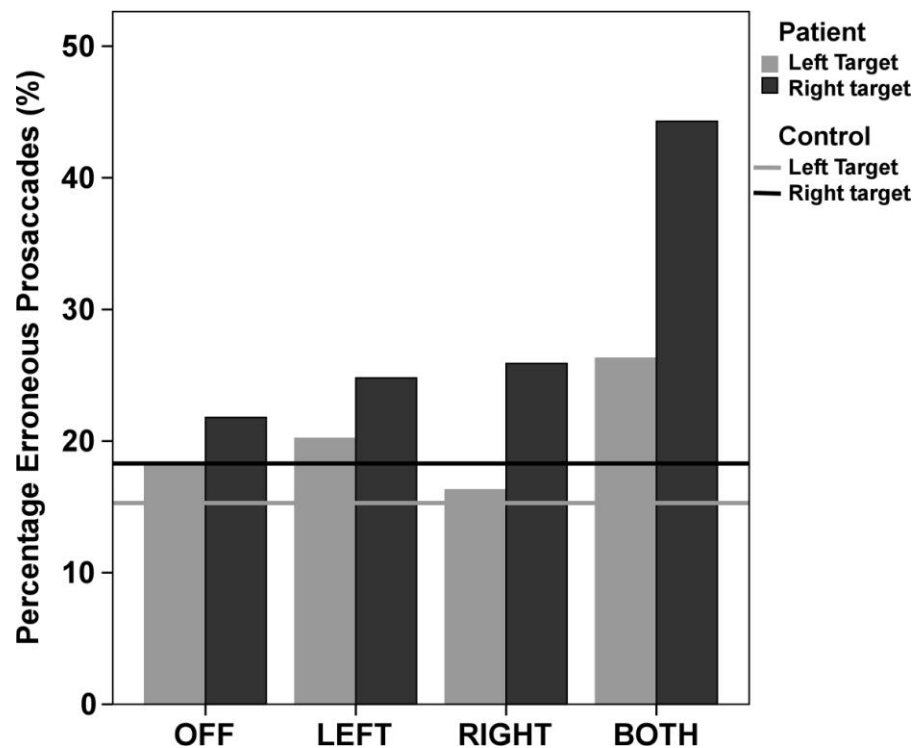
Chapter 4: Directions of Future Research

The overall purpose of this study was to determine the differential effects of unilateral and bilateral STN DBS on 2 types of saccadic eye movements that require different levels of cognitive processing. We used a visually-guided prosaccade task that is considered to be mostly reflexive and not cognitively demanding, and we used a cognitively-demanding task, the anti-saccade task, that requires the subject to intentionally inhibit a saccade to a visual target and then generate a saccade using an internal coordinate system. We found that 1) bilateral STN DBS was more effective than unilateral STN DBS at improving eye movement amplitude (ie. gain) and velocity for both tasks, and 2) stimulation did not improve saccade latency for either task. Whereas measures of amplitude and velocity primarily reveal information about brainstem structures that modulate these properties, latency reflects the time course of neural processes of the superior colliculus and the cortical and subcortical areas that project to it (Dorris et al., 1997). Our findings support the concept that STN DBS appears to be effective at improving "intensive" deficits of movement, such as gain modulation of amplitude and velocity, but is less effective at improving "coordinative" deficits, which involve coordination of different inputs and motor components (Schettino et al., 2006). Additionally, we found that bilateral, but not unilateral STN DBS impaired saccadic inhibition in the anti-saccade task. Our finding is in accordance with the Alberts et. al 2008 study that found bilateral, but not unilateral, STN DBS impaired working memory function during a motor task. Both saccadic inhibition and working memory depend upon normal dorsolateral prefrontal cortical (DLPFC) processing (Barbey, Koenigs, & Grafman, 2013; Pierrot-Deseilligny et al., 2004). Thus, it is possible that bilateral STN DBS interferes with DLPFC processes.

There is relatively little research that has investigated the differential effects of unilateral and bilateral STN DBS. To further our understanding of the effects of STN DBS, future research should focus on investigating the differential effects of unilateral and bilateral STN DBS on intensive and coordinative properties of saccades as well as the differential effects on cognitive processes known to rely on the DLPFC. The following section is a brief overview of potential future studies that would allow us to further our investigation of these effects.

4.1 Memory-guided saccade experiment

Similar to the anti-saccade task, the memory-guided saccade task requires the participant to inhibit a reflexive saccade to a visual target and then generate a saccade using an internal coordinate system. Unlike the anti-saccade task, the target is displayed then extinguished, and the participant must hold that spatial location in memory until cued to make a saccade to the remembered target location. It has been shown that the DLPFC plays a critical role in spatial memory (Pierrot-Deseilligny et al., 2004), and therefore measuring the spatial accuracy of memory-guided saccades under different stimulation conditions could potentially provide further insight into the effects of stimulation on DLPFC processing. However, caution must be used in interpreting measurements of "accuracy". Many memory-guided studies use 2 horizontal targets- one to the right of fixation and one to the left- at fixed eccentricities. It could be argued that 2 locations is not enough to challenge spatial memory processes, for the patient could learn the amplitude of the 2 locations in the beginning of the block of trials and then only have to remember direction (whether the target was presented to the left or right) during the delay period. This potential confound could be avoided by increasing the amount of possible targets. Target

locations could include additional horizontal targets at different eccentricities, vertical targets, and oblique targets. Although the addition of target locations would theoretically increase the challenge of spatial memory processing, caution must still be used in interpreting these measurements as measures of spatial accuracy when they could actually be measures of intensive properties of the saccade. In other words, if one stimulation condition resulted in saccades with an average amplitude that was close to the remembered target, and another stimulation condition resulted in saccades that fell short of the target, there could be two possible explanations for the results: one is that the first stimulation condition improved spatial accuracy to a greater extent than the second stimulation condition; the alternative explanation is that the first stimulation condition improved gain (ratio of saccade amplitude to target amplitude) to a greater extent than the second stimulation condition. To avoid this confound, a secondary task could be implemented in which the participants perform a block of trials of voluntary maximal saccades. In this task, patients would be instructed to "make one eye movement, as big as possible" in a specified direction. The measurements of these saccades could then be used to assess the effects of stimulation on intensive properties of the saccade (ie. modulation of amplitude) and to normalize the data collected from the memory-guided saccade task.

4.2 Predictive saccade experiment

Another cognitive function known to be processed by the DLPFC is prediction (Pierrot-Deseilligny et al., 2004). In a typical predictive saccade task, visual targets are presented in an alternating pattern between two targets at two fixed locations at a fixed frequency of presentation. At the beginning of the trial, participants (both healthy controls and patients with

Parkinson's) make saccades that are guided by the visual target and thus have average latencies (time between target onset and saccade onset) greater than 90 ms. Once the participant learns the location of the targets and frequency of presentation of the targets, saccade latencies fall into a predictive range (< 90 ms) indicating that the participant is predicting the presentation of the target and generating saccades using internal spatial and temporal sources rather than reacting to an external cue. Patients with Parkinson's adopt this predictive strategy later than healthy controls (T. Crawford et al., 1989). However, Crawford et. al (1989) designed a predictive paradigm in which patients performed a block of predictive saccades with visual targets followed by a block of predictive saccades without visual stimuli, and found that patients performed abnormally compared to controls when lights were presented, and were not impaired at making predictive saccades when no target lights were presented. For the block with visual targets, control subjects consistently exhibited negative latencies (ie. saccade onset occurred before target light onset), and patients with Parkinson's exhibited variable latencies that were primarily positive (ie. saccade onset occurred after target light onset). When the visual targets were removed and the subjects were instructed to continue the predictive task, latencies of the patients became consistently negative and were no longer significantly different from the controls. The authors speculated that, since the patient is fixating on one target light at the time that a saccade to the other target light should be initiated, reduced latencies during the block without visual targets could be an indication that patients experience difficulty releasing their fixation from the visual target. Another way to assess fixation release would be to implement visually-guided prosaccade tasks with and without fixation light overlap. Analyzing the effect of different stimulation conditions on the latencies exhibited during step and overlap prosaccade tasks would give insight into whether stimulation was affecting patients' ability to release fixation. It follows

that, in order to understand the effects of unilateral and bilateral STN DBS on predictive

saccades, patients should be asked to perform the following under the different stimulation

conditions (OFF, LEFT, RIGHT, and BOTH): 1) A block of predictive saccades with visual

targets presented followed by a block of predictive saccades with visual targets removed, 2) a

block of visually-guided prosaccades using the step paradigm, and 3) a block of visually-guided

prosaccades using an overlap paradigm.

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APPENDIX

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Continuing Review

October 3, 2013

Daniel Corcos, PhD
Department of Kinesiology and Nutrition
Kinesiology and Nutrition
1919 West Taylor, 650 AHSB, M/C 994
Chicago, IL 60612
Phone: (312) 355-1708 / Fax: (312) 355-2305

RE: Protocol # 1998-1161
"Motor Deficits-Experimental Correlates"

Dear Dr. Corcos:

Your Continuing Review was reviewed and approved by the Convened review process on October 2, 2013. You may now continue your research.

Please note the following information about your approved research protocol:

> **Please submit an amendment to reconcile the reimbursement across all informed consent documents. Include information regarding the total amount paid versus the amount paid per visit. Additionally, include what travel expenses are reimbursed.**

Protocol Approval Period: October 3, 2013 - October 3, 2014
Approved Subject Enrollment #:   500 (277 enrolled to date)
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC, Rush Presbyterian St. Luke's Medical Center, Institute of Neurology in London
Sponsor: NINDS, NIH
PAF#:   2005-06809, 2011-02219
Grant/Contract No: R01 NS40902-08, 2R56NS040902-11A1
Grant/Contract Title: STN Stimulation: Neural Control of Movement and Posture, STN Stimulation: Control of Movement and Posture
Research Protocol(s):

   a) HHS-NIH-NS40902, "STN Stimulation: Neural Control of Movement and Posture", Version #2, 8/26/2013

APPENDIX (CONTINUED)

Recruitment Material(s):
    a) UIC Recruitment Flyer: Flyer # 1, 5 Healthy males, Version # 2, 11/3/04
    b) UIC Recruitment Flyer: Flyer # 2, Healthy (neurologically normal) subjects, Version # 2, 11/3/04
    c) UIC Recruitment Flyer: Research Motor Control Laboratory, Flyer # 3, Version 2, 11/3/04
    d) Patient Letter, Motor Control - Statement of Interest, Version # 3, 10/30/2001
    e) Follow-up Letter, Cover Letter Version # 1, 1/7/04
    f) Recruitment Letter, Dear Dr. Daniel Corcos, Version # 2, 1/7/2004

Informed Consent(s):
    a) Waiver of Informed Consent for Recruitment Purposes granted under 45 CFR 46.116(d)
    b) Motor Deficits # 1998-1161, Version #5, Follow Up Addendum Medication, 09/06/2013
    c) Motor Deficits # 1998-1161, Version #4, Follow Up Addendum Brain Stimulation, 09/06/2013
    d) UIC Adult Consent: Motor Deficits # 1998-1161, Version # 13, Medication, 09/06/2013
    e) UIC Adult Consent: Motor Deficits # 1998-1161, Version # 16, Brain Stimulation, 09/06/2013
    f) UIC Adult Consent: Motor Deficits # 1998-1161, Version # 14, Neurologically Normal, 09/06/2013
    g) Motor Deficits, # 1998-1161, Version #6, Follow Up Addendum Neurologically Normal, 09/06/2013

HIPAA Authorization(s):
    a) Waiver of HIPAA authorization for recruitment purposes granted under [45 CFR 164.512(i)(1)(i)]
    b) UIC "Motor Deficits # 1998-1161 - Authorization", Version # 1, 3/31/03. Please continue to use the Authorization form, which was stamped and approved on April 1, 2003.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
09/16/2013	Continuing Review	Convened	10/02/2013	Approved

Please remember to:

→ Use your **research protocol number** (1998-1161) on any documents or correspondence with the IRB concerning your research protocol.

→ Review and comply with all requirements on the enclosure,
    "UIC Investigator Responsibilities, Protection of Human Research Subjects"
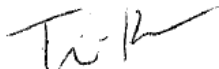   *(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)*

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

APPENDIX (CONTINUED)

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 996-0865. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Tricia Hermanek, BS
IRB Coordinator, IRB # 1
Office for the Protection of Research Subjects

Enclosure(s):

1. **Informed Consent Document(s):**
   a) Motor Deficits # 1998-1161, Version #5, Follow Up Addendum Medication, 09/06/2013
   b) Motor Deficits # 1998-1161, Version #4, Follow Up Addendum Brain Stimulation, 09/06/2013
   c) UIC Adult Consent: Motor Deficits # 1998-1161, Version # 13, Medication, 09/06/2013
   d) UIC Adult Consent: Motor Deficits # 1998-1161, Version # 16, Brain Stimulation, 09/06/2013
   e) UIC Adult Consent: Motor Deficits # 1998-1161, Version # 14, Neurologically Normal, 09/06/2013
   f) Motor Deficits, # 1998-1161, Version #6, Follow Up Addendum Neurologically Normal, 09/06/2013

2. **Recruiting Material(s):**
   a) UIC Recruitment Flyer: Flyer # 1, 5 Healthy males, Version # 2, 11/3/04
   b) UIC Recruitment Flyer: Flyer # 2, Healthy (neurologically normal) subjects, Version # 2, 11/3/04
   c) UIC Recruitment Flyer: Research Motor Control Laboratory, Flyer # 3, Version 2, 11/3/04
   d) Patient Letter, Motor Control - Statement of Interest, Version # 3, 10/30/2001
   e) Follow-up Letter, Cover Letter Version # 1, 1/7/04
   f) Recruitment Letter, Dear Dr. Daniel Corcos, Version # 2, 1/7/2004

cc: Charles B. Walter, Department of Kinesiology and Nutrition, M/C 517
     OVCR Administration, M/C 672
     Privacy Office, Health Information Management Department, M/C 772

<u>VITA</u>

Name

Lisa Chin

Education

Ph.D., Kinesiology and Nutrition
University of Illinois at Chicago
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Chicago, IL 2009

B.S., Kinesiology
University of Illinois at Chicago
Chicago, IL 1998

Professional & Teaching Experience

2007-2012, Graduate Teaching Assistant
Department of Kinesiology and Nutrition,
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Society Memberships

2012-2013, Member
Movement Disorders Society

2012-2013, Member
Society for Neural Control of Movement

Publications

Poon C, Chin-Cottongim L, Coombes S, Corcos DM, Vaillancourt DE. Spatiotemporal dynamics of brain activity during the transition from visually-guided to memory-guided force control. Journal of Neurophysiology. 2012.

Conference Presentations

Chin-Cottongim L, David FJ, Poizner H, Sweeney J, Vaillancourt DE, Corcos DM. The effects of unilateral vs. bilateral subthalamic nucleus deep brain stimulation on prosaccades and anti-saccades. 23rd Annual Meeting of the Society for Neural Control of Movement, San Juan, Puerto Rico, USA. 2013.

David FJ, Tangonan RZ, Chin-Cottongim L, Corcos DM. Foveal and peripheral vision result in similar pointing accuracy and variability during memory-

guided pointing. 23rd Annual Meeting of the Society for Neural Control of Movement, San Juan, Puerto Rico, USA. 2013.

Tangonan R, David FJ, Chin L, Corcos DM. The effect of bilateral deep brain stimulation of the subthalamic nucleus on memory-guided sequential pointing. Undergraduate Research Symposium at the University of Illinois at Chicago, 2013.

Awards

2012 Scientific Platform Award, Second Place. Chin-Cottongim L, Poon C, Coombes S, Corcos DM, Vaillancourt DE. Spatiotemporal dynamics of brain activity during the transition from visually-guided to memory-guided force control. Journal of Neurophysiology. 2012.American Association of Anatomists Regional Meeting. Rush University Medical Center, Chicago, IL. 2012