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Neuropsychological Performance After Unilateral Subthalamic Deep Brain Stimulation in Parkinson's Disease

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UNIVERSITY OF MIAMI

NEUROPSYCHOLOGICAL PERFORMANCE AFTER UNILATERAL
SUBTHALAMIC DEEP BRAIN STIMULATION IN PARKINSON'S DISEASE

By

Ilona Buscher Marion

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

August 2010

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NEUROPSYCHOLOGICAL PERFORMANCE AFTER UNILATERAL
SUBTHALAMIC DEEP BRAIN STIMULATION
IN PARKINSON'S DISEASE

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The current study examined cognitive effects of unilateral subthalamic nucleus (STN) deep brain stimulation (DBS) in Parkinson's disease (PD) patients. Neuropsychological evaluations were conducted at baseline and follow-up. Data was collected from 28 unilateral STN DBS patients (15 English- and 13 Spanish-speaking), and 15 English-speaking matched PD control patients. English-speaking DBS patients demonstrated significant declines in verbal fluency and attention/executive function, whereas PD control patients did not experience significant cognitive decline. Cognitive performance did not differ based on side of DBS. Spanish-speaking DBS patients experienced significant declines in verbal fluency, confrontational naming and visuospatial abilities. Among Spanish-speaking DBS patients, older age and later age of disease onset predicted verbal fluency decline, even after controlling for education.

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Chapter One: Rationale

Parkinson's disease (PD) is a neurodegenerative movement disorder caused by a selective degeneration of dopaminergic neurons in the basal ganglia. Cardinal motor symptoms of PD are tremor, rigidity, and bradykinesia. Other noncognitive symptoms may include autonomic dysfunction, postural instability, gait disturbances, sensory disturbances, motor speech difficulties, fatigue, and sleep impairments.

There are also cognitive and psychiatric changes that are known to occur. The most frequently reported cognitive impairments in PD are deficits in executive function, verbal fluency, memory, and visuospatial abilities (Direnfeld, Albert, Volicer, Langlais, Marquis et al., 1984; Muslimovic, Post, Speelman, & Schmand, 2005; Starkstein, Leiguarda, Gershanik, & Berthier, 1987; Williams-Gray, Foltynie, Lewis, & Barker, 2006). Executive dysfunction, memory impairments, and visuospatial deficits may develop early in the disease course (Cooper, Sagar, Jordan, Harvey, & Sullivan, 1991; Levin & Katzen, 2005; Muslimovic, Schmand, Speelman, & Haan, 2007; Williams-Gray et al., 2006). Verbal fluency deficits are a common impairment in PD, regardless of disease stage. As a group, PD patients generally show a subtle progressive decline in cognitive function over time, but certain subgroups of patients may exhibit more profound and obvious deterioration (Biggins, Boyd, Harrop, Madeley, Mindham, Randall et al., 1992; Dubois, Pillon, & Sternic, 1990; Green, McDonald, Vitek, Evan, Freeman, et al., 2002; Katzen, Levin & Llabre, 1998; Muslimovic et al., 2005).

The primary treatment for PD is pharmacological intervention. PD patients can benefit from pharmacologic treatment for some time; however, patients may become progressively less responsive to medication and often develop intolerable side effects.

When pharmacological treatment fails, surgical treatment is often considered and has been shown to palliate PD symptoms. Currently, deep brain stimulation (DBS) is the most widely used neurosurgical procedure for PD. DBS typically involves implantation of an electrode, in the subthalamic nucleus (STN) or the globus pallidus interna (GPi), which is connected to a pulse generator.

DBS significantly improves motor symptoms and reduces the need for pharmacological treatment, but long-term effects on cognitive and psychiatric symptoms are controversial. Research suggests that DBS is most beneficial for patients who are younger, have shorter disease duration, exhibit predominant tremor, and do not present with axial symptoms, dementia or psychiatric comorbidities.

Findings from meta-analyses and controlled studies indicate that significant verbal fluency declines are the most consistently observed cognitive change after bilateral DBS. Deterioration in verbal fluency is likely related to impairments in executive function or semantic memory. Declines in other cognitive domains, such as memory and executive function, have also been reported after DBS, although results are equivocal and some studies suggest improvement in select cognitive functions. There is considerable debate over the effects of DBS on cognition and the factors that influence cognitive decline. Research suggests that older age and later disease onset, as well as lower levels of education, are likely risk factors for cognitive decline following DBS.

The purpose of the current study was to examine long-term effects of unilateral STN DBS on cognitive performance. A major aim was to compare cognitive performance between unilateral STN DBS patients and PD control patients receiving pharmacological treatment, who had not undergone any neurosurgical treatment. A

secondary aim was to examine the effects of side of stimulation on cognitive performance after unilateral STN DBS.

Additionally, this study was the first to explore changes in cognitive performance after unilateral STN DBS in a subset of Hispanic Americans assessed in Spanish. Spanish-speakers have never been studied in the context of DBS research, despite exponential growth in the Hispanic-American population (U.S. Census Bureau, 2000) and evidence of higher rates of PD incidence among Hispanic-Americans compared to non-Hispanic Whites, Asian-Americans, or African-Americans (Van Den Eeden et al., 2003). In this study, Spanish-speakers comprised almost half of the total number of DBS patients; therefore, an exploratory aim was to examine cognitive changes among this subset of patients.

Chapter Two: Overview of Parkinson's Disease

Prevalence and Incidence

Parkinson's disease is the second most common neurodegenerative disease (de Lau & Breteler, 2006; Eichhorn & Oertel, 1994). Its prevalence is estimated to be 0.3% in the U.S. and 0.15% worldwide (Martin, 1998; Rao, Hofmann, & Shakil, 2006).

Prevalence estimates vary by geographic region and ethnic group (Brown, Rumsby, Capleton, Rushton, & Levy, 2006; Singhal, Lalkaka, & Sankhla, 2003; Tan, Venketasubramanian, Jamora, & Heng, 2007). Socio-economically driven differences in access to medical care and life expectancy, as well as imprecision in detection and diagnosis of PD, are sources of bias for these epidemiological findings.

The annual incidence of PD varies considerably. Among Asians, reported rates per 100,000 vary from 1.5 in China to 16.9 in Japan (Morioka, Sakata, Yoshida, Nakai, Shiba, Yoshimura et al., 2002; Wang, 1991). In the United States, the yearly incidence is estimated to be 20.5 per 100,000 (Brown et al., 2006), whereas European incidence estimates range from 5 to 346 per 100,000 annually (von Campenhausen et al., 2005). A review of 25 European studies of PD incidence revealed noteworthy variations in methods of identifying patients, as well as diagnostic and exclusionary criteria, which accounted for some of the discrepant findings (Twelves, Perkins, & Counsell, 2003). These discrepancies in incidence and prevalence rates suggest a greater need for standardized methods to improve comparability among epidemiological studies of PD.

Demographics of Parkinson's Disease

Age

Among known risk factors, age is most strongly correlated with PD (Fahn & Sulzer, 2004). Some studies estimate that PD occurs in 1% of adults over age 65 years and 4%-5% of adults over 85 years of age (Rao et al., 2006; Eichhorn & Oertel, 1994). The risk of developing PD increases by 1.1% with each year over 65, and the prevalence rises steadily, from 0.6% to 3.5%, between the ages of 65 and 89 years (Fahn & Sulzer, 2004). The average age of onset is between 60 and 65 years, though as many as 15% of cases are diagnosed before the age of 50 (Brown et al., 2006). A diagnosis of PD before the age of 40 is uncommon and is referred to as "young-onset PD" (Brown et al., 2006).

Gender

Several studies found that gender modifies the incidence, symptoms, and treatment of PD (Baba, Putzke, Whaley, Wszolek, & Uitti, 2005; De Lau, Giesbergen, de Rijk, Hofman, Koudstaal, & Breteler, 2004; Haaxma, Bloem, Borm, & Oyen, 2007; Shulman, 2007; Shulman & Bhat, 2006). In general, PD incidence is higher in men. For example, among Americans, the incidence rate for men (19.0 per 100,000) is 91% higher than that for women (9.9 per 100,000) (Van Den Eeden, Tanner, Bernstein, Fross, & Leimpeter, 2003).

Gender differences have also been shown to exist in the efficacy of antiparkinsonian medications. Shulman (2007) reported that women have greater levodopa bioavailability and therefore require lower doses of medication. Others found a trend for lower daily levodopa equivalence dosage and more severe dyskinesias among

women (Accolla, Caputo, Cogiamanian, Tamma & Mrakic-Sposta, 2007; Baba et al., 2005).

Gender differences may also exist with regard to rates of surgical treatment of PD. Hariz and Hariz (2000) found that 35% of females and 65% of males with PD underwent surgical treatment. These proportions were relatively consistent regardless of surgical procedure (e.g., thalamotomy, pallidotomy, DBS) or geographical location and were unexplained by gender differences in PD prevalence (Hariz & Hariz, 2000). Similarly, Setiawan and colleagues (2006) reported that of 91 patients referred for surgery, only 31% were female. Differences in rates of surgical treatment of PD may be attributed to patient-selection criteria, patient-referral patterns, and gender differences in attitudes toward surgery.

Race/Ethnicity

Research suggests that racial differences exist in PD, but the findings are inconsistent. Individuals of Hispanic origin appear to have a greater incidence of PD than other racial or ethnic groups (Van Den Eeden et al., 2003). A study conducted in Northern California found that age- and gender-adjusted incidence rates per 100,000 were highest among Hispanics (16.6), followed by non-Hispanic Whites (13.6), Asians/Pacific Islanders (11.3) and Blacks (10.2) (Van Den Eeden et al., 2003). Lower prevalence among individuals of African origin may reflect a greater vulnerability to vascular parkinsonism, which is associated with greater mortality (Richards & Chaudhuri, 1996). Racial differences in PD rates are likely confounded by the effects of high selective mortality, low case ascertainment, and lax application of diagnostic criteria (McInerney-Leo, Gwinn-Hardy, & Nussbaum, 2004).

Neuroanatomy of Parkinson's Disease

Several brain structures are implicated in PD, most notably the basal ganglia, a group of subcortical nuclei that play a key role in the organization of movement. The major divisions of the basal ganglia are the striatum (composed of the caudate nucleus and putamen), the globus pallidus, and the substantia nigra. The basal ganglia are of particular interest in PD because of their connections to the cortex and thalamus. The basal ganglia are part of an intricate network of neuronal circuits, organized in parallel to integrate activity from different cortical areas (Obeso, Rodriguez-Oroz, Rodrigues, Arbizu, & Gimenez-Amaya, 2002).

The subthalamic nucleus (STN), a common surgical target for PD treatment, modulates basal ganglia output and is an important relay area in the motor cortico-basal ganglia-thalamo-cortical circuit (Haegelen, Verin, Broche, Prigent, Jannin et al., 2005). The STN is composed of projection glutamatergic neurons, and has direct and indirect connections with frontal associative and limbic areas (Haegelen et al., 2005, Temel, Blokland, Steinbusch, & Visser-Vandewalle, 2005). The STN and globus pallidus are interconnected by the fibers of the subthalamic fasciculus. The STN projects efferents to both segments of the globus pallidus, both components of the substantia nigra, the striatum, the pedunculopontine nucleus, the ventral tegmental area, and the brainstem (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004). These projections comprise an essential component of the motor loop of the basal ganglia.

Neuroimaging studies describe a complex, intrinsic pattern of somatotopy in the STN, with multiple homunculi within the nucleus (Hamani et al., 2004). The STN is functionally subdivided into two rostral thirds and a caudal third. The two rostral thirds

are further subdivided into medial and lateral portions. The medial portion comprises the limbic and part of the associative territory; the ventral part of the lateral portion comprises the other part of the associative territory (Hamani et al., 2004). The dorsal area of the lateral portion and the caudal third of the nucleus are related to motor circuits (Hamani et al. 2004).

The STN receives afferents from the cerebral cortex, thalamus, globus pallidus externa (GPe) substantia nigra compacta (SNc), and brainstem (Hamani et al., 2004). Most of the cortical afferents originate in the primary motor cortex, supplementary motor area, pre-supplementary motor area, and dorsal and ventral pre-motor cortices (Hamani et al., 2004). Projections from the cingulate, somatosensory cortex, and insular cortex are also present (Hamani et al., 2004).

Dopamine modulates the glutamatergic and GABAergic afferents from the cortex and globus pallidus, respectively (Hamani et al., 2004). In neuronal slices, dopamine application reduces glutamatergic excitatory postsynaptic potentials and GABAergic inhibitory postsynaptic potentials in the STN, thereby decreasing neuronal excitability, resulting in a net increase of activity in the STN (Hamani et al., 2004). Studies suggest that dopaminergic agonists (D1, D2, and nonspecific agonists such as apomorphine) decrease STN activity (Hamani et al., 2004). Although the precise effects of dopamine agonists are undetermined, a complex cascade of responses is linked to their administration.

Neuropathology of Parkinson's Disease

Rapid degeneration of dopaminergic neurons in the ventrolateral layer of the substantia nigra results in decreased amounts of dopamine. Dopaminergic neuronal loss

occurs primarily in the nigrostriatal tract and to a lesser extent in the mesocortical pathway (Lewis, Dove, Robbins, Barker, & Owen, 2003). Symptoms of PD become evident when 50%-75% of dopaminergic neurons are damaged or destroyed (de Lau, Koudstaal, Hofman, & Breteler, 2006; Martin, 1998). The causes of neuronal degeneration are unknown; nevertheless, the degree of vulnerability to neurotoxins or other mediators of neurodegeneration may influence development of the disease (Fleming, Delville, & Schallert, 2005).

The current model of PD pathophysiology asserts that decreased dopamine levels lead to a loss of dopaminergic input to the direct and indirect pathways of the basal ganglia. This results in inhibition of the direct pathway and excitation of the indirect pathway, leaving a person unable to control movements normally (Martin, 1998). The net effect is increased inhibitory output from the globus pallidus interna (GPi) and thus reduced activation of cortical projection sites via the thalamus. STN hyperactivity occurs due to underactivation of the globus pallidus externa (GPe), because of abnormalities in the indirect pathway. Animal models suggest that overactivity of the STN enhances bursting in the SNc and leads to increased dopamine release, which may be an initial compensatory mechanism after dopamine depletion; however, excess glutamate release following STN hyperactivation may promote further loss of dopaminergic neurons and ultimately accelerate disease progression (Hamani et al., 2004).

In addition to dopaminergic degeneration of striato-cortical pathways, the substantia nigra and locus coeruleus may contain eosinophilic intracytoplasmic inclusions, known as Lewy bodies, which affect midbrain dopaminergic neurons as well as extranigral sites including the cholinergic, noradrenergic, and serotonergic systems

(Cheesman, Barker, Lewis, Robbins, Owen, & Brooks, 2005). Nondopaminergic lesions arise parallel to the dopaminergic nigrostriatal tract and are found in the cerebral cortex, nucleus basalis of Meynert, pedunculopontine nucleus, locus coeruleus, dorsal vagus nucleus, and raphe nuclei (Bejjani, Gervais, Arnulf, Papadopoulos, Demeret, et al., 2000).

Clinical Presentation

Idiopathic PD is clinically diagnosed by the presence of bradykinesia and one or more of the following cardinal signs: rigidity (increased muscle tone), distal resting tremor or postural instability (Weiner, 2008). The diagnosis also requires that the patient respond to a therapeutic challenge of antiparkinsonian medication (e.g., levodopa).

Idiopathic PD does not include parkinsonism induced by drugs, viral infections, repeated head injury, or cerebral vascular disease (Ben-Shlomo & Sieradzan, 1995).

PD is distinguished from other neurological disorders by specific symptoms as well as the disease course. The onset of PD is typically asymmetric and unilateral (de Lau et al., 2006). Asymmetrical disease onset is an indicator of disproportionate dopamine depletion in the initially affected hemisphere (Cheesman et al., 2005). Laterality becomes less distinguished as the disease progresses and affects the second cerebral hemisphere.

Common early symptoms of PD are stiffness, tremor, imbalance, and disturbances in fine motor control (de Lau et al., 2006; Martin, 1998). Other early symptoms include hoarse speech and difficulty performing simultaneous movements. Pronounced loss of olfaction, dysaesthesiae, autonomic disturbances, and depression occur in some patients (Ben-Shlomo & Sieradzan, 1995; de Lau et al., 2006), but these nonmotor abnormalities are not necessarily pathognomonic (Weiner, 2008).

Additional symptoms may include stooped posture, shuffling gait, difficulty with swallowing (dysphagia), impaired speech (e.g., dysarthria, hypophonia), dizziness or fainting due to orthostatic hypotension, or impaired proprioception (Rao et al., 2006; Martin, 1998). Autonomic dysfunction can lead to weight loss, oily skin and seborrheic dermatitis, urinary incontinence, constipation, and sexual dysfunction (Rao et al., 2006; Martin, 1998). Sustained muscle contractions that cause twisting and repetitive movements or abnormal postures, known as dystonia, also may occur (Rao et al., 2006; Martin, 1998).

Symptom progression varies from patient to patient. On average, the interindividual rate of progression is 0.4 points per year on the Hoehn and Yahr scale, a measure of PD severity (Eichhorn & Oertel, 1994). Intraindividual disease progression is approximately linear (Eichhorn & Oertel, 1994). Among pharmacologically treated patients, the mean survival time is 13-14 years after the onset of clinical symptoms (Eichhorn & Oertel, 2004).

Differential diagnosis includes other neurodegenerative disorders with parkinsonian features, such as multiple system atrophy, progressive supranuclear palsy, Alzheimer's disease, diffuse Lewy body disease, pallidonigral and corticobasal degeneration (Ben-Shlomo & Sieradzan, 1995). Prominent and early dementia, early postural instability, severe and early autonomic dysfunction, supranuclear gaze palsy, strictly unilateral symptoms after three years, and/or bilateral symptoms at onset suggest a diagnosis other than idiopathic PD (Ben-Shlomo & Sieradzan, 1995; Rao et al., 2006). The lack of response to a challenge with antiparkinsonian medications also indicates an alternate diagnosis, although patients with other disorders may respond to these drugs.

Chapter Three: Neuropsychology of Parkinson's Disease

Cognitive Symptoms

Cognitive impairments in PD patients range from select subtle impairments to severe dementia. Mild cognitive impairment may occur in up to 19% of non-demented, untreated PD patients (Aarsland, Bronnick, Larsen, Tysnes, Alves, et al., 2009). Early in the disease course, executive dysfunction, memory impairments, and visuospatial deficits are frequently reported (Levin & Katzen, 2005; Muslimovic et al., 2007; Williams-Gray et al., 2006). Some investigators note deficits in working memory, semantic fluency, set-formation, cognitive sequencing, and visuomotor construction in newly diagnosed, untreated PD patients, which suggests these deficits occur independently of medication effects (Cooper et al., 1991). The most common cognitive changes involve attention and memory deficits, cognitive inflexibility, and difficulty learning new information (Direnfeld et al., 1984; Muslimovic et al., 2005; Starkstein et al., 1987; Williams-Gray et al., 2006).

It has been suggested that greater loss of dopamine in the dorsolateral basal ganglia loop, relative to depletion in the orbitofrontal, oculomotor and anterior cingulate loops, is likely responsible for some of the commonly observed cognitive deficits, particularly those related to executive function (Kaasinen & Rinne, 2002). PD patients generally show small changes in cognitive function over time, whereas certain subgroups of patients exhibit more profound and obvious deterioration. Dementia may develop in as many as 75% of PD patients, although estimates typically range from 15% to 25% (Brown & Marsden, 1984; Janvin, Aarsland, Larsen, & Hugdahl, 2003; Saawek & Derejko, 2003).

Language Impairments

Verbal fluency deficits are the most common language impairment in PD, regardless of age of disease onset or PD stage (Henry & Crawford, 2004). Verbal fluency deficits consist of impairments in phonemic, semantic, and action fluency (Bodis-Wollner & Jo, 2006; Piatt, Fields, Paolo, & Troster, 1999; Girotti et al., 1986). Impairments in verbal fluency likely reflect problems with shifting between categories and retrieval of information from semantic memory. Naming is typically not impaired (Henry & Crawford, 2004).

The degree to which PD affects language is difficult to evaluate because many verbal tasks require intact attention, memory, and executive function (Levin & Katzen, 2005), all of which are affected by PD-related dopaminergic deficits in the cortex and limbic areas. Additionally, the use of dopaminomimetics confounds evaluation of language deficits among PD patients, as their effects on language are controversial. Several studies detected no change in fluency or naming between “on” and “off” phases, despite large fluctuations in motor performance (Girotti et al., 1986; Meco, Bonifati, Bedini, Bellatreccia, Vanacore, & Franzese, 1991; Morrison et al., 2004). However, Gotham, Brown, and Marsden (1988) found verbal fluency impairments when patients were “off” levodopa. Several studies found that verbal fluency impairments correlated with greater disease severity, later disease onset (Huber, Freidenberg, Shuttleworth, Paulson, & Christy, 1989; Locascio, Corkin, & Growdon, 2003; Troster, Stalp, Paolo, Fields, & Koller, 1995) and depressive symptoms (Troster et al., 1995; Uekermann, Daum, Peters, Wiebel, Przuntek, & Muller, 2003).

Visuospatial Impairments

PD affects visual analysis and synthesis; constructional praxis; facial recognition; spatial attention; and judgment of direction, orientation, and distance (Levin, Llabre, Riesman, Weiner, Sanchez-Ramos et al., 1991). Dopaminergic changes along the visual pathway from the retina to the cortex produce visuospatial and visuoperceptual deficits at multiple levels (Bodis-Wollner, Marx, Mitra, Bobak, Mylin, & Yahr, 1987; Bodis-Wollner & Jo, 2006; Bulens, Meerwaldt, & Van der Wildt, 1988; Regan & Maxner, 1987). Visuospatial deficits occur in all stages of PD but vary by disease severity and duration. For example, Levin et al. (1991) found that facial recognition, mental object assembly, and manual visuoconstructional skills declined as a function of disease duration.

Shortly after PD onset, contrast sensitivity deficits may occur and are thought to be due to impairment of dopaminergic neurons of the preganglionic retina and a defect of retinal nerve fibers (Bodis-Wollner et al., 1987; Bodis-Wollner & Jo, 2006; Bulens et al., 1988; Regan et al., 1987). Reductions in contrast sensitivity affect spatial and motion perception, as well as visual attention (Uc, Rizzo, Anderson, Qian, Rodnitzky et al., 2005). Patients with mild to moderate PD typically demonstrate impaired visual perception (Uc et al., 2005). Dopaminergic deficits in basal-thalamo-cortical circuits produce visuoperceptual disorders (Ruiz-Sanches & Fernandez-Guinea, 2005), such as impaired perception of large spatial configurations (Barrett, Crucian, Schwartz, Nallaamshetty, & Heilman, 2001). Executive dysfunction, characterized by reduced shifting abilities and impaired motor responses, contributes to visuoperceptual and visuoconstructional impairments, particularly in early stages of PD.

Memory Impairments

Select aspects of memory are impaired in PD, but there is debate over which facets of memory are most affected. For example, several studies found that free recall was severely diminished, while recognition and cued recall were normal (Cooper, Sagar, & Sullivan, 1993; Kaasinen & Rinne, 2002; Lee, Chan, Ho, & Li, 2005; Van Oostrom, Dollfus, Brazo, Abadie, Halbecq et al., 2003), whereas, one study found reductions in recognition (Davidson, Anaki, Saint-Cyr, Chow, & Moscovitch, 2006). Research implicates retrieval deficits, rather than diminished storage capacity, for PD-related memory problems (Katzen et al., 1998). In addition to retrieval deficits, memory problems in PD are often noted on tasks that require working memory, attention, and temporal sequencing (such as digit span backwards), indicating that executive dysfunction contributes to memory impairments.

Several variables may influence the pattern of memory deficits in PD. Katzen and colleagues (1998) found that older age of disease onset predicted poorer performance on immediate and delayed recall. In other studies, PD patients with depression had pronounced impairments in short-term memory and immediate recall (Uekermann et al. 2003; Troster et al., 1995). Zakharov, Akhutina and Yakhno (2001) noted a relationship between greater memory impairments and increased severity of gait/postural reflex disturbances, suggesting that memory deficits are a manifestation of the PD neuropathological process. A functional MRI study revealed dysfunction of striatal, prefrontal, and/or medial temporal regions during a working memory task (Lewis et al., 2003). A subsequent study found that when PD patients were “on” levodopa, deficits in working memory improved (Lewis, Slabosz, Robbins, Barker, & Owen, 2005), which

supports previous studies that found levodopa improved verbal memory (Cooper et al., 1992; Pullman et al., 1988; Mohr et al., 1987), and suggests that dopaminergic depletion produces memory deficits via disrupted interactions between the basal ganglia and cortex.

Executive Dysfunction

Executive dysfunction begins early in PD and is prevalent throughout the disease course. PD patients demonstrate executive dysfunction characterized by slowness in set shifting, impaired generation and maintenance of set, and difficulty inhibiting competing information (Cools, Barker, Sahakian, & Robbins, 2001; Downes, Roberts, & Sahakian, 1989; Mahieux, Fenelon, Flahault, Manificier, Michelet et al., 1998). Impaired set shifting and inhibition of competing information reflect a highly specific attentional dysfunction in PD (Downes et al., 1989). Disrupted interactions between the striatum and frontal cortex likely underlie difficulties with shifting and inhibiting competing information (Cools et al., 2001). Additionally, deficits in executive function, specifically during “off” phases (Cheesman et al., 2005; Gotham et al., 1988), suggest that dopaminergic depletion plays an important role in executive dysfunction. Furthermore, PD patients demonstrate impairments in a multitude of cognitive domains, such as verbal fluency and memory, because of the implicit executive demands of tasks used to measure these domains.

Factors Impacting Cognition

There is considerable debate over the factors that influence the development of cognitive impairments in PD. Discrepant findings are explained in part by small sample sizes, methodological differences in patient selection, and choice of neuropsychological

measures. Below is a review of patient and disease factors linked to cognitive decline in PD.

Age and Cognitive Function

Several studies have shown that age is directly linked to cognitive function (Dubois et al., 1990; Green et al., 2002; Heitanen & Teravainen, 1988; Marras et al., 2002; Muslimovic et al., 2007). Green et al. (2002) reported that older age and longer disease duration were correlated with poorer performance on multiple neuropsychological measures. Other studies found that older age at disease onset were correlated with a higher incidence of cognitive impairment, overall dementia, and a more rapid course of cognitive decline (Biggins et al., 1992; Dubois et al., 1990; Muslimovic et al., 2005). Katzen, Levin and Llabre (1998) reported that older age at disease onset predicted executive dysfunction, above and beyond normative aging and PD duration. However, other studies have shown that younger age at disease onset (< 50 years) is associated with greater cognitive impairment (Bodis-Wollner, 2003; Freidman, 1994). The discrepant findings may be due to differences in research methodology and multicollinearity between age, age of disease onset, and disease duration.

Level of Education and Cognitive Function

Cognitive reserve theory suggests that higher educational attainment may exert a protective effect against cognitive decline (Stern, 2002), whereas lower educational attainment is likely a risk factor for development of PD dementia (Glatt, Hubble, Lyons, Paolo, Troster et al., 1996; Muslimovic et al., 2007). Level of education is a widely used proxy for cognitive reserve. A meta-analysis of cognitive decline in PD found that level of education significantly influenced mental flexibility, reasoning, attention, processing

speed, and memory, such that PD patients with fewer years of formal education experienced greater decline in global cognitive and memory abilities (Muslimovic et al., 2007). These findings are consistent with other studies (Palazzini, Soliveri, Filippini, Fetoni, & Zappacosta, 1995; Portin & Rinne, 1986).

Lateralization of Symptoms and Cognitive Function

There is controversy as to whether symptom lateralization corresponds to specific hemispheric deficits or global cognitive impairment. Tomer, Levin and Weiner (1993) found that patients with left-sided symptoms at onset performed significantly worse on measures of visuospatial skills, verbal recall, word retrieval, semantic fluency, abstract reasoning, attention, and mental tracking, which suggests global cognitive impairment.

Other studies have shown a relationship between lateralization of PD symptoms and hemisphere specific cognitive dysfunction. Several studies reported that predominant right-sided parkinsonian symptoms (reflecting left-hemisphere dysfunction) correlate with impaired performance on verbal fluency and verbal memory, (Huber, Freidenberg, Shuttleworth, Paulson, & Clapp, 1989; Spicer, Roberts, & LeWitt, 1988; Starkstein et al., 1987; Taylor, Saint-Cyr, & Lang, 1986). Left-sided symptoms have been associated with visuospatial impairments (Direnfeld et al., 1984; Finali, Piccirilli, & Rizzuto, 1994) and mild left hemispatial neglect (Starkstein et al., 1987).

Evidence from neuroimaging studies supports lateralization of striatal function. A PET study found that verbal executive tasks required left-striatum integrity, while spatial tasks required integrity of the right striatum (Cheesman et al., 2005). Collectively, these findings suggest that lateralization corresponds with hemisphere specific functional deficits.

Additionally, research shows that the side and type of motor symptom at onset interact to influence cognition, such that patients with right-sided tremor at onset perform comparably to control patients, but those with left-sided tremor or bradykinesia/rigidity at onset (on either side) have widespread cognitive deficits (Katzen, Levin, & Weiner, 2006). These findings suggests that cognitive function is relatively spared in patients with right-sided tremor at onset.

In contrast, some studies failed to find a relationship between lateralization of PD symptoms and cognitive impairment (Bentin, Silverberg, & Gordon, 1981; Finali et al., 1995; Huber et al., 1989; St. Clair, Borod, Sliwinski, Cote, & Stern, 1998). Studies that failed to find significant differences in neuropsychological performance between patients with left- and right-sided symptoms were typically composed of patients with longer disease duration, which corresponds with greater bilateral involvement. Hence, as the disease progresses, bilateral subcortical damage likely impairs the ability to compensate for damage to cerebral areas subserving cognitive processes.

Medication Effects and Cognitive Function

Several investigators suggest that cognitive function correlates with the response to antiparkinsonian medications and medication side effects in the early stages of the disease (Growden, Kieburtz, McDermott, Panisset, & Friedman, 1998; Cooper, Sagar, Doherty, Jordan, Tidswell et al., 1992; Lange, Paul, Naumann, & Gsell, 1995; Gotham, Brown, & Marsden, 1988; Pullman, Watts, Juncos, Chase, & Sanes, 1988; Dubois, Danze, Pillon, Cusimano, Lhermitte, & Agid, 1987; Mohr, Fabbrini, Ruggieri, Fedio, & Chase, 1987), but not necessarily in more advanced disease stages. Several studies found that antiparkinsonian drugs have minimal effects on neuropsychological performance in

patients with moderate to severe PD (Girotti, Carella, Pia Grassi, Soliveri, Marano et al., 1986; Gotham et al., 1988; Morrison, Borod, Brin, Halbig, & Olanow, 2004). Some studies report that levodopa improves working memory, delayed verbal memory, reaction time, attention, and cognitive sequencing (Cooper et al., 1992; Pullman et al., 1988; Mohr et al., 1987), whereas others suggest that levodopa is not associated with memory improvement (Lange et al., 1995) or frontal lobe function (Gotham et al., 1988).

In terms of other medications, there is inconsistent evidence that dopamine agonists influence cognitive function. One study found that D1- and D2-receptor agonists, such as pergolide, did not significantly affect cognitive function in patients with mild PD (Hoehn and Yahr score ≤ 2.5) when compared to off-treatment or treatment with levodopa (Brusa, Tiraboschi, Koch, Peppe, Pierantozzi et al., 2005). Similarly, others found no effect of D2/D3 agonists on cognition in non-demented PD patients when used in combination with levodopa (Relja & Klepac, 2006). In contrast, one study found that monotherapy with a D2/D3 agonist (pramipexole) resulted in impaired short-term verbal memory, attentional-executive functions and verbal fluency in patients with mild PD (Brusa, Bassi, Stefani, Pierantozzi, Peppe et al. 2003).

Other pharmacologic treatments for PD, such as anticholinergics, are also controversial. Impaired immediate memory and recognition have been reported among PD patients taking anticholinergics (Cooper et al., 1992; Dubois et al., 1987), while others failed to find compromised memory performance (Levin, Llabre, & Riesman 1991).

Psychiatric Symptoms

Psychiatric symptoms are common in PD and typically include depression, anxiety, and psychosis (Rao et al., 2006). Estimates suggest that depressive disorders are

prevalent in 20%-40% of patients (Lieberman, 2006; Ehrt, Brannik, De Deyn, Emre, Tekin et al., 2007), anxiety disorders in 25%-40%, and psychosis in 15%-40% (Lieberman, 2006). Depression and anxiety are often comorbid in PD.

Depression

Depressive symptoms are the most widely studied psychiatric disturbance in PD. The prevalence of depression in idiopathic PD is greater than in the general population, and is estimated to be as high as 47% (Dooneief, Mirabello, Bell, Marder, Stern, et al., 1992). Many PD patients experience chronic mildly to moderately depressed mood, while a subset of patients suffer from subthreshold depression, characterized by depressive symptoms that are less severe than and do not meet strict DSM-IV criteria for a depressive disorder (Levin & Katzen, 2005). One study found that 26% of PD patients met criteria for major depressive disorder; whereas 29% of PD patients experienced subthreshold depression (Nation, Katzen, Papapetropoulos, Scanlon, & Levin, 2009).

Symptoms of depression in PD may range from unwillingness to cooperate, to complete withdrawal and social isolation (Lieberman, 2006). Structural and biochemical changes associated with PD pathology, psychosocial changes, and impaired ability to perform activities of daily living may synergistically produce symptoms of depression, however, there is considerable debate over whether depressive symptoms are truly representative of a mood disorder or merely symptomatic of the neurodegenerative disease process. The typical lack of guilt, shame, or feelings of sadness in depressed PD patients suggests that depressive symptoms are not a psychological reaction to the disease (Lieberman, 2006). Additionally, although part of the criteria for depression, symptoms such as apathy, sleep changes, slowed thinking and movements, and diminished

concentration may occur in both depressed and non-depressed PD patients, making depression difficult to diagnose.

Depressive symptoms may be related to the degeneration of dopaminergic neurons of the ventral mesencephalon (Lieberman, 2006) or levodopa withdrawal. Girotti and colleagues (1986) reported that depressive mood worsened from the “on” to “off” phases, particularly in patients who had prominent diphasic dyskinesias. These findings suggest that mood changes may reflect effects of dopamine on the mesolimbic system rather than a psychological reaction to the disease.

Anxiety

Anxiety is a common psychiatric disturbance in PD. PD patients experience significantly higher levels of anxiety than healthy controls (Walsh & Bennett, 2001). An estimated 40% of PD patients meet criteria for generalized anxiety disorder (Walsh & Bennett, 2001). Anxiety and depression are often comorbid among PD patients and occur at a higher rate than the general population (Menza, Robertson-Hoffman, & Bonapace, 1993; Walsh & Bennett, 2001). Henderson, Kurlan, Kersun, and Como (1992) found that 44% of PD patients began experiencing anxiety early in the disease course, prior to starting pharmacologic treatment. PD-related abnormalities in dopamine, serotonin, and norepinephrine likely play a role in the pathogenesis of anxiety.

As with depression, debate exists as to whether symptoms of anxiety are part of the neuropathological process or a psychological reaction to the disease. PD patients may suffer from social phobia or other anxiety disorders from fear of negative public perception (Walsh & Bennett, 2000). Anxiety can trigger or be triggered by motor fluctuations, though the exact mechanisms are unclear (Lieberman, 2006; Walsh &

Bennett, 2000). Studies have shown that the magnitude of change in anxiety levels when “off” is correlated with change in parkinsonian symptoms (Siemers, Shekhar, Quaid, & Dickson, 1993), and that patients with dyskinesias have higher levels of anxiety (Menza et al., 1993), which suggests that the etiology of anxiety in PD is multifactorial.

Psychosis

The prevalence of psychotic symptoms in PD ranges from 16% to 17% in population-based surveys and 30% to 40% in hospital-based series (Williams-Gray, Foltynie, Lewis, & Barker, 2006). Early psychotic symptoms typically include benign visual hallucinations. As the disease progresses, malignant hallucinations, delusions, paranoid ideation, delirium, and confusion become more prominent (Papapetropoulos & Mash, 2005). Risk factors for the development of psychotic symptoms include cognitive impairment, older age, greater disease duration and severity, depression, and sleep disorders (Papapetropoulos & Mash, 2005).

Behavioral symptoms

Disabling impulsive behaviors affect an estimated 3% to 14% of PD patients (Giladi, Weitzman, Schreiber, Shabati, & Peretz, 2007; Weintraub, Siderowf, Potenza, Goveas, Morles et al., 2006). Impulsive behaviors in PD typically involve hypersexuality, excessive gambling, compulsive shopping, and abuse of anti-parkinsonian medications. Such behaviors are often multiple and may be comorbid with psychotic symptoms and/or mood disturbances.

Troublesome impulsive behaviors are more likely to occur in male PD patients, those with young-onset PD, and those with a longer duration of treatment with dopamine agonists (Giladi et al., 2007). Evidence implicates treatment with antiparkinsonian drugs

in the development of impulsive behaviors (Cools et al., 2003). Reducing or eliminating a medication may be sufficient to treat such behaviors, but some patients require treatment with antipsychotics, selective serotonin reuptake inhibitors (SSRIs), or hypnotics.

Sleep

A significant proportion of PD patients have sleep disorders that interfere with their daytime functioning. It is estimated that more than two-thirds of PD patients experience sleep difficulty (Arnulf, 2006). One study found sleep problems in 42% of PD patients compared to 12% of controls (Kumar, Bhatia, & Behari, 2002). Insomnia, painful night-time abnormal movements, vivid dreams, and excessive daytime sleepiness are common complaints among PD patients (Arnulf, 2006; Kumar et al., 2002). Sleep disturbances and subsequent daytime dysfunction in PD likely arise from PD symptoms, medication side effects, and lesions in the sleep-wake regulating system. Sleep deprivation, non-restorative sleep due to sleep fragmentation, use of dopamine agonists, and neurodegeneration of central sleep-wake areas can cause excessive daytime sleepiness, which interferes with activities of daily living (ADLs) for many PD patients (Arnulf, 2006).

Chapter Four: Treatment of Parkinson's Disease

Pharmacological Treatment

In the early stages of PD, most patients receive antiparkinsonian medications, such as levodopa, dopamine agonists, and/or anticholinergics. At the initiation of pharmacological treatment, patients are extremely sensitive to dopaminomimetics because of increased D1 and D2 receptor densities in the putamen and caudate (Seeman & Niznik, 1990), however, prolonged use of antiparkinsonian medications leads to loss of effectiveness and intolerable side effects. After five years of levodopa treatment, an estimated 40% of patients develop motor fluctuations and dyskinesias (Rao et al., 2006). The duration of benefits shortens with each levodopa dose, during which symptoms reemerge, commonly known as a “wearing-off” effect (Rao et al., 2006). “On-off” effects occur, in which patients experience unpredictable, abrupt fluctuations in motor state. Dyskinesias, such as involuntary choreiform or stereotypic movements of the head, trunk, limbs, and respiratory muscles, can develop (Rao et al., 2006). COMT inhibitors extend the half-life of levodopa by decreasing degradation, thereby reducing “off” time and “wearing-off” effects (Rao et al., 2006). Long-term medication treatment normalizes dopamine receptor densities (Seeman & Niznik, 1990), and leads to loss of effectiveness, intolerable side effects and motor complications.

Surgical Treatment

Surgery is often used as an adjunct to pharmacological treatment when a patient is no longer able to achieve optimal control with medication alone. Neurosurgical treatment of PD usually targets the thalamus, the globus pallidus, or the subthalamic nucleus (STN) (Espay, Mandybur, & Revilla, 2006). Careful evaluation of the patient

and their needs determines which target is the best site for surgical treatment (Tornquist, 2001).

Ablative Procedures

Ablative stereotactic surgical procedures emerged in the mid 20th century and were performed predominantly in the 1980's and 90's. Thalamotomy and pallidotomy destroy the ventral intermediate (Vim) nucleus of the thalamus or the globus pallidus interna (GPi), respectively. A preoperative CT or MRI scan identifies the precise area to target. Then, a hollow probe is inserted through a small hole in the skull. When the probe reaches the target area, liquid nitrogen circulates inside the probe or heat from a radio wave is emitted, thereby destroying the tissue it contacts.

Thalamotomy is most effective for reducing resting and postural tremor in the arms and/or legs (Tornquist, 2001). The procedure is usually performed unilaterally and has long-lasting effects (Sobstyl, Zabek, Koziara, Kadziolka, & Mossakowski, 2006). Bilateral thalamotomy greatly increases the risk of postoperative problems with vision, speech, and cognition (Abosch & Lozano, 2003). Thalamotomy is typically performed on patients younger than 65 years who have normal cognitive function (Espay et al., 2006). Despite its beneficial effects on tremor, the use of thalamotomy is rare because it does not have a strong effect on other symptoms or levodopa-induced dyskinesias (Sobstyl et al., 2006).

Pallidotomy ameliorates dystonia, tremor, rigidity, bradykinesia, and gait disturbances (Kondziolka, Bonaroti, Baser, Brandt, Kim, & Lunsford, 1999). This procedure reduces antiparkinsonian medication requirements, thereby improving dyskinesias, and modifies neuronal activity in the basal ganglia-cortical network (Zaidel,

Moran, Marjan, Bergman, & Israel, 2008). Unilateral pallidotomy is more common than bilateral pallidotomy (Fine, Duff, Chen, Chir, Hutchinson, Lozano et al., 2000).

Although bilateral pallidotomy produces greater improvement in dyskinesias, it has been shown to increase the risk of postoperative problems with cognition, speech, and swallowing (York, Lai, Jankovic, Macias, Atassi et al., 2007). Other adverse effects of this procedure include hemorrhage, weakness, visual deficits, confusion, and weight gain (Fine et al., 2000).

Deep Brain Stimulation

Deep brain stimulation, a non-ablative procedure that was first developed in 1987, is currently the predominant surgical treatment for PD. DBS is less invasive than the aforementioned ablative surgical techniques and has adjustable programming features (Wichmann & DeLong, 2006). The procedure involves implantation of a lead (into the target brain area), an extension, and a pulse generator.

First, a preoperative MRI locates the precise target site for stimulation, typically the subthalamic nucleus (STN), the ventral intermediate (Vim) nucleus of the thalamus, or the globus pallidus interna (GPI). Second, a stereotactic frame is aligned with the anterior-posterior commissure plane and a burr hole is created. Then, stereotactic implantation is performed under local anesthesia, using MRI and CT image fusion for anatomical targeting, intraoperative microelectrode recording, and clinical monitoring by microstimulation (Zibetti, Torre, Cinquepalmi, Rosso, Ducati, Bergamasco et al., 2007).

After physiologic verification of the target, a quadripolar lead is advanced to the target, and the patient is examined for improvements in tremor or rigidity. Intraoperative macrostimulation is used to confirm the correct positioning of the lead (Zibetti et al.,

2007); however, lead placement alone, without passage of current, can cause enough swelling to give a temporary clinical microlesion effect. Leads may be implanted bilaterally or unilaterally.

After successful lead implantation, the patient is placed under general anesthesia while an implantable pulse generator (IPG) is placed subcutaneously below the clavicle or in the abdomen. The IPG is connected to the lead by an extension, which runs from the head and down the neck. The IPG is turned on approximately one month after surgery. The IPG sends electrical pulses to the electrodes in the brain, thereby interfering with neural activity.

Therapeutic electrical parameters are set using a transcutaneous programmer. The IPG is calibrated precisely to attain optimal symptom suppression and minimize side effects (Krack, 2002). Stimulation can be delivered in monopolar or bipolar fashion, using any of 4 electrode contacts, alone or in combination. Thus, a great deal of therapeutic flexibility is provided, permitting customized stimulation for each patient. Moreover, stimulation parameters can be adjusted at any time if needed.

Chapter Five: Deep Brain Stimulation in Parkinson's Disease

Patient Selection

An ideal candidate for DBS suffers from complications of chronic pharmacologic treatment and has no cognitive deficits or psychiatric symptoms (Amick & Grace, 2006; Chang & Chou, 2006). The patient's physical symptoms should be appropriate for the procedure, and the patient's general condition, especially cognitive status, should be compatible with the demands of the surgery (Hariz, 2002). Patients with dementia or severe psychiatric issues should not undergo DBS because of a significant risk for postoperative behavioral or cognitive deterioration (Trepanier, Kumar, Lozano, Lang, & Saint-Cyr, 2000). Preoperative motor improvement in response to antiparkinsonian medication is a strong clinical predictor of responsiveness to DBS, particularly in younger patients (Pahwa, Wilkinson, Overman, & Lyons 2005; Tir, Devos, Blond, Touzet, Reyns et al., 2007).

Adverse Events

Although DBS is considered a minimally invasive and nonablative procedure, it can produce serious adverse events (Hariz, 2002). Surgical complications of STN DBS can include infection (7%), intracerebral hematoma (5%), electrode fracture (4%), or incorrect lead placement (8%) (Tir et al., 2007). The most common device related complications are unexpectedly turning off the stimulator or sudden end of battery life (Romito, Scerrati, Contarino, Iacoangeli, Bentivoglio et al., 2003). Stimulation dependent side effects include dyskinesias, paresthesias, diplopia, tonic eye deviation, and facial hemispasm (Bejjani et al., 2000; Herzog et al., 2003; Romito et al., 2003). Long-term DBS side effects include dysphonia/hypophonia, dysarthria, bilateral

buccinator spasm, blepharospasm (eyelid-opening apraxia), limb dystonia, and weight gain (Romito, Scerrati, Contarino, Bentivoglio, Tonali et al., 2002; Romito et al., 2003).

The use of preoperative imaging procedures reduces the risk of adverse events after DBS, whereas physiological exploration during surgery increases the risk of adverse events (Hariz, 2002). The accuracy of preoperative stereotactic imaging influences the number of exploratory tracks needed (Hariz, 2002). The need for greater exploration prolongs surgery time, contributes to patient stress, and increases the risk of infection and hemorrhage (Hariz, 2002). Therefore, accuracy in preoperative imaging is crucial.

In recent years, increased awareness of adverse events after DBS has prompted efforts to standardize adverse event reporting. The goal is to avoid underestimation of the morbidities associated with DBS and provide a more accurate risk/benefit ratio for this procedure (Videnovic & Metman, 2007).

Site of Deep Brain Stimulation

Findings suggest that DBS outcome varies according to site of stimulation. Bronte-Stewart (2003) suggests that one of the most important predictors of DBS outcome is electrode location. Several studies have compared GPi and STN procedures and uncovered a consistent trend for STN DBS to produce greater motor benefits and more impairments in cognitive performance than GPi DBS (Ardouin, Pillon, Peiffer, Bejjani, Limousin et al., 1999; Burchiel, Anderson, Favre, & Hammerstad, 1999; Gironell, Kulisevsky, Rami, Fortuny, Garcia-Sanchez et al., 2003; Jahanshahi, Ardouin, Brown, Rothwell, Obeso et al., 2000; Trepanier et al., 2000). Furthermore, several studies found that STN DBS allowed for greater reductions in levodopa equivalent daily

dose than GPi DBS (Burchiel et al., 1999; Chang & Chou, 2006; Weaver, Follett, Hur, Ippolito & Stern, 2005; Zabek & Sobstyl, 2006).

Adverse events are more commonly reported after STN DBS (Deuschl, Schade-Brittinger, Krack, Volkmann, Schafer et al., 2006; Hariz, Rehncrona, Quinn, Speelman, Wensing et al., 2007; Rodriguez-Oroz, Obeso, Lang, Houeto, Pollak et al., 2005; Videnovic & Metman, 2007). A multicenter study reported adverse events in 53% of STN DBS patients compared to 35% of GPi DBS patients at 4 years post-surgery (Hariz et al., 2007). Adverse events may be more prevalent in STN DBS patients due to neuroanatomical features and size of the target. The STN is much smaller and more variable in orientation than the GPi, creating a greater likelihood of electrode misplacement (Castro-Garcia, Sesar-Ignacio, Ares-Pensado, Relova-Quinteiro, Gelabert-Gonzalez et al., 2006; Voon, Kubu, Krack, Houeto, & Troster, 2006). Post-mortem studies suggest that there is a loss of neurons in the brain regions surrounding active electrodes, resulting in permanent neurologic sequelae in 4-6% of cases (Grill, 2005). Thus, the effects of DBS are diffuse. Stimulation of motor and nonmotor systems that converge in close proximity to the STN may produce stimulation related adverse events and neurobehavioral symptoms. The remainder of the literature review will focus on bilateral STN DBS, unless otherwise stated, as this is most commonly used DBS procedure for PD treatment.

Neuroimaging Studies

Various neuroimaging methods show that STN DBS alters neural activity (Berardelli, Rothwell, Thompson, & Hallett, 2001; Ceballos-Baumann, Boecker, Bartenstein, von Falkenhayn, Riescher et al., 1999; Haegelen et al., 2005; Hilker, Voges,

Weisenbach, Kalbe, Burghaus et al., 2004; Jahanshahi et al., 2000; Pinto, Thobois, Costes, Le Bars, Benabid et al., 2004; Schroeder, Kuehler, Haslinger, Erhard, Fogel et al., 2002; Sestini, Ramat, Formiconi, Ammannati, Sorbi et al., 2005). Results of functional imaging studies demonstrate that STN DBS increases blood flow to the dorsolateral prefrontal cortex (DLPFC), supplementary motor area, superior premotor cortex (Ceballos-Baumann et al., 1999; Haegelen et al., 2005; Jahanshahi et al., 2000; Pinto et al., 2004), anterior cingulate (Berardelli et al. 2001), and associative frontal areas (Haegelen et al., 2005; Jahanshahi et al., 2000). Furthermore, STN DBS reverses cerebral activation abnormalities in the main motor cerebral regions, suppresses hypermetabolism in the cerebellum, and partly restores physiologic glucose consumption in the limbic and associative projection territories of the basal ganglia (Hilker et al., 2004).

STN DBS reduces cerebral blood flow and activation of the primary motor cortex during the resting state, which may represent relative normalization of cortical hyperexcitability (Ceballos-Baumann et al., 1999). Reduced primary motor cortex activity is likely due to improvements in rigidity or other involuntary muscle activity and reduced input to the cortex via basal ganglia pathways (Ceballos-Baumann et al., 1999).

Mechanisms of Deep Brain Stimulation

DBS improves many motor symptoms of PD and reverses various electrophysiological and metabolic changes occurring after dopamine depletion (Hamani, Saint-Cyr, Fraser, Kaplitt, & Lozano, 2004). DBS acts in a manner similar to levodopa, producing its greatest effects on symptoms predominantly associated with dopamine deficiency (Hamani et al., 2004). However, the precise mechanisms by which DBS

affects PD motor symptoms are not fully understood. Possible mechanisms include depolarization blockade, release of local inhibitory neurotransmitters, and jamming of abnormal neuronal firing patterns (Deep Brain Stimulation for Parkinson's Disease Study Group, 2001). In animal models of PD, electrical stimulation improves parkinsonism by reducing STN overactivity (Limousin, Krack, Pollak, Benazzouz, Ardouin et al., 1998; Romito et al., 2003).

In humans, low-frequency STN stimulation increases metabolic and electrophysiological activity in the STN, substantia nigra pars reticulata (SNr), GPi, and GPe (Hamani et al., 2004; Maltete, Jodoin, Karachi, Houeto, Navarro et al., 2007). In contrast, high-frequency STN DBS decreases firing rates in the STN, GPe, GPi, and SNr, while increasing firing in the ventrolateral nucleus of the thalamus (Liu, Postupna, Falkenberg, & Anderson, 2008; Maltete et al., 2007). Additionally, high-frequency STN stimulation increases levels of glutamate, dopamine, and GABA in the GPi, striatum, and SNr, respectively (Hamani et al., 2004).

Stimulation parameters differentially influence motor symptoms (Benabid, Pollak, Gao, Hoffmann, Limousin et al., 1996; Kiss, Kirstein, Suchowersky, & Hu, 2003; Moro, Esselink, Xie, Hommel, Benabid et al., 2002) and cognitive performance (Wojtecki, Timmermann, Jorgens, Sudmeyer, Maarouf et al., 2006). Anecdotal reports and an early study of thalamic electrical stimulation suggest that low frequency stimulation (5 Hz) exacerbates tremor (Hassler, Riechert, Mundinger, Umbach, & Ganglberger, 1960). A more recent study showed that low frequency stimulation (5 Hz) of the STN worsens akinesia (Moro et al., 2002). Conversely, high frequency stimulation (> 100 Hz) of the Vim nucleus of the thalamus improves motor function in patients with Parkinson's

disease or essential tremor (Benabid et al., 1996; Kiss et al., 2003; Moro et al., 2002). However, dyskinesias and choreiform movements can be induced by high voltage stimulation (Hamani et al., 2004; Moro, Scerratti, Romito, Roselli, Tonalai, & Albanese et al., 1999). In terms of neuropsychological performance, low frequency stimulation yields significantly better verbal fluency performance (Wojtecki et al., 2006), which suggests that modulation of cognitive circuits after STN DBS may be frequency dependent.

Medication Changes Following Deep Brain Stimulation

The vast majority of studies report antiparkinsonian medication reductions after DBS (Capecchi, Riccitu, Burini, Bombace, Provinciali et al., 2005; Molinuevo, Valldeoriola, Tolosa, Rumia, Valls-Sole et al., 2000; Moro et al., 1999; Thobois, Mertens, Guenot, Hermier, Mollion et al., 2002; Valldeoriola, Pilleri, Tolosa, Molinuevo, Rumia, & Ferrer, 2002; Vingerhoets, Villemure, Temperli, Pollo, Pralong et al., 2002; Woods, Fields, Lyons, Koller, Wilkinson et al., 2001; Zibetti et al., 2007). One study found that bilateral STN DBS reduced antiparkinsonian medications by 65% (Bordini, Garg, Gallagher, Bell, & Garell, 2007). Some investigators suggest that DBS has therapeutic effects equipotent to that of levodopa (Valldeoriola et al., 2002). For instance, several studies found that STN DBS led to improvements in motor symptoms when “on” stimulation and “off” medication (Molinuevo et al., 2000; Moro et al., 1999; Portman, van Laar, Staal, Rutgers, Journee et al., 2006; Thobois et al., 2002). Furthermore, several studies reported that the need for dopaminergic medications was entirely eliminated in more than half of patients at 18 months or more after STN DBS (Molinuevo et al., 2000; Valldeoriola et al., 2002; Vingerhoets et al., 2002).

Reductions in medication requirements have been shown to last for several years following surgery. One study noted a 25% reduction in medication requirements at 18 to 57 months after surgery (Siderowf, Jaggi, Xie, Loveland-Jones, Leng et al., 2006). Another study found a 58% reduction in the daily levodopa dose five years after STN DBS (Schupbach, Chastan, Welter, Houeto, Mesnage et al., 2005). Medication requirements may continue to decrease over time due to the amount of time needed for optimal IPG calibration and adjustment of stimulation parameters.

Motor Symptoms Following Deep Brain Stimulation

Cardinal Symptoms

The majority of studies show that bilateral STN DBS improves cardinal motor symptoms (Rodriguez-Oroz et al., 2005; Romito et al., 2002; Romito et al., 2003; Thobois et al., 2002; Weaver et al., 2005; Zibetti et al., 2007). Overall, bilateral STN DBS produces significant reductions in tremor, rigidity, and bradykinesia (Berardelli et al., 2001; Capecchi et al., 2005; Ford, Pullman, Frucht, Du, Greene et al., 2004; Krause, Fogel, Heck, Hacke, Bonsanto et al., 2001; Kumar, Lozano, Kim, Hutchison, Sime et al., 1998; Moro et al., 1999; Moro & Lang, 2006; Zabek & Sobstyl, 2006). Motor improvements after bilateral STN DBS last for several years after surgery, without any evidence of loss of efficacy (Krause et al., 1999; Romito et al., 2003; Siderowf et al., 2006; Zhang, Zhang, Ma, Hu, Yang et al., 2006). Few studies examined the effects of unilateral STN DBS on motor function, therefore, a discussion of these studies will follow.

Axial Symptoms

Axial symptoms, such as gait difficulties and postural instability, are less responsive than cardinal symptoms to bilateral STN DBS, although some investigators

report postoperative improvements in dysarthria, postural instability, gait disturbances, and freezing (Bejjani et al., 2000; Capecchi et al., 2005; Ferraye, Debu, Fraix, Xie-Brustolin, Chabardes et al., 2008; Gentil, Garcia-Ruiz, Pollak, & Benabid, 1999; Kumar et al., 1998; Pinto et al., 2004; Zhang et al., 2006).

Dyskinesias

Bilateral STN DBS dramatically reduces involuntary dyskinesias (Capecchi et al., 2005; Moro et al., 1999; Ostergaard & Sunde, 2006; Portman et al., 2006; Siderowf et al., 2006; Thobois et al., 2002; Woods, Rippeth, Conover, Carey, Parsons et al., 2006).

However, despite numerous findings that dyskinesias improve after DBS, some studies indicate that dyskinesias are a side effect of chronic bilateral stimulation (Guehl, Cuny, Benazzouz, Rougier, Tison et al., 2006; Moro et al., 1999; Romito et al., 2002; Zhang et al., 2006). Nevertheless, the potential for developing choreiform movements is much lower with STN DBS than with any ablative procedure (Hamani et al., 2004; Moro et al., 1999).

Predictors of Motor Improvement

A meta-analysis conducted by Kleiner-Fisman, Herzog, Fisman, Tamma, Lyons et al. (2006) found that levodopa responsiveness, higher baseline motor scores, and shorter disease duration predicted improvements in UPDRS motor scores after bilateral STN DBS. Nakamura, Christine, Starr and Marks (2007) and Charles, Van Blercom, Krack, Lee, Xie and colleagues (2002) found that younger age and levodopa responsiveness correlated with motor improvements following bilateral STN DBS. Similarly, Smeding, Speelman, Koning-Haanstra, Shuurman, Nijssen et al. (2006) and Ford et al. (2004) reported that baseline levodopa responsiveness and presence of tremor

correlated with improvements in motor functioning after bilateral STN DBS. In summary, bilateral STN DBS appears to be most beneficial for patients who are younger, with shorter disease duration, predominant tremor, and no axial symptoms or psychiatric comorbidities.

Unilateral vs. Bilateral Deep Brain Stimulation

The majority of studies have examined outcome following bilateral STN DBS (Czernicki, Pilon, Houeto, Welter, Mesnage et al., 2005; Krack, Batir, Van Blercom, Chabardes, Fraix et al., 2003; Liang, Chou, Baltuch, Jaggi, Loveland-Jones et al., 2006; Zhang et al., 2006), which likely reflects the fact that many surgical centers only perform bilateral procedures. When unilateral DBS is available, the patient's motor presentation, disease severity, and degree of symptom asymmetry, as well as the judgment of the surgical team, determine the decision to perform a unilateral or bilateral procedure (B.V. Gallo, personal communication, Aug. 8, 2007).

Studies of motor symptom outcome after unilateral STN DBS demonstrate improvements in cardinal parkinsonian symptoms, with the greatest benefits for contralateral tremor (Chung, Jeon, Kim, Sung, & Lee, 2006; Hershey et al., 2007; Nakamura et al., 2007; Woods et al., 2001). Unilateral STN DBS also improves contralateral features, axial features and ipsilateral symptoms (Chung et al., 2006; Slowinski, Putzke, Uitti, Turk, Kall & Wharen, 2007). However, unilateral STN DBS yields less significant improvements in gait, postural and axial symptoms than bilateral STN DBS (Kumar, Lozano, Sime, Halket & Lang, 1999; Tabbal, Ushe, Mink, Revilla, Wernle et al., 2008).

Research shows that unilateral STN DBS poses a decreased risk of adverse events compared to bilateral STN DBS, particularly for older patients or patients with marked asymmetry of symptoms (Hariz, 2002). Patients greater than 69 years of age, that undergo bilateral STN DBS, have a greater risk of developing cognitive impairments (Hariz, 2002). However, despite greater risks, bilateral DBS may be the most appropriate surgical option for patients with significant bilateral disability.

A small number of studies investigated long-term benefits of unilateral STN DBS on motor symptoms (Germano et al., 2004; Slowinski et al., 2007). One study found that a year after unilateral STN DBS, patients demonstrated 50% improvement in contralateral features, 17% improvement in ipsilateral features, and 36% improvement in axial symptoms (Germano, Gracies, Weisz, Tse, Koller & Olanow, 2004). Ten of twelve patients in this study chose not to undergo an additional procedure (Germano et al., 2004). However, it is difficult to clearly evaluate these findings because of inadequate information on the patients who chose to undergo a subsequent DBS procedure.

A study that randomly assigned 42 patients with advanced PD to undergo staged bilateral DBS of the STN or GPi found that only 29 patients chose to undergo a second, contralateral, DBS procedure (Rothlind et al., 2007). This study did not report if site of DBS or side of unilateral stimulation influenced the need for an additional procedure, nor did it examine if response to unilateral DBS or perceived benefit influenced the decision to undergo an additional DBS procedure, which limits the conclusions that can be drawn.

Side of Deep Brain Stimulation

To date, only one study examined the influence of side of stimulation among unilateral DBS patients; however the sample combined patients with STN or GPi

stimulation (Zahodne, Okun, Foote, Fernandez, Rodriguez et al., 2008). On the other hand, several studies compared unilateral and bilateral stimulation settings among bilateral STN DBS patients, typically using four stimulation conditions: “both off”, “both on”, “left on”, and “right on” (Hershey et al., 2007; Tabbal et al., 2008).

Bilateral STN DBS studies suggest that unilateral stimulation exerts differential effects on motor, cognitive and emotional functioning. In terms of motor symptoms, results are conflicting. Tabbal et al. (2008) found that bilateral stimulation improved motor function more than unilateral stimulation, but did not find significant differences between contralateral and ipsilateral stimulation; whereas Hershey et al. (2007) found greater improvements in contralateral motor function after unilateral stimulation in the more affected side of the brain, which was equivalent to bilateral stimulation.

In terms of cognitive function, Zahodne et al. (2008) found that patients with left-sided unilateral (STN or GPi) DBS experienced a trend towards greater cognitive decline. In contrast, Hershey et al. (2007) reported that among bilateral STN DBS patients, unilateral stimulation on the more affected side of the brain impaired working memory. Patients with the left side of the body more affected (right hemisphere) had more pronounced impairment in spatial working memory than those that were more affected on the right side of the body (Hershey et al., 2007). However, due to the paucity of unilateral DBS studies and fundamental differences between unilateral DBS and unilateral stimulation in the context of bilateral DBS, it is difficult to clearly evaluate the complex relationship between side of stimulation, lateralization of function, brain asymmetry and neuropsychological performance.

Chapter Six: Neuropsychological Function Following Deep Brain Stimulation

Cognitive Symptoms Following Bilateral Deep Brain Stimulation

Various studies report numerous cognitive changes after bilateral STN DBS, such as deficits in verbal fluency, executive function, processing speed, attention, response inhibition, visuospatial abilities, working memory, conditional associative learning, and abstract reasoning (Parsons, Rogers, Braaten, Woods, & Troster, 2006; Temel, Kessels, Tan, Topdag, Boon et al., 2006; Voon et al., 2006; York, Dulay, Macias, Levin, Grossman et al., 2007). The most consistently reported deficit after DBS is diminished verbal fluency (Amick & Grace, 2006; Castelli, Lanotte, Zibetti, Caglio, Rizzi et al., 2007; Daniele, Albanese, Contarino, Zuni, Barbier et al., 2003; Gironell et al., 2003; Parsons et al., 2006; Smeding et al., 2006; Woods, Fields, & Troster, 2002). Studies reported in this section refer to bilateral STN DBS procedures unless otherwise stated.

Despite the abundance of studies reporting declines in verbal fluency after DBS, changes in global cognitive abilities, memory, attention, and executive functions are controversial and often described as transient (Castro-Garcia et al., 2006). A meta-analysis found mild to moderate declines in verbal fluency in 30-50% of DBS patients, while changes in global cognitive functioning, memory, attention, and executive functions occurred in less than 1-2% of DBS patients (Parsons et al., 2006), whereas, another meta-analysis found that 41% of DBS patients experienced cognitive deficits varying from moderate declines in verbal memory to significant declines in executive function (Temel et al., 2006). Some studies report no change in global cognitive function (Perozzo, Rizzone, Bergamasco, Castelli, Lanotte et al., 2001; Zibetti et al., 2007), while

other studies demonstrate improvements in overall cognitive function after DBS (Voon et al., 2006).

Language Abilities Following Deep Brain Stimulation

Research suggests that DBS does not produce primary language impairments (Whelan, Murdoch, Therodoros, Hall, & Silburn, 2003; Zanini, Melatini, Capus, Gioulis, Vassallo & Bava, 2003); however, language impairments may emerge secondary to executive dysfunction or memory deficits. Clinically and statistically significant declines in verbal fluency are frequently reported after DBS, which is not surprising given the executive demands of this task (Amick & Grace, 2006; Castelli et al., 2007; Daniele et al., 2003; Gironell et al., 2003; Heo, Lee, Paek, Kim, Lee et al., 2008; Higginson, Wheelock, Levine, King, Pappas et al., 2008; Parsons et al., 2006; Smeding et al., 2006; Woods et al., 2002; York et al., 2007). Several studies found pronounced declines in verbal fluency (phonemic and semantic) among DBS patients three to six months after surgery (Bordini et al., 2007; Daniele et al., 2003; Morrison et al., 2004). York et al. (2007) reported that 26% of DBS patients experienced a decline in verbal fluency at 6 months after baseline assessment, compared to only 4% of PD control patients. A meta-analysis of 28 studies reported moderate declines in semantic and phonemic fluency after STN DBS (Parsons et al., 2006). Furthermore, the only randomized study to date found significant declines in phonemic and semantic fluency six months after bilateral STN DBS (Witt, Daniels, Reiff, Krack, Volkmann et al., 2008). One study with a longer follow-up period found moderate declines in verbal fluency one year after bilateral STN DBS and significant declines in verbal fluency five years after surgery (Contarino, Daniele, Sibilgia, Romito, Bentivoglio et al., 2007).

Notably, several studies found that significant declines in phonemic and semantic fluency after DBS were unrelated to dysarthric/hypophonic disturbances (Castelli et al., 2007; De Gaspari, Siri, Di Gioia, Antonini, Isella et al., 2006; Moretti, Torre, Antonello, Capus, Marsala et al., 2003). In light of these findings, several theories have been proposed to explain the verbal fluency changes. The predominant theory suggests that fluency impairments are due to executive dysfunction, specifically decreased set shifting, rather than impaired retrieval from semantic memory (De Gaspari et al. 2005). In support of this theory, Saint-Cyr et al. (2000) reported significant declines in phonemic fluency and set shifting after bilateral DBS, whereas York et al. (2007b) reported that DBS does not impair confrontation naming, a task that requires intact retrieval but places little demand on executive function. Furthermore, neuroimaging studies offer support for this theory. Executive tasks, such as set shifting, require activation of the frontotemporal system. Imaging studies show that DBS lessens activation of the frontotemporal system during verbal fluency tasks (Castelli, Perozzo, Zibetti, Crivelli, Morabito, Lanotte et al., 2006) and produces perfusion decrements in the left dorsolateral prefrontal cortex (DLPFC), anterior cingulate, and ventral caudate nucleus (Cilia, Siri, Marotta, Gaspari, Laandi et al., 2007). More specifically, STN stimulation decreases activation of the inferior frontal, insular and temporal cortex of the left hemisphere (Contarino, Daniele, Sibilio, Romito, Bentivoglio et al., 2007; Schroeder et al., 2003). Thus, these findings suggest that declines in verbal fluency after bilateral STN DBS are significantly related to decreased frontotemporal activation, particularly in the left hemisphere.

An alternative theory hypothesizes that apathy and lack of motivation lessen the patient's effort and interferes with execution of the verbal fluency task (Funkiewiez

Ardouin, Cools, Krack & Fraix, 2006). However, there is limited evidence to support this theory. Castelli et al. (2007) found no correlation between apathy and verbal fluency, despite significant declines in phonemic fluency ($p < 0.001$) and a significant worsening of apathy symptoms in 31% of patients in their sample. In contrast, De Gaspari et al. (2006) found that declines in phonemic and semantic fluency were positively correlated with depressive symptoms, but did not examine if apathy explained these findings.

Visuospatial Function Following Deep Brain Stimulation

Few studies examined visuospatial functioning after DBS, despite well-documented visuospatial deficits in PD. In uncontrolled studies of bilateral STN DBS, Alegret, Junque, Valldeoriola, Vendrell, Pilleri and colleagues (2001) and Valldeoriola et al. (2002) observed significant declines in judgment of line orientation after surgery. Line orientation tasks reflect visuospatial function more accurately than other visuospatial tasks that are confounded by motor ability or memory (Qualls, Bliwise, & Stringer, 2000).

On other measures of visuospatial function, it is more difficult to differentiate primary visuospatial impairments from those that are secondary to motor impairments or memory deficits. For example, Saint-Cyr et al. (2003) reported significant declines in encoding of visuospatial material, three to six months after bilateral STN DBS, which likely reflects memory deficits rather than, or in addition to, a primary visuospatial impairment. Voon et al. (2006) reported significant improvements in visuomotor sequencing following DBS, which likely reflects improvements in memory and motor performance.

Witt, Kopper, Deuschl and Krack (2006) discovered that left-sided STN stimulation, in bilateral DBS patients, produced a significant bias to the right on line bisection tests and increased reaction time to visual stimuli in the left extra-personal hemispace. Although these findings are likely confounded by to the motor demands of these tasks, these results imply that unilateral stimulation can produce hemianopia or hemispacial neglect. The effect of DBS on visuospatial functioning deserves further attention, since this is a cognitive domain known to be affected by PD.

Memory Following Deep Brain Stimulation

Numerous studies reported verbal memory deficits after DBS (Contarino et al., 2007; Dujardin, Defebvre, Krystkowiak, Blond & Destée, 2001; Gamez, Lezcano, Molano, Lambarri, Bilbao et al., 2003; Heo et al., 2008; Hershey, Wu, Weaver, Perantie, Karimi et al., 2007; Moretti et al., 2003; Saint-Cyr et al., 2000; Smeding et al., 2006; York et al., 2007). Several controlled studies found that bilateral STN DBS patients experienced larger declines in selective attention and verbal delayed recall than PD patients that did not undergo surgery, even after controlling for differences in educational level and age of disease onset (Moretti et al., 2003; Smeding et al., 2006; York et al., 2007).

A meta-analysis of 28 studies found small yet significant declines in verbal memory after bilateral STN DBS (Parsons et al., 2006). Similarly, others reported statistically significant declines in episodic verbal memory (Contarino et al., 2007), working memory, and consolidation of verbal material (Saint-Cyr et al., 2000), as well as clinically significant declines in list learning (Higginson et al., 2008) after bilateral STN DBS . In contrast, some studies reported improvements in working memory following

STN DBS (Castelli et al., 2006; Hershey et al., 2007; Pillon, Ardouin, Damier, Krack, Houeto et al., 2000; Voon et al., 2006).

Individual differences in stimulation parameters may account for controversial changes in memory after DBS. Francel and colleagues (2004) reported that stimulation parameters accounted for a significantly greater proportion of variance in neuropsychological performance than previously cited risk factors for post-DBS cognitive decline (Francel, Ryder, Wetmore, Stevens, Bharucha et al., 2004). Nevertheless, due to the relatively small sample size and short follow-up interval of this study, it is impossible to rule out the influence of microlesion effects or medication changes after DBS.

Executive Function Following Deep Brain Stimulation

Many studies reported improvements in executive function after DBS, particularly in cognitive flexibility (Castelli et al., 2006; Contarino et al., 2007; Daniele et al., 2003; Jahanshahi et al., 2000; Valldeoriola et al., 2002; Voon et al., 2006; Witt, Pulkowski, Herzog, Lorenz, Haamel et al., 2004). Several studies demonstrated that bilateral STN DBS improved performance on random number generation tests and significantly lowered total errors and perseverative errors on modified card sorting tasks (Contarino et al., 2007; Witt et al., 2004). Others demonstrated that bilateral STN DBS improved performance on Trail Making Part B (Ardouin et al., 1999; Jahanshahi et al., 2000; Valldeoriola et al., 2002), however, due to the motor component of this task, these results are likely confounded by improvements in motor performance.

One neuroimaging study demonstrated a probable mechanism by which DBS improves executive function. Jahanshahi and colleagues (2000) reported that

improvements in executive function after bilateral DBS were associated with changes in DLPFC activity. Bilateral STN DBS is believed to improve cognitive flexibility by influencing the indirect projection from the SNr to the DLPFC (Jahanshahi et al., 2000).

In contrast, a meta-analysis found small but significant declines in executive function after bilateral STN DBS (Parson et al., 2006). Furthermore, several studies reported impaired response inhibition on interference tasks after bilateral STN DBS (Alegret et al., 2001; Contarino et al., 2007; Dujardin et al., 2001; Moretti et al., 2003; Saint-Cyr et al., 2000; Smeding et al., 2006; Witt et al., 2004; Witt et al., 2008; York et al., 2007). A possible explanation for these discrepant findings is that executive function varies as a function of age, disease severity, medications, and stimulation parameters. More studies are needed with large sample sizes and adequate power in order to carefully evaluate these concerns.

Age and Cognitive Function Following Deep Brain Stimulation

The majority of evidence suggests that older age is a risk factor for cognitive decline after DBS. Various studies found that older patients were at a greater risk of global cognitive deterioration after DBS (Kalteis, Standhardt, Kryspin-Exner, Brucke, Volc et al., 2006), even in the absence of dementia (Saint-Cyr, Trepanier, Kumar, Lozano & Lang, 2000). Morrison, Borod, Perrine, Beric, and Brin (2004) noted that one patient in their sample who was significantly older at disease onset and at time of surgery experienced significant memory decline after DBS. Castro-Garcia et al. (2006) and Saint-Cyr et al. (2000) reported that patients over 69 years of age demonstrated cognitive deficits following STN stimulation, such as impaired verbal fluency and executive dysfunction, which resembled frontal executive dysfunction. Another study found that

80% of patients over 69 years of age experienced significant cognitive decline after DBS (Trepanier et al., 2000).

Despite several studies suggesting that advanced age is a risk factor for cognitive decline following DBS, a few studies found that age was not a significant predictor of cognitive decline (Ory-Magne, Brefel-Courbon, Simonetta-Moreau, Fabre, Lotterie et al., 2007; Rothlind, Cockshott, Starr & Marks, 2007). Discrepant findings may be partly due to differences in age ranges of samples, as well as whether the study examined current age or age of disease onset. Larger sample sizes that include patients of a wider age range are needed to clearly evaluate the role of age in cognitive performance after DBS.

Psychiatric Symptoms Following Deep Brain Stimulation

The prevalence of psychiatric disorders among DBS patients is comparable to or greater than the general PD population (Voon et al., 2006). Seventy-eight percent of DBS patients have at least one lifetime or current Axis I psychiatric diagnosis: depression 60%, anxiety 40%, and psychosis 35% (Voon et al., 2006). Depression, anxiety, mania, and psychosis are commonly reported psychiatric disturbances after DBS (Castro-Garcia et al., 2006; Amick & Grace, 2006; Witt, Daniels, Herzog, Lorenz, Volkmann et al., 2006; Temel et al., 2006). A meta-analysis found that 8% of STN DBS patients experienced depressive symptoms (which led to suicide attempts in 4%), 4% experienced manic symptoms, and 2% had symptoms of anxiety after the procedure (Temel et al., 2006).

Many studies attempted to identify predictors of psychiatric disturbances after DBS (Castro-Garcia et al., 2006; Perriol, Krystkowiak, Defebvre, Blond, Destee et al., 2005); however, none have been consistently cited. Proposed etiological factors include

premorbid psychological vulnerabilities, surgical factors (duration of procedure, electrode trajectories, complications), stimulation factors (number of electrodes, placement of electrodes, stimulation parameters), postoperative factors (antiparkinsonian drug changes), psychosocial adjustment, and underlying PD related factors (neurodegenerative processes, involvement of nondopaminergic symptoms) (Francel et al., 2004; Voon et al., 2006). Although there is some support for these proposed etiological factors, there is insufficient empirical evidence.

Chapter Seven: Summary

Parkinson's disease (PD) is a progressive neurodegenerative movement disorder, characterized by cardinal symptoms of tremor, rigidity and bradykinesia. The clinical manifestations of PD result from neuropathological changes to the basal ganglia and its projections. Axial symptoms, autonomic dysfunction, cognitive and psychiatric disturbances may occur. PD produces a wide range of cognitive deficits, which vary considerably between patients.

PD symptoms are managed pharmacologically with levodopa, dopamine agonists, anticholinergics, MAO-B inhibitors, β -blockers, amantadine, and COMT inhibitors. When a patient develops severe motor fluctuations, dyskinesias, or other poor response to medication, surgical treatment may be beneficial. Although surgical treatment helps to manage PD symptoms, it does not halt disease progression. DBS is generally preferred to ablative surgery because it is believed to produce less morbidity.

Generally, bilateral STN DBS studies report improvements in cardinal motor symptoms, physical aspects of quality of life, activities of daily living, sleep, and reductions in antiparkinsonian medications after surgery. Research demonstrates inconsistent and controversial changes in cognitive performance and mood after bilateral STN DBS. The vast majority of studies observed verbal fluency declines after bilateral STN DBS. Some research suggests that executive dysfunction and impairments in verbal memory and attention occur after bilateral STN DBS. Age, age of disease onset, and cognitive reserve may influence the development of cognitive impairments after STN DBS.

Chapter Eight: Rationale and Hypotheses

The purpose of this study was to compare neuropsychological performance among PD patients undergoing unilateral STN DBS and a group of PD control patients. The primary aim was to examine cognitive function following unilateral STN DBS. An additional aim was to examine the influence of side of stimulation on cognitive outcome among unilateral STN DBS patients. An exploratory aim of this study was to examine cognitive changes following unilateral STN DBS in a subset of Spanish-speaking patients, since outcome following DBS has never been studied in this subset of patients. The following hypotheses were proposed:

Hypothesis 1: No significant differences in demographics, disease-related or cognitive variables will be observed between the English-speaking unilateral STN DBS group and the PD control group at baseline.

Hypothesis 2: At follow-up, English-speaking patients who underwent unilateral STN DBS will show select changes in neuropsychological performance compared to PD control patients. The cognitive deficits will follow the same pattern neuropsychological performance as those undergoing bilateral STN DBS (e.g. declines in verbal fluency, executive function, attention and memory).

Hypothesis 3: Side of unilateral STN DBS will influence cognitive performance, such that right-sided STN DBS will be related to greater visuospatial impairments and left-sided STN DBS will be related to greater impairments on tasks measuring dominant hemisphere function such as confrontation naming and verbal fluency.

Hypothesis 4: Spanish-speaking unilateral STN DBS patients will show select changes in neuropsychological performance at follow-up, which will follow a similar pattern of cognitive changes as English-speaking unilateral STN DBS patients.

Chapter Nine: Method

Subjects

DBS Group

Twenty-eight patients (19 males, 9 females) who underwent unilateral STN DBS participated in the research study. Patient inclusion criteria was clinical diagnosis of idiopathic PD, responsiveness to levodopa, and age ≥ 35 years. All patients in the DBS group underwent a single unilateral STN DBS procedure. All patients in the DBS group had a baseline neuropsychological evaluation and a follow-up neuropsychological evaluation, which occurred at least 9 months later. All follow-up neuropsychological evaluations were conducted more than 6 months after the unilateral STN DBS procedure, in order to minimize placebo or microlesion effects. Patients with dementia, as indicated by a MMSE of ≤ 18 at baseline, history of neurological disorder other than PD, history of neurosurgical procedure, or significant medical illness which interfered with their ability to complete the mental status exam were excluded. Participants underwent neuropsychological evaluation in their dominant language (15 English-speakers and 13 Spanish-speakers).

PD Control Group

Fifteen patients (nine males and six females), who received pharmacological treatment and had no history of neurosurgical treatment, were selected from a historical sample of English-speaking patients with clinically diagnosed idiopathic PD. In addition to a clinical diagnosis of idiopathic PD, study criteria included age ≥ 35 years and responsiveness to levodopa. All patients in the control group had a baseline neuropsychological evaluation and a follow-up neuropsychological evaluation at least 9

months later. All control participants underwent neuropsychological evaluation in English. Exclusion criteria were the same as outlined for the DBS group.

Procedures

Unilateral STN DBS patients that met study criteria were asked to return for neuropsychological assessment one year after their surgery as part of their routine clinical care. Written informed consent and HIPAA forms were obtained from these patients at the time of recruitment as part of an IRB approved study. Since PD control patients were selected from a historical sample of patients, the IRB granted retroactive consent to review these files.

Each patient underwent a clinical interview and neuropsychological assessment at baseline and follow-up study visits. Patients were assessed in their primary language. Bilingual patients had the opportunity to undergo neuropsychological evaluation in their preferred language. Demographic information was collected as part of the clinical interview. The neuropsychological test battery assessed domains such as language, visuospatial abilities, executive function and verbal memory, as will be described in detail below.

PD control patients were all English-speaking and were individually matched to English-speaking unilateral STN DBS patients on the following factors: length of time between neuropsychological assessments, age, education, gender, handedness, disease severity, medication use, and cognitive performance at baseline.

Neuropsychological Measures

Language

The following measures were used to assess language:

1. The Controlled Oral Word Association Test (COWAT) was used to measure verbal fluency and executive function (Spreeen & Benton, 1969). Subjects were asked to generate as many words as possible in one minute to each of three phonemic categories (e.g. “F”, “A”, “S” for English-speakers, or “P”, “T”, “M” for Spanish-speakers). Each participant received a phonemic fluency score based on the total number of words generated across all three phonemic categories. All correct responses received one point. Intrusions and perseverations were not counted in the total score.

2. The Boston Naming Test (BNT) was used to measure word finding ability (Goodglass & Kaplan, 1987). Subjects were asked to name visual stimuli. A short form of the test was used (odd numbered items). Scores for the total number of spontaneous correct responses were recorded and multiplied by two, yielding scores ranging from 0 to 60.

Visuospatial Ability

The following measures were used to assess visuospatial function:

1. The Benton Judgment of Line Orientation (JLO) was used to measure visuospatial orientation, specifically angular judgment and relative localization (Benton, Varney, & Hamsher, 1978). The subject was presented with a page containing an array of 12 numbered lines distributed at 15 degree intervals through a 180 degree arc and a stimulus page consisting of a pair of lines that correspond to the 12 numbered lines. The subject was asked to match the pair of stimulus lines to the numbered lines that formed the same angle. A short form of the test was used (odd numbered items). Both lines had to be correctly identified in order to receive credit for an item. Scores ranged from 0 to 15. Subjects were presented with alternate 15 item forms of the test at each assessment (Forms V and H) to minimize practice effects. Different forms of the test have shown

high internal consistency and reliability (Qualls, Bliwise, & Stringer, 2000).

2. The Hooper Visual Organization Test (HVOT) was used to measure visuospatial organization and integration (Hooper, 1983). This 30 item test required the subject to identify objects from pictures that are broken up into pieces. The subject was asked to identify the object that the pieces would form if put together. Total scores ranged from 0 to 30. Alternate forms of the test were used at each assessment to minimize practice effects.

Executive Function

The following measure was used to assess executive function:

1. The Wechsler Adult Intelligence Scale – Third Edition (WAIS – III) Digit Span (Wechsler, 1997) was used to measure auditory attention and executive function, namely mental flexibility. A list of numbers was presented orally, which the subject was asked to repeat in the same order in the forward condition or in reverse order in the backward condition. The backward condition was used to measure executive function, mental flexibility and working memory. Longest digit span backward was recorded. Scores ranged from 0 to 8.

Verbal Memory

The following measures were used to assess verbal memory:

1. (English- and Spanish-speakers) The California Verbal Learning Test - 5 and California Learning Test – Second Edition (CVLT-5 and CVLT-II) were used to measure verbal learning and memory (Delis, Kramer, Kaplan, & Ober, 1987; 2000). A list of 16 words was presented over five consecutive trials. The order of the presentation of words was fixed. The subject was asked to recall as many words from the list as possible after

each trial. A second list (interference list) was then presented and the subject was asked to recall as many words as possible from the interference list. After recall of the interference list, the subject was asked to recall as many words as possible from the first list (immediate free recall). After a 30 minute delay, the subject was asked to recall as many words as possible from the first list (delayed free recall). Immediate and delayed free recall raw scores and delayed free recall z scores were calculated.

2. (Spanish-speakers only) The Wechsler Memory Scale – Third Edition (WMS-III) Word Lists subtest was used to measure verbal learning and memory among Spanish-speakers (Wechsler, 1997). A list of 12 words was presented over four consecutive trials. The order of the presentation of words was fixed. The subject was asked to recall as many words as possible from the first list after each trial. Then, a second list (interference list) was read and the subject was asked to recall as many words as possible from the interference list. After recall of the interference list, the subject was asked to recall as many words as possible from the first list. Then after a 30 minute delay, the subject was asked to recall as many words as possible from the first list (delayed free recall). Scaled scores were recorded for the delayed free recall condition, which were converted to z scores.

Chapter Ten: Results

Sixty-four PD patients who underwent unilateral STN DBS at the UM Miller School of Medicine between April 2000 and April 2008 were identified. Of these, 28 unilateral STN DBS patients (15 English-speakers and 13 Spanish-speakers) met study criteria and completed baseline and follow-up neuropsychological evaluations. Fifteen PD patients who underwent baseline and follow-up neuropsychological evaluation, but did not receive neurosurgical intervention, were matched to the English-speaking subset of unilateral STN DBS patients based on demographic, disease, and cognitive variables; this group served as a PD control group.

Demographic Characteristics of the DBS Group

The DBS group ($n = 28$) consisted of 19 males and 9 females. Twenty-six patients were right-handed, two were left-handed. Participants ranged in age from 44 to 74 years ($M = 61.75$ years, $SD = 7.10$). Average age of disease onset was 51.34 years ($SD = 7.36$) and average disease duration was 10.36 years ($SD = 4.36$). Mean disease severity was 1.75 ($SD = 0.66$) as indicated by Hoehn and Yahr “on” scores. Eighteen patients had left-sided DBS; ten had right-sided DBS. Educational levels varied greatly among DBS patients ($M = 11.86$ years, $SD = 4.65$, range 0 to 18 years). All patients were taking one or more medications for PD at baseline: carbidopa-levodopa 100%, dopamine agonists 64%, anticholinergics 14%, NMDA antagonists 36%, GABA inhibitors 4%, COMT inhibitors 61%, MAO B inhibitors 11%, antidepressants 21%, anxiolytics 32%, and antipsychotics 14%. The average length of time between baseline and follow-up neuropsychological assessments was 25.54 months ($SD = 12.91$).

Demographic Characteristics of the PD Control Group

The PD control group ($n = 15$) consisted of nine males and six females. Three subjects were left-handed and twelve were right-handed. Participants ranged in age from 46 to 69 years ($M = 61.47$ years, $SD = 7.33$). Average age of disease onset was 52.13 years ($SD = 7.48$), average disease duration was 9.33 years ($SD = 5.39$). Mean disease severity was 2.07 ($SD = 0.88$) as rated by Hoehn and Yahr “on” scores. PD control patients had an average of 13.80 years of education ($SD = 2.04$). All patients were taking one or more medication for PD at baseline, however, roughly a quarter of the PD control patients were not using levodopa (see Table 3). For the most part, COMT inhibitors, GABA inhibitors and cholinesterase inhibitors were not available when PD control patients underwent neuropsychological assessment; therefore, none of these patients reported using these medications. Descriptives for cognitive variables at baseline for the PD control group are reported in Table 2. The average length of time between baseline and follow-up assessments was 25.27 months ($SD = 14.96$).

Comparison of English- and Spanish-speaking DBS Patients

In order to determine if English- and Spanish-speaking unilateral STN DBS patients could be grouped together in the analyses, these patients were compared on demographic and disease variables and baseline cognitive status. English- and Spanish-speaking DBS groups differed significantly on level of education, $F(1, 27) = 8.87, p < .01$, but did not differ on other demographic variables (see Table 1). More than half (54%) of the Spanish-speaking DBS patients had less than a high school education; whereas 60% of the English-speaking DBS patients had greater than a high school education and only one had less than a high school education. In terms of medications,

English- and Spanish-speaking DBS groups differed significantly on use of dopamine agonists at baseline, $\chi^2(1, N = 28) = 7.05, p < .01$, and use of antipsychotics at follow-up, $\chi^2(1, N = 28) = 3.88, p = .05$ (see Table 3). Additionally, English- and Spanish-speaking unilateral STN DBS groups differed significantly on baseline cognitive performance for several variables: BNT, $t(26) = 2.70, p = .01$; HVOT, $t(26) = 2.51, p = .02$; and WAIS-III digits backward, $t(26) = 3.19, p < .01$, with Spanish-speakers performing more poorly on these measures (see Table 2). As a result of baseline differences in education, medication and cognitive performance, English- and Spanish-speaking unilateral STN DBS groups were analyzed separately for all subsequent analyses.

Primary Aim: Comparison of the English-speaking DBS and PD control groups

Hypothesis 1: No significant differences will be observed between English-speaking DBS and PD control groups at baseline.

Independent sample t tests and chi-square analyses revealed no significant differences between English-speaking DBS and PD control patients on demographic or cognitive variables at baseline (see Tables 1 and 2), because patients in each group were matched on these variables. However, there were significant differences between the two groups at baseline on use of levodopa, $\chi^2(1, N = 30) = 4.62, p = .03$, dopamine agonists, $\chi^2(1, N = 30) = 11.00, p < .01$, NMDA antagonists, $\chi^2(1, N = 30) = 3.97, p = .05$, and COMT inhibitors, $\chi^2(1, N = 30) = 10.91, p < .01$, and at follow-up on use of dopamine agonists, $\chi^2(1, N = 30) = 8.89, p < .01$, and COMT inhibitors, $\chi^2(1, N = 30) = 10.91, p < .01$ (see Table 3).

Hypothesis 2: At follow-up, English-speaking DBS patients will show select changes in neuropsychological performance compared to PD control patients,

which will follow the same pattern of cognitive changes observed after bilateral DBS (e.g. declines in verbal fluency, executive function, attention and memory).

Change scores were calculated for each cognitive variable, by subtracting the score at baseline from the score at follow-up, such that negative values represented a decline in performance. A summary of the cognitive change scores is presented in Table 4. One-sample t tests were performed for each group, using cognitive change scores as dependent variables, to determine if neuropsychological performance within each group changed significantly from baseline to follow-up assessment.

The English DBS group exhibited a significant decline in phonemic fluency, $t(14) = -2.29, p = .04$, and WAIS-III Digits Backward, $t(14) = -2.30, p = .04$, and a trend towards significant decline in CVLT immediate free recall, $t(14) = -1.78, p = .10$; whereas the PD control group did not exhibit significant change in performance on any cognitive variable. A summary of one-sample t test results is presented in Table 5.

Separate one-way ANOVAs were performed for each cognitive change score in order to compare changes in performance between English-speaking DBS and PD control groups. One-way ANOVA revealed a significant main effect for WAIS-III Digits Backward change scores, $F(1, 29) = 5.32, p = .03$, such that the PD control group's performance improved ($M_{\text{diff}} = 0.27, SD_{\text{diff}} = 1.22$), while the DBS group's performance declined ($M_{\text{diff}} = -0.87, SD_{\text{diff}} = 1.46$). Main effects for all other cognitive variables were nonsignificant. See Table 6 for a complete summary of ANOVA results. Although there were significant differences between groups at baseline on use of levodopa, dopamine agonists, NMDA antagonists, and COMT inhibitors, there were no group differences in cognitive performance at baseline (even after controlling for these medications), nor were

there significant changes in medications from baseline to follow-up assessment. Therefore, these medications were not included as covariates in the analyses.

Comparison of English-speaking DBS and PD Control Groups Using Reliable Change Indices

Reliable Change Indices (RCIs) were used to determine the frequency of clinically significant declines in cognitive performance. RCIs were calculated using values from the PD control group's cognitive performance at baseline and follow-up, as previously described by Jacobson and Truax (1991). The RCI method used was defined as $[(X_2 - X_1) - (M_2 - M_1)] / SD$, where X_1 was the observed baseline score, X_2 was the observed follow-up score, M_1 was the mean baseline score of the control group, M_2 was the mean follow-up score of the control group, and SD was the standard deviation of the change score for the control group (Troster et al., 2007). English-speaking DBS patients were classified as exhibiting a decline, no change, or an improvement if their RCI score fell below, within, or above the 95% confidence interval of the mean RCI value for the PD control group (see Table 4 for 95% confidence intervals for cognitive change raw scores). Chi-square analyses (2 X 3) were used to compare the proportion of patients in the English DBS and PD control groups that exhibited a decline, no change, or an improvement in cognitive performance. Results of these analyses indicated a trend towards clinically significant change in cognitive performance for the English-speaking DBS group on JLO, $\chi^2(2, N = 30) = 4.86, p = .09$, and WAIS-III Digits Backward, $\chi^2(2, N = 30) = 4.66, p = .10$. RCI category frequencies are presented in Table 7.

Secondary Aim: Comparison of Side of Stimulation Among Unilateral STN DBS Patients

Hypothesis 3: Side of unilateral DBS will influence cognitive performance. Right-sided STN DBS will be related to greater visuospatial impairments and left-sided STN DBS will be related to greater impairments on tasks measuring dominant hemisphere function such as confrontation naming and verbal fluency.

Of the 15 English-speaking DBS patients, eleven received left-sided DBS, four received right-sided DBS. Chi-square analyses and independent sample *t* tests revealed no significant differences between left- and right-sided DBS groups at baseline on demographic, disease or cognitive variables (see Tables 8 and 9).

Change scores were calculated for each cognitive variable (see Table 10). One-sample *t* tests were performed for each group, using cognitive change scores as dependent variables, to determine if there was a significant change in neuropsychological performance from baseline to follow-up. Left-sided DBS patients showed a trend towards a decline in performance on phonemic fluency, $t(10) = -2.03, p = .08$, but did not show significant change on any other variable (see Table 10). Right-sided DBS patients did not show significant change on any cognitive variable. Separate one-way ANOVAs were performed for each cognitive change score in order to compare changes in performance between left- and right-sided DBS groups. Main effects for all cognitive change scores were nonsignificant (see Table 11).

Exploratory Aim: Changes in Cognitive Performance Among Spanish-speaking Unilateral STN DBS Patients

Hypothesis 4: Spanish-speaking unilateral STN DBS patients will show select changes in neuropsychological performance at follow-up, which will follow a

similar pattern of cognitive changes as English-speaking unilateral STN DBS patients.

Change scores were calculated for each cognitive variable for the Spanish-speaking DBS group (see Table 4). One-sample t tests were performed to determine if neuropsychological performance changed significantly after DBS. The Spanish-speaking DBS group exhibited significant changes in the domains of language [phonemic fluency, $t(12) = -2.16, p = .05$; and BNT, $t(12) = -2.45, p = .03$] and visuospatial abilities [JLO, $t(12) = -2.45, p = .03$; and HVOT, $t(12) = -3.00, p = .01$]. A summary of one-sample t test results is presented in Table 5.

Pearson and point-biserial correlations were used to examine the relationships between demographic and disease variables, and change scores for each cognitive variable. Phonemic fluency change scores were significantly negatively correlated with age at baseline ($r = -.59, p = .03$) and age of disease onset ($r = -.55, p = .05$), such that patients that were older at baseline assessment and those that had an older age of disease onset exhibited greater declines in verbal fluency. Although education was not significantly correlated with phonemic fluency change scores, education was included as a covariate because the sample was not highly educated. Due to multicollinearity between age of disease onset and age at baseline ($r = .82, p < .01$), it was not appropriate to enter both variables in the regression equation. Separate regression equations revealed that age of disease onset ($\beta = -0.73, p = .02$) and age at baseline ($\beta = -0.67, p = .03$) each significantly predicted phonemic fluency change scores after controlling for education (see Table 12).

Chapter Eleven: Discussion

This study examined the effects of STN DBS on cognition. This investigation is the first to compare unilateral STN DBS patients to matched PD control patients. This is also the first study to examine cognitive outcome in a subset of Spanish-speaking PD patients who underwent unilateral STN DBS. English-speaking unilateral STN DBS patients followed a similar pattern of cognitive decline as reported in the bilateral STN DBS literature, and did not show a specific pattern of cognitive changes according to side of DBS implantation. However, a major finding is that Spanish-speaking unilateral STN DBS patients exhibited a pattern of cognitive decline which was different from that observed among English-speaking STN DBS patients. For this reason, the findings for English-speaking and Spanish-speaking subgroups will be presented separately.

Comparison of English-speaking Unilateral STN DBS and PD Control Groups at Baseline

It was hypothesized that no significant differences would be observed between the English-speaking DBS and PD control groups at baseline. The data supported this hypothesis; the groups did not differ on demographics, disease status or baseline cognitive performance. The one exception was use of specific PD medications including levodopa, dopamine agonists, NMDA antagonists, and COMT inhibitors. Patients in the PD control group were closely matched to English-speaking unilateral STN DBS patients on time between neuropsychological assessments, disease severity while “on” medication, demographic variables, and cognitive performance at baseline.

Although patients in the PD control and DBS groups differed on use of certain medications, it is unlikely that medications significantly influenced cognitive

performance in this study. First, patients in each group were matched by their cognitive performance while “on” medication, and medication use was uncorrelated with baseline cognitive performance in either group. This is consistent with several studies that have shown that antiparkinsonian drugs have a minimal influence on cognition in patients with moderate to severe PD (Girotti et al., 1986; Gotham et al., 1988; Morrison et al., 2000). Additionally, medication status did not change significantly from baseline to follow-up within either group, nor were changes in medication correlated with changes in cognition. This finding is consistent with two other DBS studies that have failed to find a relationship between changes in medication and cognitive performance (Smeding, Speelman, Huizenga, Schuurman, and Schmand, 2009; Zahodne, Okun, Foote, Fernandez, Rodriguez et al., 2008). Collectively, these findings suggest that changes in medication do not explain changes in cognitive performance; however, studies with larger samples are needed to more carefully evaluate this concern since evaluating medication effects on cognition was not the primary aim of this investigation.

Comparison of English-speaking Unilateral STN DBS and PD Control Groups at Follow-up

It was hypothesized that English-speaking unilateral STN DBS patients would demonstrate the same pattern of specific cognitive changes that has been reported in the bilateral STN DBS literature. The data supported this hypothesis. English-speaking unilateral STN DBS patients exhibited significant declines in phonemic fluency (COWAT) and executive function (WAIS-III digits backward), and a trend towards significant decline in verbal memory (CVLT immediate free recall).

These findings are consistent with the bilateral DBS literature. Verbal fluency declines are the most commonly reported change after bilateral DBS, followed by declines in executive function and working memory (Alegret et al., 2001; Amick & Grace, 2006; Ardouin et al., 1999; Castelli et al., 2007; Daniele et al., 2003; Deuschl et al., 2006; Funkiewiez et al., 2004; Gironell et al., 2003; Morrison et al., 2004; Parsons et al., 2006; Pillon et al., 2000; Smeding et al., 2006; Weaver et al., 2009; Witt et al., 2008; Woods et al., 2002). As expected, English-speaking unilateral STN DBS patients did not demonstrate significant changes on tasks which do not rely on intact executive functioning, such as confrontational naming or visuospatial judgment.

In contrast to the declines exhibited by the English-speaking DBS group, the PD control group did not demonstrate significant changes in cognitive performance at follow-up on any task. These results are consistent with other longitudinal studies reporting that 90% or more of PD patients have relatively stable cognitive performance over one to two years (Kieburtz, McDermott, Como, Growdon, Brady et al., 1994; Troster, Woods & Morgan, 2007), and suggest that cognitive changes observed following DBS are not simply due to disease progression.

Impaired cognitive performance after DBS may be due to reduced neuronal activation in relevant cortical areas (Kalbe, Voges, Weber, Haarer, Baudrexel et al., 2009). Neuroimaging studies report that bilateral STN DBS patients experience bilateral rCBF decrements in motor cortical areas, as well as the dorsolateral prefrontal cortex, anterior cingulate, and inferior frontal gyrus, mainly in the left hemisphere, compared to baseline assessment and matched PD controls (Cilia, Marotta, Landi, Isaias, Mariani et al., 2009). Perfusion decrements in these areas have been associated with clinical motor

improvements (Cilia et al., 2009), but also correlate with verbal fluency declines (Cilia et al., 2007; Kalbe et al., 2009). Collectively, these findings suggest that DBS induced normalization (i.e. decreased overactivity) of the cortico-basal ganglia-thalamo-cortical motor loop improves motor symptoms, but may also interfere with neural circuits subserving cognitive function.

Comparison of English-speaking DBS and PD control groups revealed a significant difference in changes in executive function over time (WAIS-III digits backward change scores). Performance of the DBS group declined after surgery, whereas the control group improved over time. This finding is noteworthy given this task's demands on executive function and working memory. Lack of statistically significant findings for other cognitive change scores, despite the DBS group's significant decline, may have been due to low statistical power. This is particularly true for verbal fluency where the DBS group showed marked decline but this did not achieve statistical significance and is likely still clinically meaningful. Also, given that these were group comparisons, variance in mean cognitive change scores may have obscured clinically significant changes in individual patients.

In order to address some of these issues, reliable change indices (RCI) were calculated to examine clinically significant change in individual cognitive performance. RCI revealed that compared to PD controls, approximately twice as many DBS patients experienced clinically significant declines in phonemic fluency, executive function (WAIS-III digits backward), and immediate verbal memory (CVLT immediate free recall). These findings are similar to other RCI studies that found greater declines in verbal fluency among DBS patients than expected based on disease progression

(Higginson et al., 2008; York et al., 2007) and compared to PD controls (Zahodne et al., 2008). A closer inspection of RCIs revealed that all but one English-speaking DBS patient experienced clinically significant decline on at least one cognitive task, and one DBS patient experienced clinically significant decline on all cognitive tasks. Notably, the patient that experienced decline on all cognitive tasks had the lowest educational attainment (11 years of education) in the English-speaking DBS group. In contrast, the only DBS patient that did not exhibit clinically significant decline on any task had 16 years of education, was the youngest patient, and had the second earliest disease onset among the English-speaking DBS patients. Interestingly, this patient also demonstrated clinically significant improvements in verbal memory (CVLT immediate and delayed free recall), and stable performance on all other cognitive tasks, which suggests that younger age, earlier disease onset, and higher levels of education are protective against cognitive decline after DBS. This is consistent with prior work indicating that age of onset as well as cognitive reserve may be associated with less cognitive decline in PD. Moreover, these findings underscore the importance of examining individual-level change, particularly in small samples.

Comparison of Left- and Right-sided English-speaking Unilateral STN DBS Groups

It was hypothesized that the right-sided DBS group would demonstrate greater visuospatial impairments and the left-sided DBS group would show greater verbal impairments. The data did not support this hypothesis. Neither group demonstrated a specific pattern of cognitive change based on side of unilateral STN DBS, despite statistically nonsignificant declines in phonemic fluency among the left-sided DBS group and in visuospatial ability among the right-sided DBS group. There may have been

insufficient power to detect changes in cognitive performance due to the small sample size and unequal numbers of patients in each group. In addition, the DBS patients' advanced disease stage and corresponding bilateral subcortical damage may have precluded the observation of hemisphere-specific cognitive deficits.

To date, only one other unilateral DBS study examined outcome associated with side of unilateral (STN or GPi) DBS on cognition following surgery. Zahodne et al. (2008) found a trend towards cognitive decline among left-sided DBS patients, as well as a bias towards performing left-sided DBS procedures. The current study also uncovered a bias towards performing left-sided DBS procedures: More than twice as many patients underwent left-sided DBS than right-sided DBS in our cohort, and side of DBS was not correlated with motor symptom laterality. The surgical team indicated a preference for performing left-sided DBS when a patient exhibited bilateral symptoms, in order to offer right-handers greater functional improvement. A larger sample with patients randomized by side of unilateral DBS would be necessary to more carefully evaluate this hypothesis.

Exploratory Analysis of Spanish-speaking Unilateral STN DBS Group

This study sought to examine cognitive changes after DBS in a subset of Spanish-speaking PD patients. Spanish-speakers have not been studied in the context of DBS research, despite exponential growth in the Hispanic-American population (U.S. Census Bureau, 2000) and evidence of higher rates of PD incidence among Hispanic-Americans compared to non-Hispanic Whites, Asian-Americans, or African-Americans (Van Den Eeden et al., 2003). To date, all published DBS studies in America have been conducted on English-speaking, non-Hispanic Whites, yet approximately 47 million people in the U.S. speak a language other than English at home, of which Spanish is the most spoken

language (Shin & Bruno, 2003). In this study, Spanish-speakers comprised almost half of the total number of DBS patients.

It was hypothesized that Spanish-speaking DBS patients would show a similar pattern of cognitive changes after surgery as English-speaking DBS patients; however, the data did not support this hypothesis. Spanish-speaking DBS patients showed significant declines in phonemic fluency, confrontational naming and visuospatial ability following surgery. In contrast, performance differences were not observed on attention/executive function and verbal memory. Aside from the decline in phonemic fluency, the observed pattern of cognitive changes is inconsistent with the pattern observed among English-speaking DBS patients in this study as well as the reports in the literature.

The differences between English- and Spanish-speaking patients who underwent DBS in this study may in part be linked to key differences in baseline variables. The Spanish-speaking group was older, had later disease onset, greater baseline cognitive difficulties, and significantly less formal education than the English-speaking DBS group. In fact, older age and later disease onset predicted phonemic fluency decline among Spanish-speaking patients, even after controlling for education. It has been shown that older patients are at a greater risk of cognitive decline after DBS (Kalteis et al., 2006; Smeding et al., 2009; Trepanier et al., 2000), particularly in verbal fluency and executive function (Castro-Garcia et al., 2006; Saint-Cyr et al., 2000). Therefore, it appears that demographic characteristics of the Spanish-speaking DBS group may in part account for these findings.

Low educational attainment among the Spanish-speakers may also explain the more widespread cognitive changes since low educational attainment is a well-known risk factor for cognitive decline in PD (Glatt et al., 1996; Muslimovic et al., 2007). Educational attainment has been used as a proxy for cognitive reserve, and its been shown to be a good predictor of how individuals recover following brain damage (Stern, 2002). Low educational attainment may also serve as a proxy for social and environmental, socioeconomic, and health-related variables, as well as disparities in material and psychosocial resources (Glymour & Manley, 2008). The relationship between education and cognitive performance is complex and may be mediated by many variables such as quality of education, test-taking skills and assessment bias, all of which are relevant to understanding racial and ethnic differences in neuropsychological test performance.

Limited evidence suggests neuropsychological performance differs between English-speakers and Spanish-speakers, even when subjects are tested in their native language with culturally appropriate norms (Gasquoine, Croyle, Cavazos-Gonzalez, and Sandoval 2007; Jacobs, Sano, Albert, Schofield, Dooneief et al., 1997). Discrepancies may be due in part to variability in test administration and scoring (Ostroky-Solis, Gutierrez, Flores, and Ardila, 2007), qualitative educational differences, non-equivalent Spanish/English translations, cultural bias in test materials and/or acculturation or bilingualism related factors (Gasquoine, 2001). While not the focus of the current study, differences may also be related to higher incidence of stroke, diabetes mellitus, and cardiometabolic syndrome among Hispanics (Rincon, Sacco, Kranwinkel, Xu, Paik, et al., 1999), which may be linked to greater cognitive decline. The causes of cognitive

decline among Hispanics are likely multifactorial. In light of the results of this exploratory investigation, more research is needed to better understand cognitive performance and changes after DBS among this understudied group.

Limitations

This study has several limitations that should be addressed. Foremost, the results are limited by the study's small sample size. In an attempt to address this limitation, we used a hypothesis driven neuropsychological test battery that was sensitive to the cognitive deficits typically observed in PD. When possible, alternate forms of tests were used at each assessment in order to minimize practice effects. This study also attempted to minimize practice effects by using a longer follow-up interval than most DBS studies. Using a longer follow-up interval provided the additional benefit of allowing time for patients to recover from the DBS procedure, as well as to adjust medications and stimulation parameters. This study also addressed this limitation statistically by using ANOVA with change scores *and* RCI, a technique that allows one to examine individual-level changes over time while taking into account practice effects.

Second of all, the study was limited by its design, particularly the subject recruitment and enrollment procedures, which may have introduced sample bias. Subjects were recruited one year after the DBS procedure, thus it is possible that a greater number of patients with better surgical outcomes, fewer cognitive impairments, and fewer medical or psychiatric comorbidities may have agreed to participate (Weaver, Follet, Stern, Hur, Harris et al., 2009). In contrast, patients with poorer surgical outcomes may have been less likely to return for follow-up neuropsychological evaluation. This is consistent with a prior study that demonstrated that PD patients with

greater cognitive impairments at baseline were less likely to return for follow-up evaluation (Levin, Katzen, Klein, & Llabre, 2000). Also, in support of this assertion, several eligible patients that were contacted but refused follow-up evaluation cited discontent with their surgical outcome and/or neurological care, difficulty with transportation, or unavailability of a caregiver. Furthermore, of the patients that were not available for contact, the study neurologist reported that several had been placed in assisted living facilities or inpatient psychiatric settings due to dementia and/or behavioral dysregulation after the DBS procedure. Although this evidence is anecdotal, it seems to support the idea that patients with better DBS outcomes are more likely to return for follow-up evaluation, and raises concern about underreporting of cognitive decline in the DBS literature.

In addition to the bias introduced by the study's recruitment and enrollment procedures, the results were likely influenced by the demographic characteristics of the sample. Almost half of the patients in the DBS group were monolingual Spanish-speakers, and almost three quarters were Hispanics. Although the patients in this study were more ethnically diverse than most DBS studies, this sample did not include any African American or Asian patients. The predominance of Hispanic American patients in this sample likely reflects the local demographics of South Florida, but also appears to support the findings of an epidemiological study which reported that Hispanics have a higher PD incidence than non-Hispanic Whites, African Americans or Asians (Van den Eeden et al., 2003). Despite the large number of Spanish-speaking DBS patients, this study lacked a Spanish-speaking PD control group, which limits the conclusions that may be drawn about cognitive changes observed in the Spanish-speaking DBS group.

Significant differences in baseline cognitive performance and number of years of formal education prohibited combining the English-speaking DBS and Spanish-speaking DBS groups in the analyses, or comparing the Spanish-speaking DBS group to the English-speaking PD control group. Differences in cognitive performance may be partly attributed to qualitative and quantitative educational differences, but are complicated by issues of cultural bias and socioeconomic disparities. Although there is no simple explanation for differences in cognitive performance among Spanish-speaking patients, collectively, these findings suggest that older age, later disease onset, greater baseline cognitive impairment, and lower levels of education increase the risk of cognitive decline after DBS. Evaluation of cognitive changes over time among Spanish-speaking PD control patients is necessary to better understand the changes observed among the Spanish-speaking DBS group. Future work should address this.

Another limitation is that study follow-up neurological data and post-operative neuroimaging were not available for all subjects. This is in part due to the fact that this was an observational clinical research study and this data was not readily available. Comprehensive neurological evaluations are needed to evaluate post-surgical changes in motor symptoms. Furthermore, post-operative neuroimaging is essential to confirm electrode placement in the dorsolateral STN, since misplacement of an electrode in another region of the STN or in a surrounding structure can produce motor, cognitive or psychiatric adverse events. The lack of neurologic and neuroimaging follow-up data is a weakness that should be addressed in future studies.

A final limitation of the study is that the PD control group was selected from a sample that underwent neuropsychological testing before the advent of DBS, with fewer

antiparkinsonian medications available at the time of testing. However, all of the control patients in this study would have been eligible for DBS, as determined by their baseline cognitive performance and disease status, and did not differ significantly from the DBS group on demographic, disease or cognitive variables. Other DBS studies have used patients who refused surgery as control subjects (Accolla et al., 2007; Hariz and Hariz, 2000; Setiawan et al., 2006; Zahodne et al., 2008), and found that PD patients who did not undergo DBS differed significantly from PD patients who chose DBS on important variables such as disease duration and severity, suggesting that this may also not be the ideal control group. Future DBS studies should be based on larger samples and use randomized wait-list control designs with single-blinded neurological follow-up assessments, in which DBS and PD control groups are comparable on demographic, disease, cognitive and psychological variables, as well as medication use. However, there are ethical implications surrounding the use of a wait-list control design, given that DBS is currently one of the most effective surgical treatments for levodopa induced motor complications and has the potential to alter the natural course of PD.

Clinical Implications

The current findings have important clinical implications for patients undergoing neurosurgical interventions for PD. English-speaking PD patients that underwent unilateral STN DBS followed the same pattern as bilateral STN DBS patients, which has implications for whether patients will elect to have unilateral or bilateral surgery. Given that it appears unilateral DBS is associated with the same degree of cognitive decline observed following bilateral procedures, the purported benefits of unilateral DBS (e.g. decreased risk of intraoperative adverse events, lower rates of infection post-surgery)

must be carefully considered while also taking into account the patient's age, cognitive and emotional status, disease severity, response to medications, expectations of surgery and likelihood of requiring a contralateral DBS procedure.

Spanish-speaking DBS patients demonstrated a more pervasive pattern of cognitive decline after surgery, likely due to differences in demographic characteristics and greater vulnerability at baseline. These findings underscore the need for careful selection and screening of patients prior to surgery. Extra care should be taken when discussing adverse events with DBS candidates that have one or more risk factor for cognitive decline (e.g. older age, later disease onset, fewer years of education, baseline cognitive impairment and/or dementia) and more work is needed to fully understand cognitive outcome in this understudied population.

Future Work

Future research should employ a control group when examining cognitive outcome following DBS in Spanish-speakers to determine whether cognitive differences observed among Spanish-speaking DBS patients are due to cultural biases in neuropsychological testing and/or demographic and disease related risk factors. Additionally, future research should follow larger, more diverse samples of DBS patients over several years in order to examine long-term cognitive effects of DBS. Larger samples would allow for the use of more complex statistical models and provide the opportunity to identify moderators of DBS outcome. As more patients receive DBS and its therapeutic use continues to expand to other neurological and neuropsychiatric disorders, it will be increasingly important to understand the mechanisms of DBS, and

the effects of stimulating specific regions of the brain on motor function, cognition, affect and quality of life.

References

- Aarsland, D., Bronnick, K., Larsen, J.P., Tysnes, O.B., & Alves, G. (2009). Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology*, 72(13), 1121-1126.
- Abosch, A., & Lozano, A. (2003). Stereotactic neurosurgery for movement disorders. *Canadian Journal of Neurological Science*, 30, S72-82.
- Accolla, E., Caputo, E., Cogliamarian, F., Tamma, F., & Mrakic-Sposta, S. (2007). Gender differences in patients with Parkinson's disease treated with subthalamic deep brain stimulation. *Movement Disorders*, 22(8), 1150-1156.
- Alegret, M., Junque, C., Valldeoriola, F., Vendrell, P., Pilleri, M., et al. (2001). Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. *Archives of Neurology*, 58, 1223-1227.
- Amick, M. M. & Grace, J. (2006). Deep brain stimulation surgery for Parkinson's disease: the role of neuropsychological assessment. *Medical Health Rhode Island*, 89(4), 130-133.
- Ardouin, C., Pilon, B., Peiffer, E., Bejjani, P., Limousin, P., Damier, P., et al. (1999). Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. *Annals of Neurology*, 46(2), 217-223.
- Arnulf, I. (2006). Sleep and wakefulness disturbances in Parkinson's disease. *Journal of Neural Transmission*, S70, 357-360.
- Baba, Y., Putzke, J. D., Whaley, N. R., Wszolek, Z. K., & Uitti, R. J. (2005). Gender and the Parkinson's disease phenotype. *Journal of Neurology*, 252(10), 1201-1205.
- Barrett, A. M., Crucian, G. P., Schwartz, R., Nallamshetty, H., & Heilman, K. M. (2001). Seeing trees but not the forest: limited perception of large configurations in PD. *Neurology*, 56(6), 724-729.
- Bejjani, B., Gervais, D., Arnulf, I., Papadopoulos, S., Demeret, S., et al. (2000). Axial parkinsonian symptoms can be improved: the role of levodopa and bilateral subthalamic stimulation. *Journal of Neurology, Neurosurgery & Psychiatry*, 68, 595-600.
- Benabid, A. L., Pollak, P., Gao, D., Hoffmann, D., Limousin, P., et al. (1996). Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *Journal of Neurosurgery*, 84(2), 203-214.

- Ben-Shlomo, Y., & Sieradzan, K. (1995). Idiopathic Parkinson's disease: epidemiology, diagnosis and management. *British Journal of General Practice*, *45*, 261-68.
- Bentin, S., Silverberg, R., & Gordon, H. W. (1981). Asymmetrical cognitive deterioration in demented and Parkinson patients. *Cortex*, *17*(4), 533-543.
- Benton, A. L., Varney, N. R., & Hampsher, K. (1978). Visuospatial Judgment: A clinical test. *Archives of Neurology*, *35*, 364-367.
- Berardelli, A., Rothwell, J. C., Thompson, P. D., & Hallett, M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. *Brain*, *124*, 2131-2146.
- Biggins, C. A., Boyd, J. L., Harrop, F. M., Madeley, P., Mindham, R. H., Randall, J. I., et al. (1992). A controlled, longitudinal study of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *55*(7), 566-571.
- Bodis-Wollner, I. (2003). Neuropsychological and perceptual defects in Parkinson's disease. *Parkinsonism & Related Disorders*, *9*(S2), S83-90.
- Bodis-Wollner, I., & Jo, M. Y. (2006). Getting around and communicating with the environment: visual cognition and language in Parkinson's disease. *Journal of Neural Transmission Supplement*, *70*, 333-338.
- Bodis-Wollner, I., Marx, M. S., Mitra, S., Bobak, P., Mylin, L., & Yahr, M. (1987). Visual dysfunction in Parkinson's disease. Loss of spatiotemporal contrast sensitivity. *Brain*, *110*(Pt 6), 1675-1698.
- Bordini, B. J., Garg, A., Gallagher, C. L., Bell, B., & Garell, P. C. (2007). Neuropsychological effects of bilateral deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *Stereotactic & Functional Neurosurgery*, *85*(2-3), 113-120.
- Bronte-Stewart, H. (2003). Parkinson's disease: Surgical options. *Current Treatment Options Neurology*, *5*(2), 131-147.
- Brown, T. P., Rumsby, P. C., Capleton, A. C., Rushton, L., & Levy, L. S. (2006). Pesticides and Parkinson's disease – Is there a link? *Environmental Health Perspectives*, *114*(2), 156-164.
- Brusa, L., Bassi, A., Stefani, A., Pierantozzi, M., Peppe, A., et al. (2003). Pramipexole in comparison to l-dopa: a neuropsychological study. *Journal of Neural Transmission*, *110*(4), 373-380.
- Brusa, L., Pierantozzi, M., Peppe, A., Altibrandi, G., Giacomini, P., et al. (2001). Deep brain stimulation (DBS) attentional effects parallel those of l-dopa treatment. *Journal of Neural Transmission*, *108*, 1021-1027.

- Brusa, L., Tiraboschi, P., Koch, G., Peppe, A., Pierantozzi, M., et al. (2005). Pergolide effect on cognitive function in early-mild Parkinson's disease. *Journal of Neural Transmission*, 112(2), 231-237.
- Bulens, C., Meerwaldt, J. D., & Van der Wildt, G. J. (1988). Effect of stimulus orientation on contrast sensitivity in Parkinson's disease. *Neurology*, 38(1), 76-81.
- Burchiel, K. J., Anderson, V. C., Favre, J., & Hammerstad, J. P. (1999). Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: Results of a randomized blinded pilot study. *Neurosurgery*, 45(6), 1-18.
- Capecchi, M., Riccitu, R. A., Burini, D., Bombace, V. G., Provinciali, L., et al. (2005). Functional improvement after subthalamic stimulation in Parkinson's disease: a non-equivalent controlled study with 12-24 month follow-up. *Journal of Neurology, Neurosurgery & Psychiatry*, 76, 769-774.
- Castelli, L., Lanotte, M., Zibetti, M., Caglio, M., Rizzi, L. et al. (2007). Apathy and verbal fluency in STN-stimulated PD patients: an observational follow-up study. *Journal of Neurology*, 254(9), 1238-1243.
- Castelli, L., Perozzo, P., Zibetti, M., Crivelli, B., Morabito, U., Lanotte, M., et al. (2006). Chronic deep brain stimulation of the subthalamic nucleus for Parkinson's disease: effects on cognition, mood, anxiety and personality traits. *European Neurology*, 55, 136-144.
- Castro-Garcia, A., Sesar-Ignacio, A., Ares-Pensado, B., Relova-Quinteiro, J. L., Gelabert-Gonzalez, M., et al. (2006). Psychiatric and cognitive complications arising from subthalamic stimulation in Parkinson's disease. *Review of Neurology*, 43(4), 218-222.
- Ceballos-Baumann, A. O., Boecker, H., Bartenstein, P., von Falkenhayn, I., Riescher, H., et al. (1999). A positron emission tomographic study of subthalamic nucleus stimulation in Parkinson disease. *Archives of Neurology*, 56, 997-1003.
- Chang, V. C., & Chou, K. L. (2006). Deep brain stimulation for Parkinson's disease: patient selection and motor outcomes. *Medical Health Rhode Island*. 89(4), 142-144.
- Charles, P. D., Van Blercom, N., Krack, P., Lee, S. L., Xie, J., et al. (2002). Predictors of effective subthalamic nucleus stimulation for PD. *Neurology*, 59, 932-934.

- Cheesman, A. L., Barker, R. A., Lewis, S. J. G., Robbins, T. W., Owen, A. M., et al. (2005). Lateralisation of striatal function: evidence from ^{18}F -dopa PET in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*, 1204-1210.
- Chung, S. J., Jeon, S. R., Kim, S. R., Sung, Y. H., & Lee, M. C. (2006). Bilateral effects of unilateral subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *European Neurology*, *56*(2), 127-132.
- Cilia, R., Marotta, G., Landi, A., Isaias, I., Mariani, C.B., et al. (2009). Clinical and cerebral activity changes induced by subthalamic nucleus stimulation in advanced Parkinson's disease: a prospective case-control study. *Clinical Neurology and Neurosurgery*, *111*(2), 140-146.
- Cilia, R., Siri, C., Marotta, G., Gaspari, D. D., Laandi, A., et al. (2007). Brain networks underlining verbal fluency decline during STN-DBS in Parkinson's disease: An ECD-SPECT study. *Parkinsonism and Related Disorders*, *13*(5), 290-294.
- Contarino, M. F., Daniele, A., Sibilio, A. H., Romito, L. M. A., Bentivoglio, A. R., et al. (2007). Cognitive outcome 5 years after bilateral chronic stimulation of subthalamic nucleus in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *78*, 248-252.
- Cools, R., Barker, R. A., Sahakian, B. J., & Robbins, T. W. (2001). Mechanisms of cognitive set flexibility in Parkinson's disease. *Brain*, *124*, 2503-2512.
- Cooper, J. A., Sagar, H. J., Doherty, S. M., Jordan, N., Tidswell, P., et al. (1992). Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. *Brain*, *115*(Pt 6), 170-1725.
- Cooper, J. A., Sagar, H. J., Jordan, N., Harvey, N. S., & Sullivan, E.V. (1991). Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain*, *114*(Pt 5), 2095-2122.
- Cooper, J. A., Sagar, H. J., & Sullivan, E. V. (1993). Short-term memory and temporal ordering in early Parkinson's disease: effects of disease chronicity and medication. *Neuropsychologia*, *31*, 933-949.
- Czernicki, V., Pillon, B., Houeto, J. L., Welter, M. L., Mesnage, V., et al. (2005). Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(6), 775-779.

- Daniele, A., Albanese, A., Contarino, M. F., Zuni, P., Barbier, A., Gasparini, F., et al. (2003). Cognitive and behavioral effects of chronic stimulation of the subthalamic nucleus in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 74, 175-182.
- Davidson, P. S., Anaki, D., Saint-Cyr, J. A., Chow, T. W., & Moscovitch, M. (2006). Exploring the recognition memory deficit in Parkinson's disease: estimates of recollection versus familiarity. *Brain*, 129(Pt 7), 1768-1779.
- Deep Brain Stimulation for Parkinson's Disease Study Group. (2001). Deep brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. *The New England Journal of Medicine*, 345(13), 956-963.
- De Gaspari, D., Siri, C., Di Gioia, M., Antonini, A., Isella, V., et al. (2006). Clinical correlates and cognitive underpinnings of verbal fluency impairment after chronic subthalamic stimulation in Parkinson's disease. *Parkinsonism & Related Disorders*, 12, 289-295.
- De Lau, L. M., & Breteler, M. M. (2006). Epidemiology of Parkinson's disease. *Lancet Neurology*, 5(6), 525-535.
- De Lau, L. M., Giesbergen, P. C., de Rijk, M. C., Hofman, A., Koudstaal, P. J., & Breteler, M. M. (2004). Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. *Neurology*, 63(7), 1240-1244.
- De Lau, L. M., Koudstaal, P. J., Hofman, A., Breteler, M. B. (2006). Subjective complaints precede Parkinson disease. *Archives of Neurology*, 63, 362-365.
- Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). *California Verbal Learning Test (CVLT). Adult version*. San Antonio, TX: Psychological Corporation.
- Deuschl, G., Schade-Brittinger, C., Krack, P., Volkmann, J., Schafer, H., et al. (2006). A randomized trial of deep-brain stimulation for Parkinson's disease. *New England Journal of Medicine*, 355(9), 896-908.
- Direnfeld, L. K., Albert, M. L., Volicer, L., Langlais, P. J., Marquis, J., & Kaplan, E. (1984). Parkinson's disease. The possible relationship of laterality to dementia and neurochemical findings. *Archives of Neurology*, 41(9), 935-941.
- Dooneief, G., Mirabello, E., Bell, K., Marder, K., Stern, Y., & Mayeux, R. (1992). An estimate of the incidence of depression in idiopathic Parkinson's disease. *Archives of Neurology*, 49(3), 305-307.

- Downes, J. J., Roberts, A. C., Sahakian, B. J., et al. (1989). Impaired extradimensional shift performance in medicated and unmedicated Parkinson's disease: evidence from a specific attentional dysfunction. *Neuropsychologia*, 27, 1329-1343.
- Dubois, B., Danze, F., Pillon, B., Cusimano, G., Lhermitte, F., & Agid, Y. (1987). Cholinergic dependent cognitive deficits in Parkinson's disease. *Annals of Neurology*, 22, 26-30.
- Dubois, B., Pillon, B., Sternic, N. (1990). Age-induced cognitive disturbances in Parkinson's disease. *Neurology*, 40, 38-41.
- Dujardin, K., Defebvre, L., Krystkowiak, P., Blond, S., & Destée, A. (2001). Influence of chronic bilateral stimulation of the subthalamic nucleus on cognitive function in Parkinson's disease. *Journal of Neurology*, 248(7), 603-11.
- Ehrt, U., Bronnik, K., De Deyn, P. P., Emre, M., Tekin, S., et al. (2007). Subthreshold depression in patients with Parkinson's disease and dementia - clinical and demographic correlates. *International Journal of Geriatric Psychiatry*, 22(10), 980-985.
- Eichhorn, T., & Oertel, W. H. (1994). Incidence, differential diagnosis, work capacity, mortality and cause of death in Parkinson disease. *Versicherungsmedizin*, 46(4):122-128.
- Espay, A. J., Mandybur, G. T., & Revilla, F. J. (2006). Surgical treatment of movement disorders. *Clinical Geriatric Medicine*, 22(4), 813-825.
- Fahn, S., & Elton, R. L. (1987). *Unified Parkinson's Disease Rating Scale*. Florham Park, NJ: Macmillan Healthcare Information.
- Fahn, S., & Sulzer, D. (2004). Neurodegeneration and neuroprotection in Parkinson disease. *The Journal of the American Society for Experimental Neurotherapeutics*, 1, 139-154.
- Ferraye, M. U., Debu, B., Fraix, V., Xie-Brustolin, J., Chabardes, S., Krack, P., et al. (2008). Effects of subthalamic nucleus stimulation and levodopa on freezing of gait Parkinson disease. *Neurology*, 70(16 Pt 2), 1431-1437.
- Finali, G., Piccirilli, M., & Rizzuto, S. (1995). Neuropsychological characteristics of parkinsonian patients with lateralized motor impairment. *Journal of Neural Transmission*, 9, 165-176.
- Fine, J., Duff, J., Chen, R., Chir, B., Hutchison, W., & Lozano, A. M. (2000). Long-term follow-up of unilateral pallidotomy in advanced Parkinson's disease. *New England Journal Medicine*, 342(23), 1708-1714.

- Fleming, S. M., Delville, Y., & Schallert, T. (2005). An intermittent, controlled rate, slow progressive degeneration model of Parkinson's disease: antiparkinsonian medication effects of Sinemet and protective effects of methylphenidate. *Behavioral Brain Research, 156*(2), 201-213.
- Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-Mental State." *Journal of Psychiatric Research, 12*, 189-198.
- Ford, W. L., Pullman, S. L., Frucht, S. J., Du, Y., Greene, P., et al. (2004). Subthalamic nucleus stimulation in advanced Parkinson's disease: blinded assessments at one year follow up. *Journal of Neurology, Neurosurgery & Psychiatry, 75*(9), 1255-1259.
- Francel, P., Ryder, K., Wetmore, J., Stevens, A., Bharucha, K., Beatty, W. W., & Scott, J. (2004). Deep brain stimulation for Parkinson's disease: association between stimulation parameters and cognitive performance. *Stereotactic and Functional Neurosurgery, 82*, 191-193.
- Friedman, A. (1994). Old-onset Parkinson's disease compared with young-onset: clinical differences and similarities. *Acta Neurologica Scandinavica, 89*(4), 258-261.
- Funkewiez, A., Ardouin, C., Cools, R., Krack, P., & Fraix, V. (2006). Effects of levodopa and subthalamic nucleus stimulation on cognitive and affective functioning in Parkinson's disease. *Movement Disorders, 21*(10), 1655-1662.
- Gamez, J. C., Lezcano, E., Molano, A., Lambarri, I., Bilbao, G., et al. (2003). Neuropsychological changes and bilateral subthalamic deep brain stimulation in Parkinson's disease. *Neurologia, 18*(3), 139-145.
- Gasquoine, P. G. (2001). Research in clinical neuropsychology with Hispanic American participants: A review. *The Clinical Neuropsychologist, 15*(1), 2-12.
- Gasquoine, P. G., Croyle, K. L., Cavazos-Gonzalez, C., & Sandoval, O. (2007). Language of administration and neuropsychological test performance in neurologically intact Hispanic American bilingual adults. *Archives of Clinical Neuropsychology, 22*, 991-1001.
- Gentil, M., Garcia-Ruiz, P., Pollak, P., & Benabid, A. (1999). Effect of stimulation of the subthalamic nucleus on oral control of patients with Parkinsonism. *Journal of Neurology, Neurosurgery & Psychiatry, 67*, 329-333.
- Germano, I. M., Gracies, J. M., Weisz, D. J., Tse, W., Koller, W. C., & Olanow, C. W. (2004). Unilateral stimulation of the subthalamic nucleus in Parkinson disease: a double blind 12-month evaluation study. *Journal of Neurosurgery, 101*(1), 36-42.

- Giladi, N., Weitzman, N., Schreiber, S., Shabtai, H., & Peretz, C. (2007). New onset heightened interest or drive for gambling, shopping, eating, or sexual activity in patients with Parkinson's disease: the role of dopamine agonist treatment and age at motor symptoms onset. *Journal of Psychopharmacology*, *21*(5), 501-506.
- Gironell, A., Kulisevsky, J., Rami, L., Fortuny, N., Garcia-Sanchez, C., et al. (2003). Effects of pallidotomy and bilateral subthalamic stimulation on cognitive function in Parkinson disease. *Journal of Neurology*, *250*(8), 917-923.
- Girotti, F., Carella, F., Pia Grassi, M., Soliveri, P., Marano, R., & Caraceni, T. (1986). Motor and cognitive performances of Parkinsonian patients in the on and off phases of the disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *49*, 657-660.
- Girotti, F., Soliveri, P., Carella, F., Geminiani, G., Aiello, G., & Caraceni, T. (1988). Role of motor performance in cognitive processes of parkinsonian patients. *Neurology*, *35*, 537-540.
- Glatt, S. L., Hubble, J. P., Lyons, K., Paolo, A., Troster, A. I., et al. (1996). Risk factors for dementia in Parkinson's disease: Effect of education. *Neuroepidemiology*, *15*, 20-25.
- Glymour, M. M., & Manly, J. J. (2008). Lifecourse social conditions and racial and ethnic patterns of cognitive aging. *Neuropsychology Review*, *18*, 223-254.
- Goodglass, H., & Kaplan, E. (1987). *The Assessment of Aphasia and Related Disorders*. (2nd ed.). Philadelphia, PA: Lea & Febiger.
- Gotham, A. M., Brown, R. G., & Marsden, C. D. (1988). "Frontal" cognitive function in patients with Parkinson's disease "on" and "off" levodopa. *Brain*, *111*, 299-321.
- Green, J. McDonald, W. M., Vitek, J. L., Evatt, M., Freeman, A., et al. (2002). Cognitive impairments in advanced PD without dementia. *Neurology*, *59*(9), 1320-1324.
- Grill, W. M. (2005). Safety considerations for deep brain stimulation: review and analysis. *Expert Review of Medical Devices*, *2*(4), 409-420.
- Growden, J. H., Kieburtz, K., McDermott, M. P., Panisset, M., & Friedman, J. H. (1998). Levodopa improves motor function without impairing cognition in mild non-demented Parkinson's disease patients. *Neurology*, *50*(5), 1327-1331.
- Guehl, D., Cuny, E., Benazzuoz, A., Rougier, A., Tison, F., et al. (2006). Side-effects of subthalamic stimulation in Parkinson's disease: clinical evolution and predictive factors. *European Journal of Neurology*, *13*(9), 963-971.

- Haaxma, C. A., Bloem, B. R., Borm, G. F., Oyen, W. J. G., et al. (2007). Gender differences in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, 78, 819-824.
- Haegelen, C., Verin, M., Broche, B. A., Prigent, F., Jannin, P., et al. (2005). Does subthalamic nucleus stimulation affect the frontal limbic areas? A single-photon emission computed tomography study using a manual anatomical segmentation method. *Surgical and Radiologic Anatomy*, 27(5), 389-394.
- Hamani, C., Saint-Cyr, J. A., Fraser, J., Kaplitt, M., & Lozano, A. M. (2004). The subthalamic nucleus in the context of movement disorders. *Brain*, 127, 4-20.
- Hariz, M. I. (2002). Complications of deep brain stimulation surgery. *Movement Disorders*, 17(3), S162-S166.
- Hariz, G., & Hariz, M. I. (2000). Gender distribution in surgery for Parkinson's disease. *Parkinsonism & Related Disorders*, 6(3), 155-157.
- Hariz, M. I., Rehncrona, S., Quinn, N., Speelman, J. D., Wensing, C., & Multicentre Advanced Parkinson's Disease Deep Brain Stimulation Group. (2007). Multicenter study on deep brain stimulation in Parkinson's disease: An independent assessment of reported adverse events at 4 years. *Movement Disorders*, 23(3), 416-421.
- Hassler, R., Riechert, T., Mundinger, F., Umbach, W., & Ganglberger, J. A. (1960). Physiological observations in stereotactic operations in extrapyramidal motor disturbances. *Brain*, 83, 337-350.
- Heitanen, M., & Teravainen, H. (1988). The effect of age of disease onset on neuropsychology performance in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 51, 244-249.
- Henderson, R., Kurlan, R., Kersun, J. M., & Como, P. (1992). Preliminary examination of the comorbidity of anxiety and depression in Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neuroscience*, 4(3), 257-264.
- Henry, J. D., & Crawford, J. R. (2004). Verbal fluency deficits in Parkinson's disease: a meta-analysis. *Journal of the International Neuropsychological Society*, 10, 608-622.
- Heo, J. H., Lee, K. M., Paek, S. H., Kim, M. J., et al. (2008). The effects of bilateral subthalamic nucleus deep brain stimulation (STN DBS) on cognition in Parkinson disease. *Journal of Neurological Science*, 273(1-2), 19-24.

- Hershey, T., Wu, J., Weaver, P. M., Perantia, D. C., Karimi, M., et al. (2007). Unilateral vs. bilateral STN DBS effects on working memory and motor function in Parkinson disease. *Experimental Neurology*, *210*(2), 402-408.
- Herzog, J., Volkmann, J., Krack, P., Kopper, F., Potter, M., et al. (2003). Two-year follow-up of subthalamic deep brain stimulation in Parkinson's disease. *Movement Disorders*, *18*(11), 1332-1337.
- Higginson, C. I., Wheelock, V. L., Levine, D., King, D. S., Pappas, C. T., et al. (2008). The clinical significance of neuropsychological changes following bilateral subthalamic nucleus deep brain stimulation for Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*, *31*(1), 65-72.
- Hilker, R., Voges, J., Weisenbach, S., Kalbe, E., Burghaus, L., et al. (2004). Subthalamic nucleus stimulation restores glucose metabolism in associative and limbic cortices and in cerebellum: evidence from a FDG-PET study in advanced Parkinson's disease. *Journal of Cerebral Blood Flow & Metabolism*, *24*(1), 7-16.
- Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: Onset, progression, and mortality. *Neurology*, *17*, 427-442.
- Hooper, H. E. (1983). *Hooper Visual Organization Test*. Los Angeles: Western Psychological Services.
- Huber, S. J., Freidenberg, D. L., Shuttleworth, E. C., Paulson, G. W., & Clapp, L. E. (1989). Neuropsychological similarities in lateralized parkinsonism. *Cortex*, *25*(3), 461-70.
- Huber, S. J., Freidenberg, D. L., Shuttleworth, E. C., Paulson, G. W., & Christy, J. A. (1989). Neuropsychological impairments associated with severity of Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, *1*(2), 154-158.
- Jacobs, D. M., Sano, M., Albert, S., Schofield, P., Dooneief, G., & Stern, Y. (1997). Cross-cultural neuropsychological assessment: a comparison of randomly selected, demographically matched cohorts of English- and Spanish-speaking older adults. *Journal of Clinical and Experimental Neuropsychology*, *19*(3), 331-339.
- Jacobson, N. S., & Truax, P. (1991). Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, *59*(1), 12-19.
- Jahanshahi, M., Ardouin, C. M. A., Brown, R. G., Rothwell, J. C., Obeso, J., et al. (2000). The impact of deep brain stimulation on executive function in Parkinson's disease. *Brain*, *123*, 1142-1154.

- Kaasinen, V., & Rinne, J. O. (2002). Functional imaging studies of dopamine system and cognition in normal aging and Parkinson's disease. *Neuroscience and Biobehavioral Reviews*, 26, 785-793.
- Kalbe, E., Voges, J., Weber, T., Haarer, M., Baudrexel, S., et al. (2009). Frontal FDG-PET activity correlates with cognitive outcome after STN-DBS in Parkinson disease. *Neurology*, 72, 42-49.
- Kalteis, K., Standhardt, H., Kryspin-Exner, I., Brucke, T., Volc, D., et al. (2006). Influence of bilateral STN-stimulation of psychiatric symptoms and psychosocial functioning in patients with Parkinson's disease. *Journal of Neural Transmission*, 113, 1191-1206.
- Katzen, H. L., Levin, B. E., & Llabre, M. L. (1998). Age of disease onset influences cognition in Parkinson's disease. *Journal of the International Neuropsychological Society*, 4, 285-290.
- Katzen, H. L., Levin, B. E., & Weiner, W. (2006). Side and type of motor symptom influence cognition in Parkinson's disease. *Movement Disorders*, 21(11), 1947-1953.
- Kieburz, K., McDermott, M., Como, P., Growdon, J., Brady, J., Carter, J., et al. (1994). The effect of deprenyl and tocopherol on cognitive performance in early untreated Parkinson's disease. Parkinson Study Group. *Neurology*, 44(9), 1756-1759.
- Kiss, Z., Kirstein, D., Suchowersky, O., & Hu, B. (2003). Frequency dependent effects of deep brain stimulation: Clinical manifestations and neural network modeling. *Proceedings of the International Functional Electrical Stimulation Society*, 155-157.
- Kleiner-Fisman, G., Herzog, J., Fisman, D. N., Tamma, F., Lyons, K. E., et al. (2006). Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. *Movement Disorders*, 21(14), S290-304.
- Kondziolka, D., Bonaroti, E., Baser, S., Brant, F., Kim, Y.S., et al. (1999). Outcomes after stereotactically guided pallidotomy for advanced Parkinson's disease. *Journal of Neurosurgery*, 90(2), 187-202.
- Krack, P. (2002). Parkinson's disease: deep cerebral stimulation. *Revue Neurologique (Paris)*, 158, S135-141.
- Krack, P., Batir, A., Van Blercom, N., Chabardes, S., Fraix, V., et al. (2003). Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine*, 33(20), 1888-1891.

- Krause, M., Fogel, W., Heck, A., Hacke, W., Bonsanto, M., Trenkwalder, C., & Tronnier, V. (2001). Deep brain stimulation for the treatment of Parkinson's disease: subthalamic nucleus versus globus pallidus internus. *Journal of Neurology, Neurosurgery, and Psychiatry*, *70*, 464-470.
- Kumar, R., Lozano, A. M., Kim, Y. J., Hutchison, W. D., Sime, E., et al. (1998). Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology*, *51*, 850-855.
- Kumar, R., Lozano, A. M., Sime, E., Halket, E., & Lang, A. E. (1999). Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation. *Neurology*, *53*, 561.
- Kumar, S., Bhatia, M., & Behari, M. (2002). Sleep disorders in Parkinson's disease. *Movement Disorders*, *17*(4), 775-781.
- Lange, K. W., Paul, G. M., Naumann, M., & Gsell, W. (1995). Dopaminergic effects on cognitive performance in patients with Parkinson's disease. *Journal of Neural Transmission* *46*, S423-432.
- Lee, T. M., Chan, C. C., Ho, S. L., & Li, L. S. (2005). Prose memory in patients with idiopathic Parkinson's disease. *Parkinsonism and Related Disorders*, *11*(7), 453-458.
- Lewis, S. J., Dove, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2003). Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *Journal of Neuroscience*, *23*(15), 6351-6356.
- Lewis, S. J., Slabosz, A., Robbins, T. W., Barker, R. A., & Owen, A. M. (2005). Dopaminergic basis for deficits in working memory but not attentional set shifting in Parkinson's disease. *Neuropsychologia*, *43*(6), 823-832.
- Levin, B. E., & Katzen, H. L. (2005). Early cognitive changes and nondementing behavioral abnormalities in Parkinson's disease. *Advances in Neurology*, *96*, 84-94.
- Levin, B. E., Katzen, H. L., Klein, B., & Llabre, M.L. (2000). Cognitive decline affects subject attrition in longitudinal research. *Journal of Clinical and Experimental Neuropsychology*, *22*(5), 580-586.
- Levin, B. E., Llabre, M. M., & Riesman, S. (1991). A retrospective analysis of the effects of anticholinergic medication on memory performance in Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neuroscience*, *3*, 412-416.

- Levin, B. E., Llabre, M. M., Riesman, S., Weiner, W. J., Sanchez-Ramos, J., et al. (1991). Visuospatial impairment in Parkinson's disease. *Neurology*, *41*, 365-369.
- Lieberman, A. (2006). Depression in Parkinson's disease – a review. *Acta Neurologica Scandinavica*, *113*, 1-8.
- Liang, G. S., Chou, K. L., Baltuch, G. H., Jaggi, J. L., Loveland-Jones, C., et al. (2006). Long-term outcomes of bilateral subthalamic nucleus stimulation in patients with advanced Parkinson's disease. *Stereotactic & Functional Neurosurgery*, *84*(5-6), 221-227.
- Limousin, P., Krack, P., Pollak, P., Benazzouzz, A., Ardouin, C., et al. (1998). Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *New England Journal of Medicine*, *339*(16), 1105-1111.
- Liu, Y., Postupna, N., Falkenberg, J., & Anderson, M. E. (2008). High frequency deep brain stimulation: What are the therapeutic mechanisms? *Neuroscience and Biobehavioral Review*, *32*(3), 343-351.
- Locascio, J. J., Corkin, S., & Growdon, J. H. (2003). Relation between clinical characteristics of Parkinson's disease and cognitive decline. *Journal of Clinical & Experimental Neuropsychology*, *25*(1), 94-109.
- Mahieux, F., Fenelon, G., Flahault, A., Manificier, M. J., Michelet, D., et al. (1998). Neuropsychological prediction of dementia in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *64*(2), 178-183.
- Maltete, D., Jodoin, N., Karachi, C., Houeto, J. L., Navarro, S., et al. (2007). Subthalamic stimulation and neuronal activity in the substantia nigra in Parkinson's disease. *Journal of Neurophysiology*, *97*(6), 4017-4022.
- Marras, C., Rochon, P., Lang, A. E. (2002). Predicting motor decline and disability in Parkinson's disease: a systematic review. *Archives of Neurology*, *59*(11), 1724-1728.
- Martin, G. N. (1998). *Human Neuropsychology* (pp. 258-263). Europe: Prentice Hall.
- McInerney-Leo, A., Gwinn-Hardy, K., & Nussbaum, R. L. (2004). Prevalence of Parkinson's disease in populations of African ancestry: a review. *Journal of National Medical Association*, *96*(7), 974-979.
- Meco, G., Bonifati, V., Bedini, L., Bellatreccia, A., Vanacore, N., & Franzese, A. (1991). Relations between on-off phenomena and cognitive functions in Parkinson disease. *Italian Journal of Neurological Science*, *12*, 57-62.

- Menza, M. A., Robertson-Hoffman, D. E., & Bonapace, A. S. (1993). Parkinson's disease and anxiety: comorbidity with depression. *Biological Psychiatry*, *34*(7), 465-470.
- Mohr, E., Fabbrini, G., Ruggieri, S., Fedio, P., & Chase, T. N. (1987). Cognitive concomitants of dopamine system stimulation in parkinsonian patients. *Journal of Neurology, Neurosurgery & Psychiatry*, *50*, 1192-1196.
- Molinuevo, J. L., Valldeoriola, F., Tolosa, E., Rumia, J., Valls-Sole, J., et al. (2000). Levodopa withdrawal after bilateral subthalamic nucleus stimulation in advanced Parkinson disease. *Archives of Neurology*, *57*, 983-988.
- Moretti, R., Torre, P., Antonello, R., Capus, L., Marsala, S., et al. (2003). Neuropsychological changes after subthalamic nucleus stimulation: a 12 month follow-up in nine patients with Parkinson's disease. *Parkinsonism and Related Disorders*, *10*, 73-79.
- Morioka, S., Sakata, K., Yoshida, S., Nakai, E., Shiba, M., et al. (2002). Incidence of Parkinson disease in Wakayama, Japan. *Journal of Epidemiology*, *12*(6), 403-407.
- Moro, E., Esselink, R. J., Xie, J., Hommel, M., Benabid, A. L., & Pollak, P. (2002). The impact on Parkinson's disease of electrical parameter settings in STN stimulation. *Neurology*, *59*(5), 706-713.
- Moro, E., & Lang, A. E. (2006). Criteria for deep-brain stimulation in Parkinson's disease: review and analysis. *Expert Review of Neurotherapeutics*, *6*(11), 1695-1705.
- Moro, E., Scerratti, M., Romito, L.M., Roselli, R., Tonalai, P., & Albanese, A. (1999). Chronic subthalamic nucleus stimulation reduces medication requirements in Parkinson's disease. *Neurology*, *53*(1), 85-90.
- Morrison, C. E., Borod, J. C., Brin, M. F., Halbig, T. D., & Olanow, C. W. (2004). Effects of levodopa on cognitive functioning in moderate-to-severe Parkinson's disease (MSPD). *Journal of Neural Transmission*, *111*, 1333-1341.
- Morrison, C. E., Borod, J. C., Perrine, K., Beric, A., Brin, M. F., et al. (2004). Neuropsychological functioning following bilateral subthalamic nucleus stimulation in Parkinson's disease. *Archives of Clinical Neuropsychology*, *19*(2), 165-181,
- Muslimovic, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology*, *65*(8), 1239-1245.

- Muslimovic, D., Schmand, B., Speelman, J., & De Haan, R. J. (2007). Course of cognitive decline in Parkinson's disease: A meta-analysis. *Journal of the International Neuropsychological Society*, *13*, 920-932.
- Nakamura, K., Christine, C. W., Starr, P. A., & Marks, W. J. (2007). Effects of unilateral subthalamic and pallidal deep brain stimulation on fine motor functions in Parkinson's disease. *Movement Disorders*, *22*(5), 619-626.
- Nation, D.A., Katzen, H.L., Papapetropoulos, S., Scanlon, B.K., & Levin, B.E. (2009). Subthreshold depression in Parkinson's disease. *International Journal of Geriatric Psychiatry*, *24*(9), 937-943.
- Obeso, J. A., Rodriguez-Oroz, M. C., Rodrigues, M., Arbizu, J., & Gimenez-Amaya, J. M. (2002). The basal ganglia and disorders of movement: pathophysiological mechanisms. *News in Physiological Sciences*, *17*, 51-55.
- Ory-Magne, F., Brefel-Courbon, C., Simonetta-Moreau, M., Fabre, N., Lotterie, J. A., et al. (2007). Does ageing influence deep brain stimulation outcomes in Parkinson's disease? *Movement Disorders*, *22*(10), 1457-1463.
- Ostergaard, K. & Sunde, N. A. (2006). Evolution of Parkinson's disease during 4 years of bilateral deep brain stimulation of the subthalamic nucleus. *Movement Disorders*, *21*(5), 624-631.
- Ostrosky-Solis, F., Gutierrez, A. L., Flores, M. R., & Ardila, A. (2007). Same or different? Semantic verbal fluency across Spanish-speakers from different countries. *Archives of Clinical Neuropsychology*, *22*(3), 367-377.
- Pahwa, R., Wilkinson, S. B., Overman, J., & Lyons, K. E. (2005). Preoperative clinical predictors of response to bilateral subthalamic stimulation in patients with Parkinson's disease. *Stereotactic and Functional Neurosurgery*, *83*(2-3), 80-83.
- Palazzini, E., Soliveri, P., Filippini, G., Fetoni, V., Zappacosta, B., et al. (1995). Progression of motor and cognitive impairment in Parkinson's disease. *Journal of Neurology*, *242*, 535-540.
- Papapetropoulos, S., & Mash, D.C. (2005). Psychotic symptoms in Parkinson's disease. From description to etiology. *Journal of Neurology*, *252*(7), 753-764.
- Parsons, T. D., Rogers, S. A., Braaten, A. J., Woods, S. P., & Troster, A. I. (2006). Cognitive sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a meta-analysis. *Lancet Neurology*, *5*(7), 578-588.

- Perriol, M. P., Krystkowiak, P., Defebvre, L., Blond, S., Destee, A., et al. (2006). Stimulation of the subthalamic nucleus in Parkinson's disease: cognitive and affective changes are not linked to motor outcome. *Parkinsonism & Related Disorders*, *12*, 205-210.
- Perozzo, P., Rizzone, M., Bergamasco, B., Castelli, L., Lanotte, M., et al. (2001). Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: comparison of pre- and postoperative neuropsychological evaluation. *Journal of the Neurological Sciences*, *192*(1-2), 9-15.
- Piatt, A.L. Fields, J.A. Paolo, A.M. & Troster, A.I. (1999). Action (verb naming) fluency as an executive function measure: convergent and divergent evidence of validity. *Neuropsychologia*, *37*(13):1499-503
- Pillon, B., Ardouin, P., Damier, P., Krack, P., Houeto, J. L., et al. (2000). Neuropsychological change between "off" and "on" stimulation in Parkinson's disease. *Neurology*, *55*(3), 411-418.
- Pinto, S., Thobois, S., Costes, N., Le Bars, D., Benabid, A, et al., (2004). Subthalamic nucleus stimulation and dysarthria in Parkinson's disease: a PET study. *Brain*, *127*, 602-615.
- Portin, R., & Rinne, U. K. (1986). Predictive factors for cognitive deterioration and dementia in Parkinson's disease. In M.D. Yahr & K.J. Bergmann (Ed.), *Advances in Neurology*, Vol. 45. New York: Raven Press.
- Portman, A. T., van Laar, T., Staal, M. J., Rutgers, A. W. Journee, H. L., et al. (2006). Chronic stimulation of the subthalamic nucleus increases daily on-time without dyskinesia in advanced Parkinson's disease. *Parkinsonism & Related Disorders*, *12*(3), 143-148.
- Pullman, S. L., Watts, R. L., Juncos, J. L., Chase, T. N., & Sanes, J. N. (1988). Dopaminergic effects of single and choice reaction time performance in Parkinson's disease. *Neurology*, *38*, 249-254.
- Qualls, C. E., Bliwise, N. G., & Stringer, A. Y. (2000). Short forms of the Benton Judgment of Line Orientation Test: development and psychometric properties. *Archives of Clinical Neuropsychology*, *15*(2), 159-163.
- Rao, S. S., Hofmann, L. A., & Shakil, A. (2006). Parkinson's disease: diagnosis and treatment. *American Family Physician*, *74*(12), 1-12.
- Regan, D., & Maxner, C. (1987). Orientation-selective visual loss in patients with Parkinson's disease. *Brain*, *110*(Pt 2), 415-432.

- Relja, M., Klepac, N. (2006). A dopamine agonist, pramipexole, and cognitive functions in Parkinson's disease. *Journal of Neurological Science*, 248(1-2), 251-254.
- Richards, M., & Chaudhuri, K. R. (1996). Parkinson's disease in populations of African origin: a review. *Neuroepidemiology*, 15(4), 214-221.
- Rincon, F., Sacco, R.L., Kranwinkel, G., Xu, Q., Paik, M.C., Boden-Albala, B., et al. (2009). Incidence and risk factors of intracranial atherosclerotic stroke: the Northern Manhattan Stroke Study. *Cerebrovascular Disease*, 28(1), 65-71.
- Rodriguez-Oroz, M. C., Obeso, J. A., Lang, E., Houeto, J. L., Pollak, P., et al. (2005). Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. *Brain*, 128, 2240-2249.
- Romito, L. M., Scerrati, M., Contarino, M. F., Bentivoglio, A. R., Tonali, et al. (2002). Long-term follow up of subthalamic nucleus stimulation in Parkinson's disease. *Neurology*, 58(10), 1546-1550.
- Romito, L. M., Scerrati, M., Contarino, M. F., Iacoangeli, M., Bentivoglio, A. R., et al. (2003). Bilateral high frequency subthalamic stimulation in Parkinson's disease: long-term neurological follow-up. *Journal of Neurosurgical Science*, 47, 119-128.
- Rothlind, J. C., Cockshott, R. W., Starr, P. A. & Marks, W. J. (2007). Neuropsychological performance following staged bilateral pallidal or subthalamic nucleus deep brain stimulation for Parkinson's disease. *Journal of the International Neuropsychological Society*, 13(1), 68-79.
- Ruiz-Sanchez, J. M., & Fernandez-Guinea, S. (2005). Visuo perceptual processing in Parkinson's disease: from the retina to the frontal cortex. *Revista de Neurologia*, 40(9), 557-562.
- Saint-Cyr, J. A., Trepanier, L. L., Kumar, R., Lozano, A. M., & Lang, A. E. (2000). Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease. *Brain*, 123, 2091-2108.
- Schroeder, U., Kuehler, A., Lange, K. W., Haslinger, B., Tronnier, V. M., et al. (2003). Subthalamic nucleus stimulation affects a frontotemporal network: a PET study. *Annals of Neurology*, 54(4), 445-450.
- Schupbach, W. M., Chastan, N., Welter, M. L., Houeto, J. L., Mesnage, V., et al. (2005). Stimulation of the subthalamic nucleus in Parkinson's disease: A 5 year follow up. *Journal of Neurology, Neurosurgery & Psychiatry*, 76, 1640-1644.

- Seeman, P., & Niznik, H. B. (1990). Dopamine receptors and transporters in Parkinson's disease and schizophrenia. *Journal of the Federation of American Societies for Experimental Biology*, 4, 2737-2744.
- Sestini, S., Ramat, S., Formiconi, A. R., Ammannati, F., Sorbi, S., et al. (2005). Brain networks underlying the clinical effects of long-term subthalamic stimulation for Parkinson's disease: a 4-year follow-up study with rCBF SPECT. *The Journal of Nuclear Medicine*, 46(9), 1444-1454.
- Setiawan, M., Kraft, S., Doig, K., Hunka, K., Haffenden, A., Trew, M., Longman, S., et al. (2006). Referrals for movement disorder surgery: under-representation of females and reasons for refusal. *Canadian Journal of Neurological Science*, 33(1), 53-57.
- Shin, H. B. & Bruno, R. (2003). Language use and English-speaking ability: 2000. *Census 2000 Brief*. U.S. Department of Commerce, Economics and Statistics Administration, U.S. Census Bureau. Retrieved from <http://www.census.gov/prod/2003pubs/c2kbr-29.pdf> on 2/15/05.
- Shulman, L. M. (2007). Gender differences in Parkinson's disease. *Gender Medicine*, 4(1), 8-18.
- Shulman, L. M., & Bhat, V. (2006). Gender disparities in Parkinson's disease. *Expert Review of Neurotherapeutics*, 6(3), 407-416.
- Siderowf, A., Jaggi, J., Xie, S., Loveland-Jones, C., Leng, L. et al. (2006). Long-term effects of bilateral subthalamic nucleus stimulation on health-related quality of life in advanced Parkinson's disease. *Movement Disorders*, 21(6), 746-753.
- Singhal, B., Lalkaka, J., & Sankhla, C. (2003). Epidemiology and treatment of Parkinson's disease in India. *Parkinsonism and Related Disorders*, 9(Suppl 2), S105-109.
- Slowinski, J. L., Putzke, J. D., Uitti, R. J., Turk, M. F., Kall, B. A., & Wharen, R. E. (2007). Unilateral deep brain stimulation of the subthalamic nucleus for Parkinson disease. *Journal of Neurosurgery*, 106(4), 626-632.
- Smeding, H. M., Speelman, J. D., Huizenga, H.M., Schuurman, P.R., & Schmand, B. (2009). Predictors of cognitive and psychosocial outcome after STN DBS in Parkinson disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, May 21, Epub ahead of print.
- Smeding, H. M., Speelman, J. D., Koning-Haanstra, M., Shuurman, P. R., Nijssen, P., et al. (2006). Neuropsychological effects of bilateral STN stimulation in Parkinson disease: a controlled study. *Neurology*, 66(12), 1830-1836.

- Sobstyl, M., Zabek, M., Koziara, H., Kadzioka, B., & Mossakowski, Z. (2006). Unilateral thalamotomy for the treatment of tremor dominant Parkinson's disease. *Neurologica Neurochirurgia Polska*, 40(2), 119-126.
- Spicer, K. B., Roberts, R. J., & LeWitt, P. A. (1988). Neuropsychological performance in lateralized parkinsonism. *Archives of Neurology*, 45(4), 429-432.
- Spreeen, O., & Benton, A. L. (1969). *Neurosensory Center Comprehension Examination for Aphasia (NCCEA)*. Victoria: University of Victoria, Neuropsychology Laboratory.
- Starkstein, S. E., Leigurda, R., Gershanik, O., & Berthier, M. (1987). Neuropsychological disturbances in hemiparkinson's disease. *Neurology*, 37(11), 1762-1764.
- St. Clair, J., Borod, J. C., Sliwinski, M., Cote, L. J., & Stern, Y. (1998). Cognitive and affective functioning in Parkinson's disease patients with lateralized motor signs. *Journal of Clinical and Experimental Neuropsychology*, 20(3), 320-327.
- Stefaruk, T., Mikulis, D., Mayberg, H., Lang, A. E., Hevenor, S., et al. (2003). Deep brain stimulation for Parkinson's disease dissociates mood and motor circuits: a functional MRI case study. *Movement Disorders*, 18(12), 1508-1516.
- Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *Journal of the International Neuropsychological Society*, 8, 448-460.
- Tabbal, S. D., Ushe, M., Mink, J. W., Revilla, F. J., Wernle, A. R., et al. (2008). Unilateral subthalamic nucleus stimulation has a measurable ipsilateral effect on rigidity and bradykinesia in Parkinson's disease. *Experimental Neurology*, 211(1), 234-242.
- Tan, L.C., Venketasubramanian, N., Jamora, R.D., & Heng, D. (2007). Incidence of Parkinson's disease in Singapore. *Parkinsonism and Related Disorders*, 13(1), 40-43.
- Taylor, A. E., Saint-Cyr, J. A., & Lang, A. E. (1990). Memory and learning in early Parkinson's disease. *Brain*, 113, 211-232.
- Temel, Y., Blokland, A., Steinbusch, H. W., Visser-Vandewalle, V. (2005). The functional role of the subthalamic nucleus in cognitive and limbic circuits. *Progress in Neurobiology*, 76(6), 393-413.
- Temel, Y., Kessels, A., Tan, S., Topdag, A., Boon, P., et al. (2006). Behavioural changes after bilateral subthalamic stimulation in advanced Parkinson disease: A systematic review. *Parkinsonism and Related Disorders*, 12, 265-272.

- Thobois, S., Mertens, P., Guenot, M., Hermier, M., Mollion, H., Bouvard, M., et al. (2002). Subthalamic nucleus stimulation in Parkinson's disease: Clinical evaluation of 18 patients. *Journal of Neurology*, *249*, 529-534.
- Tir, M., Devos, D., Blond, S., Touzet, G., Reyns, N., et al. (2007). Exhaustive, one-year follow-up of subthalamic nucleus deep brain stimulation in a large, single center cohort of parkinsonian patients. *Neurosurgery*, *61*(2), 297-304.
- Tomer, R., Levin, B. E., & Weiner, W. J. (1993). Side of onset of motor symptoms influences cognition in Parkinson's disease. *Annals of Neurology*, *34*(4), 579-584.
- Tornquist, A.L. (2001). Neurosurgery for movement disorders. *Journal of Neuroscience and Nursing*, *33*(2), 79-82.
- Trepanier, L. L., Kumar, R., Lozano, A. M., Lang, A. E., & Saint-Cyr, J. A. (2000). Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease. *Brain and Cognition*, *42*, 324-347.
- Troster, A. I., Stalp, L. D., Paolo, A. M., Fields, J. A., & Koller, W.C. (1995). Neuropsychological impairment in Parkinson's disease with and without depression. *Archives of Neurology*, *52*(12), 1164-1169.
- Troster, A. I., Woods, S. P., Morgan, E. E. (2007). Assessing cognitive change in Parkinson's disease: development of practice effect corrected reliable change indices. *Archives of Clinical Neuropsychology*, *22*, 711-718.
- Twelves, D., Perkins, K.S., & Counsell, C. (2003). Systematic review of incidence studies of Parkinson's disease. *Movement Disorders*, *18*(1), 19-31.
- Uc, E. Y., Rizzo, M., Anderson, S. W., Qian, S., Rodnitzky, R. L., & Dawson, J. D. (2005). Visual dysfunction in Parkinson disease without dementia. *Neurology*, *65*(12), 1907-1913.
- Uekermann, J., Daum, I., Peters, S., Wiebel, B., Przuntek, H., & Muller, T. (2003). Depressed mood and executive dysfunction in early Parkinson's disease. *Acta Neurologica Scandinavica*, *107*(5), 341-348.
- Valdeoriola, F., Pilleri, M., Tolosa, E., Molinuevo, J., Rumia, J., & Ferrer, E. (2002). Bilateral subthalamic stimulation monotherapy in advanced Parkinson's disease: Long-term follow-up of patients. *Movement Disorders*, *17*(1), 125-132.
- Van den Eeden, S. K., Tanner, C. M., Bernstein, A. L., Fross, R. D., Leimpeter, A., et al. (2003). Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *American Journal of Epidemiology*, *157*, 1015-1022.

- Van Oostrom, I., Dollfus, S., Brazo, P., Abadie, P., Halbecq, I., et al. (2003). Verbal learning and memory in schizophrenic and Parkinson's disease patients. *Psychiatry Research, 117*(1), 25-34.
- Videnovic, A., & Metman, L. V. (2007). Deep brain stimulation for Parkinson's disease: Prevalence of adverse events and need for standardized reporting. *Movement Disorders, 23*(3), 343-349.
- Vingerhoets, F., Villemure, J., Temperli, P., Pollo, C., Pralong, E., & Ghika, J. (2002). Subthalamic DBS replaces levodopa in Parkinson's disease. Two-year follow-up. *Neurology, 58*, 396-401.
- Von Campenhausen, S., Bornschein, B., Wick, R., Bötzel, K., Sampaio, C., Poewe, W., et al. (2005). Prevalence and incidence of Parkinson's disease in Europe. *European Neuropsychopharmacology, 15*(4), 473-490.
- Voon, V., Kubu, C., Krack, P., Houeto, J., & Troster, A. (2006). Deep brain stimulation: Neuropsychological and Neuropsychiatric Issues. *Movement Disorder Society, 21*(14), S305-S326.
- Walsh, K., & Bennett, G. (2001). Parkinson's disease and anxiety. *Postgraduate Medical Journal, 77*, 89-93.
- Weaver, F. M., Follet, K., Stern, M., Hur, K., Harris, C., et al. (2009). Bilateral deep brain stimulation vs. best medical therapy for patients with advanced Parkinson's disease: A randomized controlled trial. *Journal of the American Medical Association, 301*(1), 63-73.
- Weaver, F. M., Follett, K., Hur, K., Ippolito, D., & Stern, M. (2005). Deep brain stimulation in Parkinson disease: a meta-analysis of patient outcomes. *Journal of Neurosurgery, 103*(6), 956-967.
- Wechsler, D. (1997). *Wechsler Adult Intelligence Scale* (3rd ed.). New York: The Psychological Corporation.
- Weiner, W. J. (2008). There is no Parkinson disease. *Archives of Neurology, 65*(6), 705-708.
- Weintraub, D., Siderowf, A. D., Potenza, M. N., Goveas, J., Morles, K. H., et al. (2006). Association of dopamine agonist use with impulse control disorders in Parkinson disease. *Archives of Neurology, 63*(7), 969-973.
- Whelan, B. M., Murdoch, B. E., Therodoros, D. G., Hall, B., & Silburn, P. (2003). Defining a role for the subthalamic nucleus within operative theoretical models of subcortical participation in language. *Journal of Neurology, Neurosurgery & Psychiatry, 74*, 1543-1550.

- Wichmann, T., & DeLong, M. R. (2006). Deep brain stimulation for neurologic and neuropsychiatric disorders. *Neuron*, 52(1), 197-204.
- Williams-Gray, C. H., Foltynie, T., Brayne, C. E., Robbins, T. W. & Barker, R. A. (2007). Evolution of cognitive dysfunction in an incident Parkinson's disease cohort, *Brain*, 130(7), 1781-1798.
- Williams-Gray, C. H., Foltynie, T., Lewis, S. J., & Barker, R. A. (2006). Cognitive deficits and psychosis in Parkinson's disease: a review of pathophysiology and therapeutic options. *CNS Drugs*, 20(6), 477-505.
- Witt, K., Daniels, C., Herzog, J., Lorenz, D., Volkmann, J., et al. (2006). Differential effects of L-dopa and subthalamic stimulation on depressive symptoms and hedonic tone in Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neurosciences*, 18(3), 397-401.
- Witt, K., Daniels, C., Reiff, J., Krack, P., Volkmann, J., et al. (2008). Neuropsychological and psychiatric changes after deep brain stimulation for Parkinson's disease: a randomized, multicentre study. *Lancet Neurology*, DOI:10.1016/S1474-4422(08)70114-5.
- Witt, K., Kopper, F., Deuschl, G., & Krack, P. (2006). Subthalamic nucleus influences spatial orientation in extra-personal space. *Movement Disorders*, 21(3), 354-361.
- Witt, K., Pulkowski, U., Herzog, J., Lorenz, D., Hamel, W., Deuschl, G., & Krack, P. (2004). Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. *Archives of Neurology*, 61, 697-700.
- Wojtecki, L., Timmermann, L., Jorgens, S., Sudmeyer, M., Maarouf, M., Treuer, H., et al. (2006). Frequency-dependent reciprocal modulation of verbal fluency and motor functions in subthalamic deep brain stimulation. *Archives of Neurology*, 63(9), 1273-1276.
- Woods, S. P., Fields, J. A., Lyons, K. E., Koller, W. C., Wilkinson, S. B., Pahwa, R., et al. (2001). Neuropsychological and quality of life changes following unilateral thalamic deep brain stimulation in Parkinson's disease: a one year follow-up. *Acta Neurochirurgica (Wien)*, 143(12), 1273-1277.
- Woods, S. P., Fields, J. A., & Troster, A. I. (2002). Neuropsychological sequelae of subthalamic nucleus deep brain stimulation in Parkinson's disease: a critical review. *Neuropsychology Review*, 12(2), 111-126.

- Woods, S. P., Rippeth, J. D., Conover, E., Carey, C. L., Parsons, T. D., & Troster, A. I. (2006). Statistical power of studies examining the cognitive effects of subthalamic nucleus deep brain stimulation in Parkinson disease. *Clinical Neuropsychology*, *20*(1), 27-38.
- York, M. K., Dulay, M., Macias, A., Levin, H., Grossman, R., Simpson, R., & Jankovic, J. (2007). Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*(7), 789-795.
- York, M. K., Lai, E. C., Jankovic, J., Macias, A., Atassi, F., Levin, H. S., et al. (2007). Short and long-term motor and cognitive outcome of staged bilateral pallidotomy: a retrospective analysis. *Acta Neurochirurgica*, *149*(9), 857-866.
- Zabek, M., & Sobstyl, M. (2006). Deep brain stimulation in the management of Parkinson's disease. *Neurologia i Neurochirurgia Polska*, *40*(3), 203-211.
- Zahodne, L. B., Okun, M. S., Foote, K. D., Fernandez, H. H., Rodriguez, R. L., et al. (2008). Cognitive declines one year after unilateral deep brain stimulation surgery in Parkinson's disease: a controlled study using reliable change. *The Clinical Neuropsychologist*, *23*(3), 385-405.
- Zaidel, A., Moran, A., Marjan, G., Bergman, H., & Israel, Z. (2008). Prior pallidotomy reduces and modifies neuronal activity in the subthalamic nucleus of Parkinson's disease patients. *European Journal of Neuroscience*, *27*(2), 483-491.
- Zakharov, V. V., Akhutina, T. V., & Yakhno, N. N. (2001). Memory impairment in Parkinson's disease. *Neuroscience and Behavioral Physiology*, *31*(2), 157-163.
- Zanini, S., Melatini, A., Capus, L., Gioulis, M., Vassallo, A., & Bava, A. (2003). Language recovery following subthalamic nucleus stimulation in Parkinson's disease. *Neuroreport*, *14*(3), 511-516.
- Zhang, J. G., Zhang, K., Ma, Y., Hu, W. H., Yang, A. C., et al. (2006). Follow-up of bilateral subthalamic deep brain stimulation for Parkinson's disease. *Acta Neurochirurgica*, *99*, S43-S47.
- Zibetti, M., Torre, E., Cinquepalmi, A., Rosso, M., Ducati, A., Bergamasco, B., et al. (2007). Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *European Journal of Neurology*, *58*(4), 218-223.

Appendix

Table 1

Descriptive Statistics for Demographic Variables at Baseline

Variable	<i>M (SD)</i>		
	[Range]		
	PD Control (<i>n</i> = 15)	English DBS (<i>n</i> = 15)	Spanish DBS (<i>n</i> = 13)
Age	61.47 (7.33)	60.27 (7.44)	63.46 (6.54)
	[46 – 69]	[44 – 74]	[54 – 71]
Age of disease onset	52.13 (7.48)	49.87 (6.87)	53.04 (7.82)
	[39 – 62]	[38 – 60]	[42 – 65]
Disease duration (years)	9.33 (5.39)	10.40 (4.42)	10.31 (4.47)
	[1 – 21]	[4 – 21]	[4 – 17]
Education (years) ^a	13.80 (2.04)	14.00 (2.10)	9.38 (5.58)
	[11 – 17]	[11 – 18]	[0 – 18]
MMSE	27.86 (2.06)	28.07 (1.49)	26.31 (1.60)
	[23 – 30]	[26 – 30]	[24 – 30]
Time between assessments (months)	25.27 (14.96)	25.73 (14.32)	25.31 (11.68)
	[12 – 60]	[13 – 60]	[10 – 46]
H & Y “on” score	2.07 (0.88)	1.67 (0.49)	1.92 (0.79)
	[1 – 4]	[1 – 3]	[1 – 4]
Gender (M / F)	9 / 6	9 / 6	10 / 3
Handedness (R / L)	12 / 3	13 / 2	13 / 0
Side of DBS (R / L)		4 / 11	6 / 7

Note. Independent sample *t* test value represents difference between English- and Spanish-speaking DBS groups. ^a $F(1, 27) = 8.87, p < .01$.

Table 2

Descriptive Statistics for Cognitive Variables at Baseline

Variable	<i>M (SD)</i>		
	[Range]		
	PD Control (<i>n</i> = 15)	English DBS (<i>n</i> = 15)	Spanish DBS (<i>n</i> = 13)
Phonemic fluency	34.67 (14.82) [13 – 73]	35.53 (15.00) [13 – 63]	27.77 (15.16) [0 – 57]
BNT ^a	53.33 (4.88) [42 – 60]	51.87 (8.72) [26 – 60]	41.31 (11.95) [20 – 56]
JLO	10.20 (3.55) [3 – 14]	11.07 (2.15) [7.5 – 14]	9.29 (2.67) [5 – 13]
HVOT ^b	24.20 (6.94) [6 – 30]	23.50 (4.74) [12 – 28]	18.50 (5.79) [5 – 25]
WAIS-III Digits Backward ^c	4.60 (1.40) [2 – 7]	4.60 (1.45) [2 – 8]	3.15 (0.80) [2 – 4]
CVLT – Immediate free recall ^d	8.07 (3.62) [0 – 14]	7.93 (3.33) [2 – 14]	
CVLT – Delayed free recall ^d	8.93 (3.73) [1 – 15]	7.80 (3.23) [0 – 13]	
Delayed verbal memory <i>z</i> score ^e		-0.67 (1.14) [-3.00 – 1.00]	-0.25 (0.73) [-1.68 – 0.99]

Note. Independent sample *t* test values represent differences between English- and Spanish-speaking DBS groups. ^a*t*(26) = 2.70, *p* = .01. ^b*t*(26) = 2.51, *p* = .02. ^c*t*(26) = 3.19, *p* < .01.

^dCVLT raw scores not available for Spanish-speaking DBS group.

^eDelayed verbal memory *z* scores not available for PD control group.

Table 3

Frequencies of Medication Usage

Medication		PD Control (<i>n</i> = 15)	English DBS (<i>n</i> = 15)	Spanish DBS (<i>n</i> = 13)
Carbidopa-Levodopa	Baseline ^a	73%	100%	100%
	Follow-up	80%	100%	100%
DA agonists	Baseline ^{b,c}	27%	87%	39%
	Follow-up ^d	13%	67%	69%
Anticholinergics	Baseline	27%	13%	15%
	Follow-up	27%	20%	15%
NMDA antagonists	Baseline ^e	13%	47%	23%
	Follow-up	20%	27%	23%
COMT inhibitors	Baseline ^f	0%	53%	69%
	Follow-up ^g	0%	40%	31%
MAO-B inhibitors	Baseline	13%	13%	8%
	Follow-up	13%	0%	8%
Antidepressants	Baseline	13%	33%	8%
	Follow-up	20%	7%	15%
Anxiolytics	Baseline	13%	20%	46%
	Follow-up	13%	13%	23%
Antipsychotics	Baseline	0%	7%	23%
	Follow-up ^h	0%	0%	23%

Note. Chi-square values represent significant differences between PD control and English-speaking

DBS groups: ^a $\chi^2(1, N = 30) = 4.62, p = .03$. ^b $\chi^2(1, N = 30) = 11.00, p < .01$.

^d $\chi^2(1, N = 30) = 8.89, p < .01$. ^e $\chi^2(1, N = 30) = 3.97, p = .05$. ^f $\chi^2(1, N = 30) = 10.91, p < .01$.

^g $\chi^2(1, N = 30) = 10.91, p < .01$. Chi-square values represent significant differences between English- and

Spanish-speaking DBS groups: ^c $\chi^2(1, N = 28) = 7.05, p < .01$. ^h $\chi^2(1, N = 28) = 3.88, p = .05$.

Table 4

Summary of Cognitive Variable Change Scores

Variable	<i>M (SD)</i>			
	RCI [95% CI]	PD Control (<i>n</i> = 15)	English DBS (<i>n</i> = 15)	Spanish DBS (<i>n</i> = 13)
Phonemic fluency	[-6.21, 3.68]	-1.27 (8.93) [-16 – 22]	-6.80 (11.49) [-32 – 12]	-7.77 (12.98) [-42 – 3]
BNT	[-2.84, 0.70]	-1.07 (3.20) [-6 – 4]	-0.53 (2.62) [-5 – 3]	-4.77 (7.03) [-18 – 8]
JLO	[-2.10, 1.30]	-0.40 (3.07) [-9 – 4]	-0.93 (4.52) [-12 – 4]	-2.86 (3.87) [-10 – 1]
HVOT	[-4.97, 1.77]	-1.60 (6.09) [-15 – 6]	-2.37 (5.68) [-16 – 3]	-4.00 (4.81) [-14 – 2]
WAIS-III Digits Backward	[-0.41, 0.94]	0.27 (1.22) [-1 – 3]	-0.87 (1.46) [-4 – 2]	-0.46 (1.81) [-4 – 2]
CVLT – Immediate free recall ^a	[-1.20, 0.93]	-0.13 (1.92) [-4 – 2]	-1.67 (3.62) [-7 – 7]	
CVLT – Delayed free recall ^a	[-2.33, 0.87]	-0.73 (2.89) [-6 – 4]	-1.13 (2.77) [-6 – 5]	
Delayed verbal memory <i>z</i> score ^b			-0.37 (1.03) [-2.5 – 1.5]	-0.56 (1.19) [-2.67 – 1.34]

Note. ^aCVLT raw scores not available for Spanish-speaking DBS group.

^bDelayed verbal memory *z* scores not available for PD control group.

Table 5

Summary of One Sample t Tests for Cognitive Variable Change Scores

Variable	<i>t</i> (14)	<i>t</i> (14)	<i>t</i> (12)
	PD Control	English DBS	Spanish DBS
Phonemic fluency	-0.55	-2.29 *	-2.16*
BNT	-1.29	-0.79	-2.45*
JLO	-0.51	-0.80	-2.45*
HVOT	-1.02	-1.61	-3.00**
WAIS-III Digits Backward	0.85	-2.30 *	0.92
CVLT – Immediate free recall ^a	-0.27	-1.78 †	
CVLT – Delayed free recall ^a	-0.98	-1.58	
Delayed verbal memory <i>z</i> score ^b		-1.38	-1.62

Note. ^aCVLT raw scores not available for Spanish-speaking DBS groups.

^bDelayed verbal memory *z* scores not available for PD control groups.

† $p \leq .10$. * $p \leq .05$. ** $p \leq .01$.

Table 6

Summary of Analysis of Variance of Cognitive Variable Change Scores for English-speaking DBS and PD Control Groups (N = 30)

Cognitive Variable	<i>F</i> (1, 29)	η^2	<i>p</i>
Between groups			
Phonemic fluency	2.17	.07	.15
Within-group error	(105.91)		
BNT	0.25	.01	.62
Within-group error	(8.52)		
JLO	0.14	.01	.71
Within-group error	(14.93)		
HVOT	0.13	.01	.72
Within-group error	(34.71)		
WAIS-III Digits Backward	5.32	.16	.03
Within-group error	(1.81)		
CVLT – Immediate free recall	2.10	.07	.16
Within-group error	(8.40)		
CVLT – Delayed free recall	0.15	.01	.70
Within-group error	(8.02)		

Note. Values enclosed in parentheses represent mean square errors.

Table 7

Summary of Reliable Change Index Frequencies (N = 30)

Variable	Group	Decline	No Change	Improvement
Phonemic fluency	PD control	20%	60%	20%
	English DBS	47%	40%	13%
BNT	PD control	33%	33%	33%
	English DBS	27%	33%	40%
JLO †	PD control	13%	67%	20%
	English DBS	33%	27%	40%
HVOT	PD control	33%	33%	33%
	English DBS	27%	40%	33%
WAIS-III Digits Backward ‡	PD control	33%	27%	40%
	English DBS	53%	40%	7%
CVLT – Immediate free recall	PD control	27%	20%	53%
	English DBS	60%	20%	20%
CVLT – Delayed free recall	PD control	33%	27%	40%
	English DBS	33%	40%	27%

Note. † $\chi^2(2, N = 30) = 4.86, p = .09$.

‡ $\chi^2(2, N = 30) = 4.66, p = .10$.

Table 8

Descriptive Statistics for Demographic Variables at Baseline for Left- and Right-Sided DBS Groups

Variable	<i>M (SD)</i>	
	[Range]	
	Left-Sided DBS (<i>n</i> = 11)	Right-Sided DBS (<i>n</i> = 4)
Age	59.82 (8.70) [44 – 74]	61.50 (1.73) [60 – 64]
Age of disease onset	49.09 (7.54) [38 – 60]	52.00 (4.69) [46 – 57]
Disease duration (years)	10.73 (4.86) [4 – 21]	9.50 (3.32) [7 – 14]
Education (years)	14.18 (2.23) [11 – 18]	13.50 (1.92) [12 – 16]
MMSE	28.36 (1.43) [26 – 30]	27.25 (1.50) [26 – 29]
Time between assessments (months)	23.36 (11.26) [13 – 52]	32.25 (21.36) [14 – 60]
H & Y “on” score	1.64 (0.32) [1 – 2]	1.75 (0.87) [1 – 3]
Gender (M / F)	7 / 4	2 / 2
Handedness (R / L)	10 / 1	3 / 1

Table 9

*Descriptive Statistics for Cognitive Variables at Baseline for Left- and Right-Sided DBS**Groups*

Variable	<i>M (SD)</i>	
	[Range]	
	Left-Sided DBS (<i>n</i> = 11)	Right-Sided DBS (<i>n</i> = 4)
Phonemic fluency	33.09 (12.93) [13 – 63]	42.25 (20.26) [15 – 60]
BNT	50.36 (9.26) [26 – 58]	56.00 (6.16) [47 – 60]
JLO	11.36 (2.15) [7.5 – 14]	10.25 (2.22) [8 – 13]
HVOT	23.68 (3.83) [15.5 – 28]	23.00 (7.44) [12 – 28]
WAIS-III Digits Backward	4.45 (0.93) [3 – 6]	5.00 (2.58) [2 – 8]
CVLT – Immediate free recall	7.73 (3.07) [3 – 14]	8.50 (4.44) [2 – 12]
CVLT – Delayed free recall	7.91 (2.30) [5 – 12]	7.50 (5.57) [0 – 13]

Table 10

Summary of Cognitive Variable Change Scores for Left- and Right-Sided DBS Groups

Variable	<i>M (SD)</i>	
	[Range]	
	Left-Sided DBS (<i>n</i> = 11)	Right-Sided DBS (<i>n</i> = 4)
Phonemic fluency	-7.45 (12.20) ^a	-5.00 (10.68)
	[-32 – 12]	[-15 – 10]
BNT	0.00 (2.53)	-2.00 (2.58)
	[-4 – 3]	[-5 – 1]
JLO	-0.55 (4.63)	-2.00 (4.69)
	[-12 – 4]	[-8 – 3]
HVOT	-2.45 (5.96)	-2.13 (5.66)
	[-16 – 3]	[-10 – 2]
WAIS-III Digits Backward	-0.64 (1.50)	-1.50 (1.29)
	[-4 – 2]	[-3 – 0]
CVLT – Immediate free recall	-1.64 (4.03)	-1.75 (2.63)
	[-7 – 7]	[-4 – 2]
CVLT – Delayed free recall	-1.36 (2.94)	-0.50 (2.52)
	[-6 – 5]	[-4 – 2]

Note. ^a $t(10) = -2.03, p = .08$.

Table 11

Summary of Analysis of Variance of Cognitive Variable Change Scores for Left- and Right-Sided DBS Groups

Cognitive Variable	$F(1, 13)$	η^2	p
	Between groups		
Phonemic fluency	0.13	.01	.73
Within-group error	(140.83)		
BNT	1.82	.12	.20
Within-group error	(6.46)		
JLO	0.29	.02	.60
Within-group error	(21.56)		
HVOT	0.01	.00	.93
Within-group error	(34.76)		
WAIS-III Digits Backward	1.03	.07	.33
Within-group error	(2.12)		
CVLT – Immediate free recall	0.00	.00	.96
Within-group error	(14.10)		
CVLT – Delayed free recall	0.27	.02	.61
Within-group error	(8.12)		

Note. Values enclosed in parentheses represent mean square errors.

Table 12

*Hierarchical Linear Regression Analyses for Variables Predicting Phonemic Fluency**Change Scores of Spanish-speaking DBS Group (N = 13)*

Variables	β	ΔR^2	<i>F of ΔR^2</i>	<i>p</i>
<u>Step 1</u>				
Education	-.03			
		.00	0.01	.92
<u>Step 2</u>				
Education	-.38			
Age of disease onset	-.73			
		.42	7.16	.02
<hr/>				
Variables	β	ΔR^2	<i>F of ΔR^2</i>	<i>p</i>
<u>Step 1</u>				
Education	-.03			
		.00	0.01	.92
<u>Step 2</u>				
Education	-.25			
Age at baseline	-.67			
		.40	6.73	.03