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Trajectory of Quality of Life in Advanced Parkinson's Patients Receiving Bilateral Subthalamic Nucleus Deep Brain Stimulation

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Trajectory of Quality of Life in Advanced Parkinson’s Patients Receiving Bilateral Subthalamic Nucleus Deep Brain Stimulation

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of the Requirements for the Degree
Doctor of Philosophy

by
Karl S. Chiang
August 2009
Advisor: Cynthia A. McRae
Abstract

Quality of Life (QOL) in Parkinson’s disease (PD) patients after Deep Brain Stimulation (DBS) neurosurgery generally improves between 3 to 24 months post-operatively. However, QOL beyond 2 year follow-up is generally unknown. This study examined the QOL in 16 advanced PD patients who received DBS at an average of 7.5 year follow-up with the Parkinson’s Disease Questionnaire (PDQ-39). Participants had an average Disease Duration of 20.57 years (SD 5.7) and a mean Age of 63.50 (SD 8.05). Linear regression analyses suggested a constellation of changes involving Time, Age, and Disease Duration. As Time progressed since DBS intervention, the PDQ-39 Cognitions subscale worsened ($p < .05$). Increasing Age was associated with improvement in Stigma-related QOL ($p < .01$). Rising Disease Duration correlated with improvements in three PDQ-39 subscales: (a) Stigma ($p < .01$), (b) Emotional Well-Being ($p < .01$), and (c) Social Support ($p < .05$). Findings suggested the need to further explore the domains and dimensions of QOL change post-DBS intervention, as well as other methods to measure the depth and breadth of QOL in DBS recipients.
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Chapter 1

Background of the problem

Parkinson’s disease is a neurodegenerative disorder characterized by cardinal motor symptoms that include: (a) resting tremor, that involves shaking in the limbs while at rest; (b) bradykinesia, meaning slowness of movement; (c) rigidity, which is abnormal stiffness and tension in the range of motion of a limb or other body parts; and (d) postural instability, entailing balance problems and postural abnormalities (Fahn, 2003). First reported in 1817 and named after James Parkinson, an English surgeon, Parkinson’s disease (PD) is considered to be the prototypical movement disorder (Jankovic, 2003). At the time, the cause of the “shaking palsy” was unknown to the surgeon but well-documented (Parkinson, 1817/2002). Unfortunately, the etiology of PD continues to be unknown today (Pryse-Phillips & Murray, 2001). However, the neuropathological mechanisms of PD are somewhat understood in that cells involved in dopamine production are lost in areas of the brain related to motor activity (Ward, 2006). Thus, PD is generally understood as a progressive neurodegenerative disorder resulting from depletion of dopaminergic cells and their production of dopamine (Okun, Rodriguez, et al., 2007). This loss of dopamine-generating neurons in the brain is thought to account for the cardinal motor symptoms of PD (Task Force commissioned by the Movement Disorder Society, 2002). There is no cure for PD and its symptoms become progressively worse over time (Fargel, Grobe, Oesterle, Hastedt, & Rupp, 2007).
A large number of treatments are currently available which generally manage the symptoms of PD (Lang & Lees, 2002). Despite nearly 200 years of knowledge of the disease, there are many inadequacies in the treatment and management of PD, which include an increased mortality rate. In a recent analysis, the risk of death of PD patients is estimated to be 2.3 times higher than matched controls from the general population (Morgante et al., 2000). This has not changed much since 1967 when it was estimated that people who suffer from PD had 2.9 times greater risk of death compared to the general population (Hoehn & Yahr, 1967).

Another inadequacy of treatments is the ability to slow, stop, or reverse the progression of the disease (Olanow & Jankovic, 2005). Introduced in the late 1960s, levodopa was the first highly effective drug (Koller & Tse, 2004) and remains the most effective drug (Jankovic, 2002) for treating the symptoms of PD. Levodopa reduces the symptoms of tremor, bradykinesia, and rigidity and often allows people who suffer from PD to perform activities related to daily living and maintain employment. Almost all PD patients will need levodopa treatment at some point during their progression through the disease; however, chronic use leads to unwanted side effects. These side effects can include dyskinesias, or involuntary movements, motor fluctuations or “on” and “off” periods where the medication fluctuates between periods of high and low effectiveness, and mental changes such as confusion, paranoia, and visual hallucinations. In general, most patients are able to benefit from levodopa for approximately five years before these side effects begin to occur (Koller & Tse).

Once the effectiveness of levodopa has waned and led to significant side effects, a trend in the treatment of PD has been to turn to surgical options. As early as the 1930s
surgical procedures have been performed on patients with PD; however, these procedures had high mortality rates and were quickly abandoned. In 1987, two groups independently reported the effectiveness of Deep Brain Stimulation (DBS) in which almost all patients had a substantial reduction in resting tremor (Siegfried & Lippitz, 1994; Walter & Vitek, 2004). Since its introduction, it is estimated that 35,000 DBS surgeries have been performed worldwide (Benabid, Deuschl, Lang, Lyons, & Rezai, 2006). Several factors have led to its widespread usage which entails an improvement in motor symptoms and the reduction of motor fluctuations and dyskinesia. In addition, DBS is reversible and adjustable so that idiographic programming can occur in the management of movement disorders (Benabid et al., 2006).

Stereotypical of any treatment, there are potential risks and complications to DBS. The efforts of the fields of neurology and neurosurgery have been to demonstrate the safety and efficacy of DBS, although there have been reported motor, neuropsychological, and emotional side effects (Benabid et al., 2006). Two recently published longitudinal studies have examined long-term cognitive and behavioral outcomes of samples of PD patients who have received DBS (Contarino et al., 2007; Schupbach et al., 2005). Each study has recognized the conflicting nature of the extant literature on the effects of DBS on patients in which some studies report positive outcomes in which improvements in motor symptoms and levodopa side effects have been successfully managed resulting in a reduction of daily dosage (Limousin et al., 1998; Rodriguez-Oroz et al., 2005). It has also been noted that within the literature there are reported cases with negative side effects such as depression (Doshi, Chhaya, & Bhatt, 2002), increased apathy (Funkiewiez et al., 2004) and mania (Romito et al., 2002).
Contarino et al. (2007) concluded that DBS was a relatively safe procedure although two out of 11 patients assessed longitudinally had experienced transient mania with hypersexuality, and one patient experienced persistent apathy. Schupbach et al. found that movement disorder management gains were maintained over a five year period although one patient in their sample of 37 committed suicide, which is consistent with the findings of a previous longitudinal study (Krack et al., 2003). In a nine year longitudinal study in which 140 recipients of DBS were assessed continuously at six month periods, it was found that six had committed suicide resulting in a 4.3% prevalence rate which is higher than the general population’s risk (Burkhard et al., 2004). Although the sample included a combination of patients with PD, dystonia, and essential tremor, four of the suicides were committed by younger men suffering from PD (Voon et al., 2008).

In a meta-analysis of 34 published studies which included 37 cohorts comprised of 921 patients, 778 patients enrolled in 29 studies reported adverse events (Kleiner-Fisman et al., 2006). This suggests the need for further research into the adverse effects of DBS and whether these adverse events may have an influence upon quality of life.

Quality of Life

Quality of life (QOL) can be broadly conceptualized as the patient’s overall sense of well-being (Spilker, 1996). QOL is considered to be a relevant construct when examining the efficacy of treatments from the patients’ perspective (Spilker). QOL is thought of as multifactorial, measuring more than single aspects of a patient’s well-being and functioning (Schipper, Clinch, & Olweny, 1996). Because PD is a degenerative neurological disease, QOL can be affected by the body in many ways such as physical functioning and the ability to perform activities of daily living (Wilson, Goetz, &
Stebbins, 1996). A worldwide study of the factors influencing QOL in PD patients has found that (a) disease severity, (b) medication, and (c) depression can have significant impact on QOL (Global Parkinson’s Disease Survey Steering Committee, 2001).

Drapier, et al. (2005) examined QOL in PD patients receiving DBS in which a cohort was assessed twelve months after surgery and found that motor symptoms improved significantly. However, constructs such as emotional well-being, social support, cognition, and communication showed little improvement. The researchers suggested that there is dissociation between motor and non-motor symptom control after DBS.

There have been longitudinal studies examining the effects of DBS (Contarino et al, 2007; Funkiewiez et al., 2004; Krack et al., 2003; Schupbach et al., 2005), which have examined motor symptoms, cognitive symptoms and single QOL factors such as measures of depression. There appear to be ten studies in English which have specifically examined QOL using the PDQ-39 in advanced PD patients who received bilateral subthalamic nucleus (STN) deep brain stimulation in cohorts of surgical recipients worldwide. Martinez-Martin et al. (2002) examined the QOL of 17 consecutive Spanish PD patients treated with STN-DBS and given the Spanish version of the PDQ-39 pre-operatively and at six month follow-up. Findings indicated that overall HRQOL improved. Just and Ostergaard (2002) examined a cohort of 11 Danish patients who received the surgery and a comparison group of 13 patients on the waiting list for surgery who were administered the PDQ-39, UPDRS, and the Hoehn and Yahr scale at three time points (a) before surgery, (b) three and (c) six months after surgery. Ten of the 11 patients reported improvements in health related quality of life (HRQOL) in contrast to the
comparison group who reported no change. These two studies represent some of the first to be conducted on PD patients who received DBS generally finding QOL improvements within six months of intervention. Later studies did not appear to be as overwhelmingly positive in terms of improvements in QOL. Additionally, the length of time since intervention increased. Drapier et al. (2005) examined QOL in 27 consecutive bilateral STN DBS recipients in France with the PDQ-39 and the SF-36 at two time points; pre-surgery and twelve months post-surgery. At 12 months, QOL improved globally as indicated by the PDQ-39 summary index score with the Mobility, Activities of Daily Living, Stigma, and Bodily Discomfort scales improving significantly ($p < .01$).

However, when comparing the summary score with a community sample of PD patients examined by Peto, Fitzpatrick, and Jenkinson, (1997), the authors concluded that overall QOL was similar to that of patients with less than five years disease duration, suggesting that QOL may return to an earlier PD disease stage at 12 month follow-up. Additionally, they noted that, in general, subscales related to physical symptoms improved in contrast to scales unrelated to motor improvement, suggesting that at 12 months only QOL in terms of physical symptoms remained improved.

At roughly two-year follow-up, there is evidence from several studies to suggest that improvement in motor symptoms may not equate to continued improvement in QOL. Lezcano et al. (2004) examined QOL using the PDQ-39 in a cohort of 14 consecutive patients in Spain. They found that overall gains in QOL as measured by the PDQ-39 summary index were maintained between one and two-year follow-up. However based on a non-significant correlation at two-year follow-up between a clinical measure of motor functioning (UPDRS III) and the PDQ-39 summary index that was previously significant
at one year follow-up, they surmised that motor improvements had less of an impact on QOL two years after DBS. Schupbach, Gragiulo et al. (2006) followed a cohort of 29 consecutive STN DBS recipients in France finding that the PDQ-39 summary index significantly ($p < .01$) improved between pre-surgical evaluation and follow-up (between 18 to 24 months.) Using unstructured clinical interviews, they noted discrepancies between improvements in motor symptoms and QOL compared to dissatisfaction with social adjustment. The researchers uncovered three areas of difficulty that they thought related to social adjustment: (a) neurosurgical impact upon self-perception, (b) impact on couple, and (c) impact on professional life.

Statement of the Problem

The existing literature on QOL of advanced PD patients receiving bilateral STN DBS suggests that QOL improves between 3 to 24 months postoperatively (Drapier et al., 2005; Gronchi-Perrin et al., 2006, Just & Ostergaard, 2002; Lagrange et al., 2002; Lezcano et al. 2004; Martinez-Martin et al., 2002; Schupbach, Gragiulo et al. 2006; Troster et al., 2003). At 12 months, improvements in QOL appear to occur due to gains in motor functioning and reduction in side effects from long term dopaminergic drug treatment. Furthermore, there is evidence to suggest that improved motor functioning as a result of STN DBS is maintained for at least five years (Krack et al., 2003). However at roughly two-year QOL follow-up (Lezcano et al; Schupbach, Gragiulo et al.), there is evidence to suggest that improvements in motor functioning alone may not sustain gains in QOL. One of the limitations of existing QOL studies is the relatively short length of follow-up, 3 to 24 months, which may be inadequate to determine whether changes are
transient, maintained, or decline. None of the studies have examined the trajectory of change over time to provide a longitudinal picture of QOL in PD recipients of STN DBS.

Research Questions

Based on the need for longitudinal research in this area, the following research questions were formulated and investigated in the present study:

1) What is the trajectory of change in the following aspects of QOL from baseline to present follow-up?
   a. Overall QOL as measured by the PDQ-39 Summary Index
   b. Eight Domains of QOL as measured by the PDQ-39 subscales:
      i. Mobility
      ii. Activities of daily living
      iii. Emotional well-being
      iv. Stigma
      v. Social support
      vi. Cognitions
      vii. Communication
      viii. Bodily discomfort

2) Are there differences between older and younger patients in the trajectory of QOL from pre-surgical measurement to present follow-up?

3) Are there trajectory differences related to duration of disease in QOL from pre-surgical measurement to present follow-up?
Chapter 2

Review of the Related Literature

*Parkinson’s History*

In 1817, James Parkinson published a monograph describing accounts of a “shaking palsy” which he had observed and investigated among a number of patients he had seen and believed to have not yet found a place in the classification of diseases (Parkinson, 1817/2002). He thought that the condition he described was distinct and different from other diseases based on its symptoms. In this monograph, Parkinson appeared to be cautious in his classification of the potential disease and was clear that he was uncertain of the cause. However, he was able to document general characteristics and a progression to the disease, noting that trembling occurs in one of the hands or the arms that then spreads throughout the body and that the disease becomes increasingly more debilitating. In describing the final progression, he stated, “the will over the muscles fades away… and at last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for-release” (Parkinson, 1817/2002, p.225). Based upon the symptoms he observed, Parkinson believed the disease had a neurological origin, and he appeared to have an understanding of the mechanism by which the symptoms occurred consistent with medical knowledge of the time. Although, he was uncertain of the cause, it was Parkinson’s hope that a medical intervention to slow or reverse the progress of the disease could soon be found.
Unfortunately, the situation with the shaking palsy Parkinson described, now called Parkinson’s disease, has not changed much in terms of understanding the cause. Arguably, our understanding of the disease process and our ability to temporarily slow the progression of the disease has improved. Yet, there is no cure for Parkinson’s disease and it remains a progressive neurodegenerative disease that eventually leads to death.

*Modern Parkinson’s disease*

Today, Parkinson’s disease is characterized by three cardinal features (a) tremor at rest, (b) rigidity, and (c) bradykinesia (Samii, Nutt, & Ransom, 2004). Often, there is a fourth cardinal symptom, postural instability; however, this tends to be absent early in the disease, particularly in younger onset. Tremor at rest is usually the first symptom in 70% of patients and typically occurs asymmetrically, on one side of the body (Samii et al.). Rigidity is evident during joint movement when normative range of motion appears to meet resistance and is usually more pronounced in the limb suffering from tremor during contralateral movement or performing a mental task. Bradykinesia is the loss of automatic movements in addition to initiation of voluntary movement (Fahn, 2003) and is typically the most debilitating symptom because it can affect a person’s fine motor movement, such as being able to button a shirt (Samii et al.). This often will result in the feeling of a loss of independence with the reduced ability to perform everyday living tasks. Postural instability is the gradual development of poor balance and rarely occurs early in the progression of PD. When postural instability becomes severe, patients may not be able to stand without assistance (Fahn).

A definitive diagnosis of PD usually requires an autopsy. However, there are diagnostic criteria for determining whether a person suffers from the disease. This entails
two out of the three cardinal symptoms (resting tremor, rigidity, or bradykinesia) with a
definite response to anti-parkinson medication. If these criteria are not met, it is possible
that the patient may be suffering not from idiopathic PD but a related disorder such as
essential tremor or a form of parkinsonism (Samii et al., 2004).

Epidemiology

In a review of worldwide studies, prevalence rates of PD range from 18 to 234 per
100,000 worldwide with an average adjusted prevalence 103 per 100,000 over a 35 year
period (Zhang & Roman, 1993). When more stringent criteria are applied which adjusts
for age and examines studies using similar methodology, the prevalence rate variation
appears to be around 102 to 190 per 100,000 in Western countries (Schrag, 2007). With a
culturally diverse population in New York City, Mayeux, et al. (1995) found a prevalence
rate of 107 per 100,000 among African Americans, Whites, and Hispanics over a four
year period from 1988-1991 with an incidence rate of 13 per 100,000 people for
idiopathic PD.

The age of onset for PD varies and may span several decades (Zareparsi et al.,
2002). An arbitrary delineation is usually made between young-onset at the ages of 21-39
and older-onset at ages 40 and older. However, it appears that young-onset and older-
onset are the same pathological entity (Golbe, 1991). Genetic factors are thought to play a
role in explaining the variation in age of onset. Zareparsi et al. examined genetic factors,
APOE genotypes, finding onset for one genotype was significantly earlier, with a mean
onset of 56.1 years, compared to a mean onset of 59.6 years for a different genotype.
Young onset is usually associated with a slower progression of PD and in Western
countries about 5-7% of the overall population who seek out medical help for PD develop
the disease before age 40 (Golbe). Muthane et al. (1994) compared early-onset, before age 40, with juvenile-onset, before age 20, and found the mean age of onset was 32.4 years in the early-onset group and 17.9 years in the juvenile onset group.

PD appears to affect all ethnic groups and appears to occur despite differences in demographics, climate, diet, sociocultural background, and industrialization (Zhang & Roman, 1993). Factors such as ethnicity and gender appear to play a role. For example, men seem to have a higher incidence rate of developing PD. Baldreshi et al. (2000) found men to have twice the incidence rate than women when stratified by five-year-age-groups ranging from 65-84 in Italy. In the United States, Mayeux et al. (1995) found African American men to have a significantly higher incidence rate when compared with African American women, 7.6% and 2.8% respectively. There seem to be differences in ethnicity worldwide with the lowest reported prevalence and incidence rates among Africans and Chinese, and the highest rates among Caucasians (Zhang & Roman). However, the findings are not consistent across cultures. Mayeux et al. compared African Americans, Caucasians, and Hispanics in the United States and found incidence rates were highest among African Americans and lowest in Hispanics, whereas prevalence rates were lowest among African Americans and highest in Hispanics.

Pathogenesis

The cause of Parkinson’s disease is largely unknown (Samii et al., 2004). However, the underlying pathology is understood in that dopaminergic cells in the mid-brain that project to the basal ganglia cease to function. Two exceptions to this are a genetic mutation and exposure to methyl-phenyl-tetra-hydropyridine (MPTP). There are five genes and four gene loci, specific places on a chromosome where a gene is located,
that have been associated with PD. Although studying these genes has contributed to our knowledge of potential mechanisms for neurodegeneration, only 15% of people who suffer from PD have first-degree relatives with PD and most PD patients do not have a family history of the disease (Samii et al.).

MPTP is a neurotoxin which kills dopaminergic cells when ingested and is a side product of the creation of a pethidine, a Demerol-like drug. It is the only substance shown to have causality in the development of levodopa responsive PD. Many similar chemicals exist which has led to the hypothesis that substances in the environment are a factor in the development of PD. Aging is thought to be a factor in the development of PD particularly because it is thought to contribute to the decline of dopaminergic cells in the brain. Although the incidence of PD tends to increase with age, it is generally thought that PD is not the result of accelerated aging. Overall, PD may be the result of multiple factors acting together that could include any one of the aforementioned factors (Samii et al., 2004).

*Treatment Interventions for PD*

When considering treatment interventions, there are three arenas which can be considered: (a) prevention of disease progression, (b) control of motor symptoms, and (c) treatment of non-motor symptoms. The estimated progression of PD is a 10% decline in dopaminergic brain cells per year (Rascol, Goetz, Koller, Poewe, & Sampaio, 2002). Eventually, PD becomes worse and the need for medication increases. However, drug response eventually deteriorates, resulting in the development of new symptoms. Because the cause of the disease is unknown, prevention of disease progression has been a goal of neuroprotective medication. Unfortunately, neuroprotection is an unmet need and no drug
can be recommended for this purpose (Koller & Tse, 2004). As a result, the general strategy by which treatment occurs is based upon the understanding that brain cells, which are involved in dopamine production, begin to deteriorate. Therefore, it was determined that increasing dopamine stimulation would improve symptoms. (Rascol et al.).

In terms of controlling motor symptoms, dopaminergic drug treatment is considered the most effective and its usage began in the late 1960’s (Koller & Tse, 2004). Levodopa is a dopaminergic drug and was better than other dopaminergic drugs during randomized drug trials (Rascol et al., 2002). Levodopa is effective at managing the symptoms of bradykinesia and rigidity in PD. Its effect on tremor is more variable but it seems to do as well as other drugs used to manage PD motor symptoms. Levodopa is not effective with speech and swallowing problems, postural instability, freezing or gait, but this is common with all dopaminergic treatment (Koller & Tse). However, there are side effects to levodopa that include nausea, vomiting, hypotension, confusion, and hallucinations (Rascol et al.). Levodopa is usually not effective with dementia which may occur in up to 30% of PD patients (Koller & Tse). In fact, levodopa side effects can induce confusion and hallucinations which can complicate dementia and other mental changes often requiring reduction or discontinuation. Levodopa is also not effective against depression, which can occur in up to 50% of patients at some time in the course of PD. Depression is thought to occur as a result of two general causes: (a) the loss of dopamine cells in the brain because dopamine can have an effect on mood and is associated with providing feelings of enjoyment, and (b) coping with a chronic, progressive neurodegenerative disease. Although levodopa may lead to mood
improvement in some PD patients, treatment for depression may also involve anti-depressants (Koller & Tse).

After several years of levodopa treatment, complications become frequent and disabling (Rascol et al., 2002). The most common complication is dyskinesia, or involuntary movement, which occurs when the patient is over-medicated. The possibility of dyskinesia also increases with longer duration of levodopa usage. For example, dyskinesia usually develops in all young-onset patients and 30-50% of patients who have been treated with levodopa for five years or more (Koller & Tse, 2004).

Another side effect of levodopa is motor fluctuations, which are at their worst during “on” periods when patients appear to be overmedicated and respond to levodopa with dyskinesia and “off” periods when patients are undermedicated and there is minimal or no response. With the passage of time, levodopa takes effect more slowly and lasts for shorter duration. Fifty percent of patients can develop motor fluctuations after two to five years of levodopa usage (Koller & Tse, 2004).

There are ways to try to optimize levodopa therapy, such as giving dopamine agonists during early stages of PD. When dopamine agonists are no longer effective, levodopa treatment can begin. There have been attempts to manipulate levodopa treatment by using controlled release, changing frequency and dosage, but to little avail in terms of reducing the risk of side effects or better managing PD in the advanced stages (Koller & Tse, 2004).

Although some of the non-motor symptoms were discussed in the previous section, PD patients are progressively affected by symptoms that begin with autonomic dysfunction, cognitive decline, and depression that lead to dementia, sleep problems,
sensory complaints, and pain. Autonomic dysfunction involves orthostatic hypotension which is a sudden drop in blood pressure when a person stands, resulting in dizziness, headache, and fainting, and can occur in up to 15-20% of PD patients. Other autonomic dysfunction symptoms include constipation, bladder disturbances and sexual dysfunction. Many of the drugs used to treat autonomic dysfunction have not been studied in randomized trials. Instead, treatments known to work with non-Parkinson’s populations are typically used, which highlights the need to study the efficacy and safety of their usage with PD patients (Rascol et al., 2002).

Ablative surgical treatment for PD, which entailed cutting out sections of the brain, began in the 1930s. Unfortunately, this led to high rates of mortality and these techniques were abandoned. While performing surgery on a PD patient in 1952, a surgeon accidentally discovered that when he tied off an artery decreasing blood flow to an area of the basal ganglia creating an infarct in the globus pallidus, improvement in PD motor symptoms resulted. Thus, it was found that lesions in the pallidum could be used as a surgical therapy for PD. This led to the development of pallidotomies or removal of the pallidum in the 1960s (Walter & Vitek, 2004).

Pallidotomy was found to relieve tremor, rigidity and bradykinesia in PD patients (Eskander, Cosgrove, & Shinobu, 2001). Because of difficulties in obtaining consistent results with pallidotomies and increasing knowledge in neuroanatomy, thalamotomies became the most common surgical treatment for PD (Walter & Vitek, 2004). Thalamotomy reduces tremor and rigidity but is ineffective against bradykinesia (Eskander et al.). However, these surgical developments were overshadowed by the
discovery of levodopa’s efficacy in the late 1960s which came to dominate treatment of PD during 1960s and 1970s.

In 1987, deep brain stimulation (DBS) came to be used in PD treatment when two independent groups in France and Switzerland reported that stimulation in the thalamus resulted in significant tremor reduction (Walter & Vitek, 2004). DBS is a viable treatment option after five to 10 years of levodopa and other dopaminergic drug treatment when PD becomes more difficult to manage because of medication side effects and PD symptoms become progressively worse (Eskander et al., 2001).

During the 1990s, researchers gained a greater understanding of the basal ganglia with a prevailing model describing it as four separate circuits: (a) a motor circuit involved in movement, (b) a limbic circuit related to emotions, (c) an associative circuit involved in the learning of skills and habits, and (d) an oculomotor circuit which impacts eye movement. This information led to the surgical approaches in use today (Widnell, 2005). The motor circuit of the basal ganglia is thought to be involved in the control of movement and the development of motor symptoms of PD (Walter & Vitek, 2004). There are two techniques for surgically intervening in the motor circuit, either through ablation which involves creating a small lesion by heating the tip of an electrode, or deep brain stimulation which entails implanting an electrode in the brain (Walter & Vitek).

Ablative Surgeries

Ablative surgery involves creating a permanent lesion. If the lesion is incorrect, it can result in little or no benefit or can cause adverse side effects. It does have the advantage of being a single procedure and if well-placed can result in significant benefit (Eskander et al., 2001). There are currently three ablative procedures which could be used
in the surgical treatment of PD (Walter & Vitek, 2004). In the 1990s, pallidotomy was reintroduced as a method for managing advanced PD and was found to have an average of 45% improvement in off-state motor symptoms, 80% reduction in dyskinesias, and a reduction in the severity of on and off fluctuations (Eskander et al.). It involves lesioning the globus pallidus and the long-term results appear to be variable. Because pallidotomy is an ablative procedure, it is irreversible once completed (Walter & Vitek).

Thalamotomy is a treatment that has been shown to be effective in the treatment of tremor (Eskander et al.), reducing 85% of parkinsonian tremor in patients. This surgery involves lesioning the thalamus. However, it is currently not recommended for usage in PD patients because it has been associated with a high probability of speech and cognitive problems and will not treat the other cardinal symptoms of PD that develop as PD progresses (Walter & Vitek).

Subthalamotomy surgery entails lesioning the subthalamic nucleus. However, because lesions in this area have been associated with hemiballism, uncontrolled flinging movements on the opposite side of the lesion, there is reluctance to perform ablative treatment in this area. Bilateral subthalamotomy has been associated with a 58% improvement off medicine and a 63% improvement on medication at two year follow-up. Unfortunately, it has been reported that up to half of the recipients of this surgery may develop chorea, a convulsive disorder where the muscles contort involuntarily. This can be corrected by another surgery and is considered to be a less expensive alternative to DBS (Walter & Vitek, 2004).
Deep Brain Stimulation Surgeries

The implantation of an electrode into a target area of neurons to produce the same functional effect of a lesion in ablative surgery is the goal of deep brain stimulation (DBS) surgery. Although the mechanism of action is not fully understood, high frequency stimulation leads to a reduction in tremor when placed in three target areas of the brain: (a) thalamus, (b) pallidum, and (c) subthalamic nucleus (Eskander et al., 2001). Placement of the electrode in these three areas differentiates the surgeries from each other.

As in thalamotomy, the studies examining the effectiveness of thalamic stimulation in the ventral intermediate nucleus (Vim) agree that it is highly effective in treating tremor. Unfortunately, the extant research has not found Vim stimulation to have a significant effect on other symptoms of PD. The most common adverse effect is dysarthria which is defective articulation in speaking. There has been limited use of Vim stimulation with PD patients due to the limitations of treatment, which affects only tremor. Due to the progressive nature of PD, it is likely that other symptoms will develop that would have been better managed by placement of the electrode in a different location in the brain (Walter & Vitek, 2004). In a review of the different areas for electrode placement, Limousin, Fraix, Benabid, and Pollak, (2001) stated that thalamic stimulation surgery is no longer being considered for treatment of PD. Okun, Rodriguez, et al.(2007) think that patients with PD should receive stimulation in either the internal globus pallidus (GPi) or subthalamic nucleus (STN). However, there is controversy surrounding the mechanism of how DBS works related to whether it excites or inhibits neuronal elements (Vitek, 2002). It is undecided which location is more effective because of
insufficient evidence (Okun, Rodriguez, et al.). Additionally, the extant research reflects variability in the results of DBS surgery in the two locations (Gpi vs. STN). Further research is needed to determine the potential advantages of one site over another (Okun, Rodriguez, et al.). The following describes general recommendations.

The internal globus pallidus (Gpi) is another location where the electrode can be placed. Surgery in this location is used to treat PD patients who suffer from motor fluctuations and severe dyskinesias with consistent results found in improvements on dyskinesia scores ranging from 77% to 85% improvement (Limousin, Fraix, et al., 2001). In a review of outcome studies, Walter and Vitek, (2004) found that Gpi reliably alleviates the cardinal motor symptoms of PD including akinesia, loss of voluntary movement, bradykinesia, rigidity, tremor, and problems with gait. It also reduces “on” medication dyskinesia and improves postural instability if the surgery is performed bilaterally with follow-up at two years post-surgery finding stable improvements. There have been reported side effects involving speech, mood, cognition, mania, apathy, and a decline in verbal memory (Walter & Vitek). In another review, Eskander et al. (2001) found that there was a 37% improvement on UPDRS motor scores and a 67% reduction in dyskinesias.

The subthalamic nucleus (STN) is another area of the brain that responds well to electrode stimulation in treating PD. STN DBS produces consistent improvement in off periods and it is thought that large decreases in dopaminergic medication results in improvements in dyskinesias (Limousin, Fraix, et al.). Walter and Vitek (2004) reviewed outcome studies and found that STN DBS improves all cardinal motor symptoms of PD with 45-55% motor improvement off medicine. Bilateral STN may also improve gait,
balance, and posture. Bilateral STN DBS is more commonly performed in Europe and the United States than other surgeries (Walter & Vitek). Another benefit of this surgical intervention is that patients can reduce their dopaminergic medication (Walter & Vitek). Molineuvo et al. (2000) reported an 80% reduction in levodopa dosage of 15 patients after bilateral STN DBS using a technique of gradual tapering of dopaminergic medications and adjustment in stimulators. Eight patients were able to stop taking levodopa completely six months after surgery (Molineuvo et al.). However, the research indicates that reducing medication level can be more difficult with recipients of STN in that dramatic reduction in medication can lead to side effects related to mood such as depression and apathy. There appear to be more cognitive, mood, and behavioral side effects with STN than GPI. Although this may be related to the higher rate that STN is performed, resulting in a larger number of STN surgeries compared to GPI and Vim, it has also been suggested that these side effects are related to the small surgical target of the STN and that implantation of the electrode is close to regions that affect limbic system and frontal lobe functioning (Walter & Vitek). As a result, current from electrode stimulation may inadvertently affect behavior and cognition (Walter & Vitek).

**DBS Motor Changes**

Although bilateral STN DBS has been found to improve the cardinal symptoms of PD, the degree of overall benefit is often compared and contrasted with levodopa or dopaminergic drug treatment. DBS can improve tremor symptoms that may be resistant to levodopa; however, most symptoms that do not improve with levodopa will not improve with DBS (Lang & Widener, 2002). The best response to bilateral STN DBS is usually equivalent to the best levodopa response (Krack et al., 1998). Therefore, a good
response to levodopa can be predictive of a good response to DBS (Lang & Widener). Although no standardized guidelines exist for selecting DBS candidates, one article suggested that patients who have a pronounced response to dopaminergic medication with at least 30% improvement or higher would be good candidates for DBS (Okun, Fernandez, Rodriguez, & Foote, 2007).

Long term studies have attempted to address the question of how long the improvements seen after STN DBS are maintained. Krack et al. (2003) found that improvements in motor functioning compared to baseline were generally maintained for five years. Reductions in tremor and rigidity and reduction of dystonia while off-medication were stable over five years. Improvement in akinesia and speech occurred at one year but were not maintained over time. Although the assessment of ADLs with the UPDRS showed improvement compared to baseline at one year, there was significant decline in these improvements over the five year period. Functionally, as measured by the Schwab and England, most recipients were able to be independent in ADLs while off medication. Schupbach et al. (2005) also found similar improvements in motor functioning were maintained over five years. However, ADL was maintained for two years and returned to baseline by five year follow-up.

Krack et al. (2003) thought that some of the decline in axial symptom management seen in their cohort of patients, that included: (a) reduction of speech, (b) postural instability, and (c) freezing of gait, could be accounted for by disease progression. Among non-DBS PD patients, Markham and Diamond (as cited in Krack et al.) observed that these symptoms became less responsive to levodopa treatment over time. Thus, Krack et al. speculated that this decline would have occurred regardless of
treatment type. Schupbach et al. (2005) found motor disability scores returned to pre-surgical levels at five year follow-up as well as significant worsening of the same axial symptoms observed by Krack et al. They also hypothesized that these declines were due to disease progression, resulting from the development of non-dopaminergic lesions among PD patients as observed by Agid (as cited in Schupbach et al.).

**DBS Mood and Cognitive Changes**

The literature on mood and cognitive changes often contains case reports describing one or two patients who appear to have suffered from adverse effects after DBS surgery. Smeding et al., (2007) described a PD patient who received bilateral STN DBS and developed signs of pathological gambling one month post-surgery, although this individual had no reported prior history of gambling. This may be similar to other findings in which pathological gambling has been associated with dopaminergic drug treatment. After starting levodopa treatment, 10 PD patients with no reported prior history of gambling out of a cohort of 250 developed pathological gambling (Molina et al., 2000). Dodd et al. (2005) found that dopamine agonists such as pramipexole, which mimic the effects of dopamine, were associated with the development of pathological gambling in nine out of 11 PD patients seen over a three year period. Dopamine is thought to be involved in systems that mediate movement, reinforcement, and planning (Freberg, 2006). Temel, Blokland, Steinbusch, and Visser-Vandewalle (2006) reported a 60% average post-operative dopaminergic drug reduction among DBS studies examined from 1999-2004. They wondered if this reduction has a role in explaining cognitive and mood changes seen post-surgically, although they noted that these problems tend to occur when the reduction occurs quickly instead of gradual reduction of medication over a two
to three month period. These findings suggest that DBS treatments potentially impact dopaminergic systems resulting not only in gains in motor functioning, but having effects on other parts of the brain which result in outcomes on mood, cognitions, and behavior.

Although case reports such as these may highlight the need to study mood and cognitive changes of DBS, it is difficult to weigh all the evidence due to a lack of well-controlled evidence-based studies examining mood and cognitive changes after DBS. To address this problem, Rodriguez et al. (2005) reviewed 44 published articles between 1995 and 2003 covering different electrode placements in the brain that included: (a) subthalamic nucleus (STN), (b) globus pallidus internus (GPI), and (c) thalamus (Vim). Disorders that were included in the review were: (a) Parkinson’s disease (PD), (b) tremor, (c) dystonia, and (d) obsessive compulsive disorder. Of the 44 articles, 12 were case reports and did not meet criteria for providing sufficient evidence, 31 were categorized as non-controlled studies or case series and one was a non-randomized controlled study reflecting the difficulty in making an empirical determination of mood and cognitive changes. Nevertheless, patients with PD were found to have greater reported mood and cognitive side effects than DBS recipients with essential tremor, dystonia, or obsessive compulsive disorder. Mood alterations were noted in many studies examining STN DBS, with euphoria and depression being the most consistent finding across studies (Rodriguez et al.). Although the results were mixed in terms of cognitive changes after STN DBS, common themes across studies found worsening speeded verbal fluency, verbal learning, and visual memory. PD patients were found to have more mood and cognitive side effects when compared to patients with essential tremor, dystonia, and obsessive compulsive disorder. Rodriguez et al. concluded that there appear to be many mood and
cognitive changes as a result of DBS, yet it is unclear with which patients and under what circumstances these changes appear to occur.

Rodriguez et al. (2005) noted tremendous variability among the 44 studies examined, which reported opposite findings and opposite conclusions for cognition and mood on the same measures. Several explanations were thought to account for this variability: (a) small sample sizes, (b) different test states between on/off medication and on/off DBS stimulation, (c) different techniques for implantation and DBS programming, (d) enrollment of older and younger patients, and (e) lack of standardization in pre-operative screening and psychiatric assessments. This review reflects some of the difficulty in analyzing some of the evidence related to mood and cognitive effects of DBS. However, it showcases the need for studying these same changes with specific populations who have received specific DBS surgeries.

In contrast, Temel et al. (2006) conducted a meta-analysis that included 1398 patients who underwent bilateral STN DBS. They found that cognitive problems had occurred in 41% of the patients with varying degrees of severity from moderate decline in verbal memory to drastic changes in executive functions. According to Temel et al., cognitive changes were often chronic with variability in their impact upon DBS recipients. Some recipients were heavily impacted while others experienced minor symptoms. Overall, cognitive dysfunctions occurred in the highest percentage of patients (41%), followed by depression (8%), and mania (4%).

Another problem appears to be statistical power. Woods et al. (2006) reviewed 30 studies on the cognitive effects of STN DBS performed from 1997 to 2004 and conducted post-hoc estimates of statistical power and the effect sizes. Low power values increase
the risk of committing a type II error, failing to reject a null hypothesis that is actually false, raising the issue that studies in the literature may not have enough power to detect adverse postsurgical outcomes. It could also erroneously increase variability seen in studies and result in a situation in which studies with adequate power report adverse cognitive effects whereas underpowered studies report no effect on cognition. Woods et al. found that effect sizes ranged from .05 to .91 with only 7%, or two of the studies having adequate power ($\leq 0.80$) to detect a large effect. The median sample size across studies was 14. Verbal fluency was examined and five studies with a greater mean effect size of .25 reported significant declines in verbal fluency whereas nine studies with a mean effect size of .11 reported no changes. Woods et al. concluded that although it is generally thought that motor gains from STN DBS surgery outweigh the risk of cognitive decline, low power prevents us from making conclusions about the impact of STN DBS on cognitive functioning. Additionally, adverse cognitive effects could have a large influence on activities of daily functioning which could in turn influence QOL in PD patients.

Age

Age appears to be a factor in terms of side effects and older recipients tend to have more cognitive changes than younger recipients (Walter & Vitek, 2004). Behavioral changes such as apathy, depression, and mania have been observed. Side effects from STN can be improved by changing stimulation patterns (Walter & Vitek). It is thought that mood and cognitive changes may not be immediately apparent because they may not be readily observable (Walter & Vitek).
In a review of DBS studies published in the literature between 1965 and May 2004, age and disease duration were examined as preoperative factors by a committee of neurologists, neurosurgeons, neuropsychologists, neuropsychiatrists, and researchers with expertise and experience in DBS for PD (Lang et al., 2006). Based on this review, the mean age at the time of STN DBS was between 40 and 60 years with the youngest implantation occurring at age 30 and the oldest at age 78. The committee noted that an arbitrary age limit of 75 was set by some studies yet specific justification could not be found for this limit. It appears that many studies and many centers that perform DBS surgery, use age 75 or older as the cut-off in terms of age (Deuschl et al., 2006; Drapier et al., 2005; Martin-Martinez et al., 2002). The authors concluded that there was not sufficient evidence to determine the influence of age on post-operative outcomes related to STN DBS. Based upon expert opinion, the committee emphasized a potentially less favorable cost benefit in the elderly for STN DBS due to age-related comorbidity such as cognitive dysfunction. Specifically, they recommended that individualized decisions be made based upon therapeutic need, risks from comorbidity, and life expectancy.

Of the three studies reviewed by the committee (Lang et al., 2006) that examined correlations between age and post-surgical outcome, two studies supported better outcomes among younger patients. Welter et al. (2002) used a cutoff age of 56 to distinguish older from younger patients and found UPDRS activities of daily living (ADL) and motor scores were significantly better in the younger group than the older group at six month follow-up. Charles et al. (2002) found a negative correlation between age and post-DBS improvement in a cohort of 56 consecutive STN-DBS recipients with a mean age of 56.0 at surgery. Their results suggested that more post-surgical benefit
occurred among younger PD patients. One study by Kleiner-Fisman et al. (2003) found that age was not predictive of STN-DBS surgical outcome in a group of 25 consecutive patients with a mean age at surgery of 57.2. Although the median follow-up was 24 months, there was quite a bit of variability in the time of follow-up, which ranged from 12 to 52 months.

Examining other studies beyond the scope of what Lang et al. (2006) evaluated, Krack et al. (1998) examined 13 consecutive patients with an age of PD onset under 40 years in a comparison between STN and Gpi DBS surgery. At six month follow-up, STN was found to have more benefits, suggesting better outcomes in younger onset patients. Although the delineation appears to be arbitrary, young-onset PD occurs between ages 21-40 (Schrag, Ben-Shlomo, Brown, Marsden, & Quinn, 1998). According to Schrag et al., it is rare for PD to begin before age 40; however, an earlier age at onset usually means longer survival often resulting in longer disease duration.

Weaver et al. (2009) included DBS recipients over age 70 in a multi-center, randomized, controlled, blinded study comparing DBS effects with best available medical therapy. Roughly 25% of the 122 PD patients were in the surgical intervention group. They found that the surgical group received more effective improvements in reducing disability due to motor complications without significant cognitive impairment compared to the best medical management group. However, older patients had a higher percentage of adverse events. Weaver et al. found that the surgical group had a risk 3.8 times higher than the medical management group for adverse events such as falls, surgical site infection and depression. However, one limitation of these findings is that the DBS surgery group was combined with recipients who received either STN or Gpi
interventions, making it difficult to determine what risks apply to which intervention group.

**Disease Duration**

Based upon their review of pre-surgical considerations, Lang et al. (2006) noted that the ideal disease duration before performing DBS surgery is unknown. They further remarked that although advanced PD patients typically receive the surgery, the issue of disease duration requires the consideration of many factors. Examining the mean disease duration for advanced PD patients, Lang et al. found it to range between 12 to 15 years. It is thought that at advanced stages of PD, major social and psychological disability have already occurred in terms of interruption of social and vocational activities as well as family and affect maladjustment (Lang et al.). In contrast, they noted case study evidence that PD patients receiving STN-DBS with shorter disease duration were able to return to work (Mesnage, Houeto, Welter, & Agid, 2002). However, Lang et al. noted that performing the surgery within five years of disease duration was not recommended because of the possibility that the candidate may not be suffering from idiopathic PD. Thus, consistent with the Core Assessment Program for Surgical Intervention Therapies in Parkinson’s Disease (CAPSIT-PD) protocol (Defer, Widner, Marie, Remy, Levier et al., 1999), they recommended that disease duration should be at least five years to allow non-idiopathic forms of parkinsonism to manifest.

In examining the evidence that Lang et al. (2006) evaluated, Mesnage et al. (2002) presented case study evidence of four STN DBS recipients with a range of disease duration from five to nine years. They found that all four patients who had received bilateral STN DBS were able to return to work four months post-surgery. Mesnage et al.
concluded that their findings suggest that STN DBS given early in the progression of PD may prevent motor disability and levodopa side-effects from interrupting the work and family life of patients; perhaps, giving PD patients a chance for a “normal” life.

Schupbach et al. (2007) conducted a randomized, controlled trial on 20 patients matched by disease duration and age who suffered from PD between 5 to 10 years who were assigned to receive either bilateral STN DBS or medical treatment involving dopaminergic drugs. Each group was measured at baseline, 6, 12, and 18 months. Motor scores off medication improved for the surgical group compared to the medical treatment group, who worsened. Significant differences were found between the surgical group and medical treatment group with improvement in rigidity, bradykinesia, and tremor. Using the PDQ-39 to measure QOL at all time points, the surgical group had better scores in the activities of daily living, stigmatization, and bodily discomfort subscales compared to the medical treatment group who showed no improvement. Adverse effects such as transient depression and hypomania occurred in both treatment groups. Schupbach et al. concluded that the superior outcome of surgically treated patients suggests that bilateral STN DBS could be a viable treatment option for PD patients who are not in the advanced stage before motor disability, fluctuations, and dyskinesias become less controllable by dopaminergic drug treatment. More recent randomized, controlled trials with large samples have had participants with disease duration within an average range of 12 to 15 years (Deuschl et al., 2006; Weaver et al., 2009).

Adverse Events

One of the risks of DBS is that not all recipients improve, usually resulting in less than positive outcomes often called adverse events. Recent findings have suggested that
having DBS surgery puts a PD patient at 3.8 times higher risk of adverse events compared to those receiving best medical treatment (Weaver et al., 2009). One of the risks is death. Umemura et al. (2003) examined 109 consecutive patients receiving DBS surgery for movement disorders and found a 4.6% morbidity rate. In one of the first five year longitudinal studies of STN DBS, Krack et al. (2003) followed a cohort of 49 patients, noting that three recipients died, with one death related to the surgical procedure. Other possible adverse events involve surgical complications, treatment related side-effects, weight gain, transient hypomania, transient depression, and transient apathy. Ultimately, the decision to proceed with DBS or not, involves PD candidates as well as their physicians, who all should make informed decisions that weigh the risks and the benefits and take into consideration recommendations from results of randomized trials (Deuschl et al., 2006; Weaver et al., 2009). Adverse events may be a significant consideration. Schupbach et al. (2007) reported that two participants in their study chose to postpone surgery out of fear of death.

Quality of Life

Although quality of life (QOL) is broadly conceptualized as a patient’s overall sense of well-being and is thought to be a relevant measure when considering the efficacy of treatments, little agreement exists regarding the specific types of QOL (Spilker, 1996). Although the World Health Organization (WHO) released a position paper discussing how to assess QOL (World Health Organization Quality of Life Group, 1995), this lack of agreement is beneficial in being able to give QOL the flexibility of being defined in specific contexts and for specific illnesses and treatments. For example, the QOL of a child suffering from a food allergy could be different than the QOL for an advanced PD
patient. The child with the food allergy is likely not concerned about motor dysfunction and is able to probably embark in many activities normative of other children; however, there may be anxiety around eating. Alternatively, the advanced PD patient may be more concerned with level of independence related to daily functioning. For example, the act of eating may require assistance due to resting tremor. Because QOL is multifactorial, an examination of QOL in advanced PD patients requires that we define QOL relative to this study.

Parkinson’s disease

The definition of QOL in PD patients has been addressed and defined in many ways. From previous data collection points of this overall study, QOL was defined as a multidimensional construct which sought to measure three fundamental factors: (a) physical functioning, (b) social functioning, and (c) emotional functioning (McRae, Cherin, Yamazaki, Diem, Vo, Russell, et al., 2004).

Concepts of QOL may differ and in the literature terms such as QOL and HRQOL may be used interchangeably. In a review of QOL, Den Oudsten, Van Heck, and DeVries (2007) made distinctions between quality of life (QOL), health-related quality of life (HRQOL), and perceived health status (HS) in PD. They described QOL as the subjective evaluation of life as a whole. HRQOL is a narrower view of QOL and focuses on the subjective evaluation of QOL as it relates to health. HS is even more specific and refers to patient perspectives of functioning as the result of PD. This review illustrated the variability of the concept of QOL even within studies examining QOL in Parkinson’s disease.
In an examination of data collected from an international survey involving six countries and 1,020 PD patients, The Global Parkinson’s Disease Survey (GPDS) Steering Committee (2001) sought to examine factors beyond disease severity and medication influencing HRQOL. They found that depression measured by the Beck Depression Inventory (BDI) was a significant predictor of variability in HRQOL. Other predictors were “satisfaction with the explanation of the condition at diagnosis” and “current feelings of optimism.” They concluded that their analysis was a first step towards developing management guidelines that may highly influence HRQOL in PD patients. This study further exemplifies the amorphous and relatively undefined nature of QOL in PD patients.

In terms of influencing QOL as measured by the PDQ-39, Schrag, Jahanshahi, and Quinn (2000) examined the medical records of patients suspected of having PD from 15 general medical practices in the London, UK area. Out of 124 patients classified as having probable PD, those with depression, cognitive decline, postural instability, gait difficulties, and a history of falls had significantly (p<.001) worse PDQ-39 summary scores reflecting overall QOL than those without these features. Depression followed by disability were found to be most predictive of QOL scores, accounting for 64% of the variance. Postural instability and cognitive impairment accounted for another 8%. The most predictive factor, depression, was thought to account for up to 60% of the variance in QOL scores.

Diamond and Jankovic (2005) reviewed eight QOL studies after DBS surgery between 1965 and 2005. QOL was defined as health related quality of life (HRQOL) using WHO criteria. A strong relationship was seen between motor complications and
deterioration of HRQOL. Motor complications were described as disrupting mobility and activities of daily living (ADL), which results in a loss of independence and more reliance on caregivers.

_Deep Brain Stimulation Studies_

One of the potential direct impacts of bilateral STN DBS is improvement in motor functioning with a strong association between motor complications and deterioration of QOL. Diamond and Jankovic (2005) examined HRQOL and conceptualized it as measuring the burden of disease and the impact of therapeutic interventions on activities of daily living, employment, and other functions. The studies reviewed were found to have varying levels of evidence based upon Oxford Centre for Evidence-Based criteria. One study was considered to be a randomized controlled trial. The remaining seven studies were considered to be cohort studies or low quality randomized controlled trials with less than 80% follow-up.

Esselink et al. (2004) randomized 34 patients to receive unilateral pallidotomy or bilateral STN DBS. Patients were given the Parkinson’s Disease Quality of Life Questionnaire (PDQL) as an HRQOL outcome measure. Both groups showed similar improvements on PDQL total scores at three month follow-up. However, there were not significant differences between the two groups receiving the different surgeries. It was thought that this was due to low statistical power but that there had been a trend towards significance ($p < .15$).

Spottke et al.(2002) examined 16 consecutive patients receiving STN DBS and found the Sickness Impact Profile (SIP) improved at six months with 67% improvement in physical and 51% in psychosocial dimensions. Closer examination of the items
revealed that body care and movement, sleep and rest, ambulation, social interaction, and recreation and pastimes showed the most improvement. Lagrange et al. (2002) found that 60 STN DBS patients who were followed up at 12 months had a 43% improvement in overall PDQL scores with all dimensions improving including, social function, PD-related symptoms, systemic functions, and emotional functioning. Additionally, a significant improvement was found in depression on the Beck Depression Inventory.

Diamond and Jankovic (2005) examined the remaining five cohort studies, which included 84 patients evaluated with the PDQ-39 and compared with pre-surgical scores. Overall, improvements up to 62% were reported on the summary index scale. Mobility, activities of daily living, stigma, emotional well-being, and bodily discomfort subscales had consistent improvements. However, social support, cognition, and communication with others were less improved. Troster et al. (2003) found that overall improvements of the PDQ-39 summary index scale (PDQ-39SI) correlated with improvements in depression rather than motor gains. Lezcano et al. (2004) and Martinez-Martin et al. (2002) found that depression and anxiety did not correlate with QOL on PDQ-39 summary index scores but instead improvements in levodopa side effects, and UPDRS scores correlated with increases in QOL.

Diamond and Jankovic (2005) found improvements in HRQOL to correlate with motor improvements in levodopa side effects. However, psychological aspects such as depression and anxiety appeared to have a role as well and need to be adequately addressed in assessing patient outcomes. They suggested that QOL measures specifically address issues related to DBS. Kuehler et al. (2003) created the Questionnaire of Life Satisfaction Deep Brain Stimulation (QLS-DBS) that attempts to measure five factors...
related to DBS that include (a) reliability (b) inconspicuousness (c) manipulation of neurostimulator, (d) physician’s care, and (e) absence of bodily symptoms and side effects of neurostimulator which could be used in subsequent research.

**STN-DBS Studies as measured by the PDQ-39**

In an examination of studies that used STN DBS for treatment and examined QOL with the PDQ-39 as an outcome measure, ten worldwide studies in English were found in the extant literature.

Martinez-Martin et al. (2002) examined the QOL of 17 consecutive Spanish PD patients in Barcelona, Spain treated with STN-DBS between 1997 to 1999 and given the Spanish version of the PDQ-39 pre-operatively and at six month follow-up. The summary index for the PDQ-39 was found to significantly \( p < .01 \) improve at six month follow-up. The Mobility and Activities of Daily Living subscales were found to significantly \( p < .01 \) improve as well. Less significant \( p < .05 \) improvement was found in three subscales involving Emotional Well-Being, Stigma, and Bodily Discomfort. The researchers concluded that QOL in their patients improved due to reduction in motor fluctuations that remained stable throughout the day in most of their patients. It was thought that not only did motor symptom improvement positively impacted QOL at six months, but that other factors such as gain in functional state and decrease in dependence also contributed to the QOL improvement.

Just and Ostergaard (2002) conducted a study on 11 consecutive PD patients in Denmark who received STN-DBS from February to September of 2000. 13 PD patients who were waitlisted to receive the surgery were used as a comparison group. The PDQ-39 was administered to the two groups at three month intervals with the surgical group
being evaluated pre-surgically. The surgical group’s QOL improved at three months on the Summary Index scale as well as on the Mobility, Activities of Daily Living, and Bodily Discomfort subscales in contrast to the control group who showed little change. At six months, the surgical group showed improvement in the Summary Index scale as well as on the Mobility, Activities of Daily Living, and Cognition. Ten of 11 patients in the surgery group reported QOL improvements. Although the remaining patient showed significant improvement on clinical rating scales such as the UPDRS and the Hoehn and Yahr, there were improved scores in Mobility and ADL but worsening scores in Emotional Well-Being, Social Support, and Communication. It was concluded that the DBS surgery group showed significant improvement in QOL in comparison to a similar group of patients who had not yet undergone the surgery.

Troster et al. (2003) sought to examine whether QOL changes were related to changes in motor function and depression. A cohort of 26 PD patients in the United States were evaluated pre-surgically and three and a half months post-surgically with the PDQ-39 for QOL and with the Beck Depression Inventory (BDI) for depression. Overall QOL based on the PDQ-39 Summary Index, improved significantly ($p < .001$) at three and a half month follow-up. A significant relationship was found between change in PDQ-39 and change in BDI score even when motor improvement, the UPDRS score, was controlled for. The authors concluded that motor gains could improve QOL indirectly by decreasing depression. Furthermore, they concluded that depression could be a stronger correlate to QOL.

Patel et al. (2003) studied a cohort of 16 consecutive PD patients in the United Kingdom by assessing QOL pre-surgically and at 12 months. The overall summary index
of the PDQ-39 was found to significantly \((p < .01)\) improve over the 12 month period suggesting an improvement in overall QOL. In addition, there were significant \((p < .05)\) improvements the Activities of Daily Living and Stigma subscales.

Lezcano et al. (2004) followed a cohort of 14 PD patients who received bilateral STN DBS in Spain examining QOL at one and two year follow-up. QOL, indicated by the PDQ-39 Summary Index, was significantly \((p < .001)\) improved at two year follow-up and this improvement appears to have been maintained from one year follow-up. There were significant \((p < .001)\) improvements in the Mobility, Activities of Daily Living, Stigma, and Emotional Well-Being subscales. The Communication and Bodily Discomfort subscales also showed significant \((p < .05)\) improvement at a decreased alpha level. A correlation was found between motor improvement and QOL increases at one year follow-up. However, the researchers surmised that motor improvement was less important at two year follow-up likely due to more impacting improvements in other QOL areas.

Diamond and Jankovic (2005) reviewed the five studies previously summarized and noted that of the total 84 patients in these studies assessed for QOL by the PDQ-39, increases up to 62% were reported in the Summary Index. In particular, Mobility, Activities of Daily Living, Stigma, Emotional Well-Being, and Bodily Discomfort were found to have consistently greater QOL improvement than Social Support, Cognition, and Communication.

Drapier et al. (2005) followed a cohort of 27 consecutive PD patients in France treated with STN DBS assessing them pre-surgically and at 12 month follow-up. Overall QOL significantly \((\alpha<.001)\) improved at 12 month follow-up as well as Mobility,
Activities of Daily Living, Stigma, and Bodily Discomfort. Although they found STN DBS to be generally an effective intervention, examination of the PDQ-39 subscales revealed that QOL only improved for physical items. Additionally, when comparing their results to a population study of PD patients without surgical intervention, the researchers found that overall QOL was equivalent to PD patients with disease duration under five years. They concluded that at 12 month follow-up, only physical QOL improved with little change in mental and social dimensions of the PDQ-39 subscales.

Gronchi-Perrin et al. (2006) examined the QOL of 14 consecutive PD patients who received STN DBS in Switzerland assessing the cohort six months post-surgically. Overall QOL was found to improve significantly ($p < .05$). However, none of the subscales were found to reach significance and were generally found to improve except for the Communication subscale. The subscales with the most improvement were Mobility and Stigma. Interestingly, they asked their patients retrospectively to estimate their pre-operative QOL and when these retrospectively reports were used no significant differences were found in pre and post operative QOL. They raised issues related to whether subtle changes in the cognitive processes of patients as a result of surgery may negatively impact self-reported QOL and challenged the validity of retrospective QOL self-evaluations.

Schupbach, Gargiulo, et al. (2006) examined a cohort of 29 consecutive PD patients who received DBS in France, assessing them pre-operatively and post-operatively between 18 to 24 months. They found that disease specific QOL as measured by the PDQ-39 significantly ($p < .01$) improved. Using open, unstructured clinical interviews, they found a discrepancy between dramatic improvements in parkinsonian
symptoms and dissatisfaction with social adjustment. Although none of patients wanted stimulation to be turned off and to return to management by medicine, the researchers uncovered difficulties in patients’ perceptions of themselves, relationships with their significant others, and their professional lives. They recommended a multidisciplinary approach to patient care involving psychosocial preparation pre-operatively and post-operatively for coping with changes beyond improvement in motor functioning.

Deuschl et al. (2006) appears to have performed one of the first multi-center, randomized trials on PD patients receiving STN DBS. Recruiting patients from 10 academic centers in Germany and Austria, 78 pairs of PD patients matched by age and other factors such as duration of levodopa treatment were randomized to receive either STN DBS or standard medical treatment with medication. QOL was assessed by comparing the scores of the PDQ-39 between the two groups six months after assignment to a treatment group. Overall QOL as measured by the PDQ-39 summary score significantly \((p < .05)\) improved at six month follow-up for DBS recipients compared those who received standard medical treatment. In addition, four QOL domains represented by four subscales of the PDQ-39 significantly \((p < .001)\) differed between the treatment and comparison group. These differences involved the Mobility, Activities of Daily Living, Emotional Well-being and Stigma subscales. The researchers also examined the risk of adverse events finding the neurostimulation surgical treatment group had a significantly higher percentage \((p < .04)\) of severe adverse events, which included death, worsening mobility, and infection at the stimulator site. They concluded that improvements in QOL need to be considered against the risk of post-surgical complications.
Montel and Bungener (in press), using the PDQ-39, compared the QOL in 40 patients who were treated with STN DBS and a matched comparison group of 40 patients on medication treatment in France. At 12 month follow-up post-DBS, they found significant \( p < .01 \) worsening in the Communication Subscale among the DBS group when compared to the medication group. They surmised that this difference relates to potential differences in verbal functioning in that DBS can affect a recipient’s voice and articulation. Surprisingly, there were no other differences in QOL between the DBS group and the medication treatment group, particularly in the Mobility subscale. Interestingly, they found that coping strategies in the DBS group were not correlated with QOL whereas coping strategies in the medication group significantly correlated with QOL. The authors suggested that examination of expectations and development of coping strategies be used when working with PD patients prior to receiving DBS intervention.

Weaver et al. (2009) performed a randomized, controlled trial of 255 PD patients from 13 medical centers in the United States. Approximately half of the 121 participants were assigned to receive DBS surgery with roughly 50% receiving STN and 50% receiving Gpi. Because one of the long-term goals of the study was to examine outcome based upon surgical target (STN vs Gpi), they were able to perform blinded assessments of participants at six month follow-up. Additionally, they included PD patients over age 70 in roughly 25% of the sample. This aspect of inclusion was a departure from the Deuschl et al. (2006) study and allowed the researchers to examine the effects of age. Although QOL findings are potentially difficult to compare because the sample included both STN and Gpi DBS recipients, Weaver et al. reported that overall QOL measured by the PDQ-39 improved significantly \( p < .05 \) at six month follow-up. Additionally, DBS
recipients significantly \( (p < .05) \) improved on seven out of eight of the PDQ-39 subscales. The only domain that did not improve was Social Support. Similar to Deuschl et al., they found an increased risk of severe adverse events in the surgical intervention group, especially among patients over age 70. Additionally, they found an increased risk of falls in the DBS group. Corroborating the findings of the Deuschl et al. study, they concluded that gains in motor functioning and QOL need to be weighed against the increased risk of adverse events.
Chapter 3

Methodology

The purpose of this study was to examine potential trajectories of long term gains, losses, or maintenance in Quality of Life (QOL) of an advanced Parkinson’s Disease (PD) cohort who received Deep Brain Stimulation (DBS) surgery beginning in 1999 to control motor symptoms of PD. QOL was viewed as a multifactorial construct measured by the PDQ-39 which constituted nine domains: (a) overall QOL, (b) Mobility, (c) Activities of Daily Living, (d) Emotional Well-Being, (e) Stigma, (f) Social Support, (g) Cognitions, (h) Communication, and (i) Bodily Discomfort. This study had three research questions.

The first question involved examining the trajectory of change in all domains of QOL measured by the PDQ-39 from pre-surgical evaluation to present follow-up. A total score for the instrument, the PDQ-39 summary index, was used to represent overall QOL. PDQ-39 subscales were developed to examine eight sub-domains of QOL in PD patients (Jenkinson, Fitzpatrick, & Peto, 1998). To our knowledge, this data set provided one of the longest periods of follow-up in the extant literature, allowing the exploration of a seven and a half year average longitudinal change in QOL over time. An attempt at examining individual growth curves was made using hierarchical linear modeling, specifically using a mixed model approach that accounts for random and non-random variance. Due to limitations of the data set, the mixed model analysis was restricted in analyzing a trajectory of change over time. A supplemental analysis was undertaken
using linear regression to examine whether time significantly correlated with the overall dependent variable, QOL as measured by the PDQ-39 summary index score. Regression analyses were also used to examine relationships between time and the eight sub-domains of QOL as measured by the PDQ-39 subscales.

The second question examined differences in trajectory by age for QOL domains measured by the PDQ-39. As stated above, the mixed model approach was limited due to restrictions of the data set. Originally, it was hoped that age could be used as a predictor in the model in order to examine whether there are different trajectories of change after DBS related to age (older vs. younger participants). However, this was not possible. As part of the supplemental analysis, age was used as a predictor of all domains of QOL measured by the PDQ-39. If a significant correlation was found between age and PDQ-39 QOL, a search for early onset participants, younger than age 40 and older onset PD participants, older than age 40 was undertaken. In addition, participants needed to be measured pre-surgically, at one intermediate point of measurement, and at present follow-up. Individual empirical growth plots were examined providing preliminary evidence of differing trajectories due to age.

The third question examined whether there were differing trajectories of change based on disease duration. Again, due to the limitations of the data set resulting in a restricted mixed model analysis, supplemental linear regression analyses were undertaken. If a significant correlation was found between disease duration and PDQ-39 QOL domains, a search was undertaken for participants with short disease duration, close to five years as recommended by the CAPSIT-PD protocol (Defer, Widner, Marie, Remy, Levier et al., 1999), and a longer disease duration, close to the 12 to 15 year average
disease duration among DBS recipients reported by Lang et al. (2006). Participants successfully identified also needed measurements at three time points: (a) pre-surgically, (b) one intermediary measurement, and (c) at present follow-up. Individual growth plots were examined providing preliminary evidence for potentially differing trajectories based upon disease duration.

Design

This was a longitudinal study where a QOL questionnaire was administered at baseline, three months, six months, 12 months, 18 months, 24 months, and 36 months from each recipient of the DBS surgery in the cohort. In the present study, the QOL questionnaire was re-administered to obtain a measure at approximately 84 months, allowing an examination of long-term trajectories of potential gains, losses or maintenance.

Participants

The sample consisted of 52 consecutive patients with advanced Parkinson’s disease who underwent DBS between June 1999 and December 2001. This sample was also involved in a previous study examining the medical effects of the surgery (Ford et al., 2004). The inclusion criteria for the surgical study by Ford et al. entailed: (a) the presence of idiopathic Parkinson’s disease defined by three of the four cardinal signs of the disease (e.g., tremor at rest, rigidity, bradykinesia, and postural instability), (b) age of onset of Parkinson’s disease over 29 years, (c) the existence of disabling motor fluctuations or dyskinesias despite optimal medical management, (d) absence of severe dementia, (e) the ability to give informed consent, and (f) acceptable general health. In terms of location of the placement of the electrode, patients received bilateral,
subthalamic nucleus (STN) placements. Participants were evaluated after being “off” their Parkinson’s medications overnight. A standardized surgical evaluation procedure was used to screen potential candidates. A quality of life questionnaire was given to patients during a pre-surgical visit and constitutes the base line, pre-surgical measurement for the longitudinal data set used in this study. Inclusion criteria for the present study involved having received the surgery during Ford et al. study and one previous response to the QOL questionnaire.

**Sampling Procedure**

Purposive sampling was used. Questionnaires were sent to the recipients of the DBS from the study described above (Ford et al., 2004) to collect longitudinal data. This sampling method was used so that we could use the data previously collected to examine a trend, and ensure homogeneity in terms of following the same cohort who had received treatment. Re-administration of the QOL questionnaire was done in order to operationalize latent constructs of QOL. The QOL battery was sent from the Neurological Institute at Columbia-Presbyterian Medical Center to previous participants and recipients of STN DBS from the institute.

**Instruments**

The QOL battery in the study contained a brief demographic section to collect information on gender, age, racial/ethnic background, and years of school completed. Other items were asked to determine living situation, marital status, level of employment, and possible participation in volunteer work. These were followed by health specific questions such as when PD was first diagnosed, length of time participant was
symptomatic prior to diagnosis, family history of the disease, existence of other chronic health problems, and current level and history of cigarette smoking.

36 Item Short Form Health Survey

Rand Health, a research division of the Rand Corporation, developed the 36 Item Short Form Health Survey (SF-36) as part of the Medical Outcomes Study (MOS). The MOS is a multi-year, multi-site study examining variation in patient outcomes (Rand Health, 2008). The SF-36 contains generic QOL questions that rely on patient self-report commonly used by Medicare and health management organizations for assessment of health outcomes in adult patients (Rand Health). One question from the SF-36 was utilized in the QOL questionnaire that asks participants to rate their general health on a five-point Likert scale. This item was used to determine participants’ self-reported perception of their general health.

Schwab and England Activities of Daily Living Scale

The Schwab and England Activities of Daily Living Scale (S&E) is a standard assessment instrument specifically developed for use with PD patients. In this study, it was used to assess the success of the surgical intervention in terms of improving activities of daily living (ADL) (Schwab & England, 1969). The measure uses a scale that represents the percentage of capacity for daily living such as the ability to stand up, sit down, and walk. A rating system between 100% (complete independence) and 0% (vegetative state) is anchored at 10% increments. A higher score indicates more independent functioning. There are no studies which have directly examined reliability and validity of the Schwab and England Activities of Daily Living Scale. However, reliability and validity have been examined in studies whose primary aim was to assess
characteristics of other rating scales. Results of previous research suggest that the scale has good reliability and validity (Ramaker, Marinus, Stiggelbout, & Van Hilten, 2002). In terms of Quality of Life (QOL), this scale appears to measure the level to which a person with PD is able to function independently.

*Hoehn and Yahr Stage of Disease Scale*

The Hoehn and Yahr Stage of Disease scale (H&Y) was designed as a reproducible measure to assess the level of general functioning in Parkinson’s patients (Hoehn & Yahr, 1967). Level of functioning is measured in six stages ranging from 0 (no signs of the disease) to 5 (wheelchair bound or bedridden.) The H&Y is the standard measure of stage of disease in PD and is used to measure the progression of PD. In terms of quality of life, the H&Y may be an indicator of the current changes in the stage of PD. In one study, the inter-rater reliability between the neurologist, patient and caregiver was found to range from .63 to .73 (McRae, Diem, Vo, O’Brien, & Seeberger, 2002).

Although the H&Y was developed for use by neurologists, patient and caregiver versions have been created (McRae et al.). It is possible that as a result of treatment, we may see a reduction in the degree of disability which could be associated with improved management of motor symptoms.

*Parkinson’s Disease Questionnaire*

The Parkinson’s Disease Questionnaire (PDQ-39) was developed as a Parkinson’s disease specific measure to assess problems such as disturbance in concentration, difficulties in communication, and unusual bodily symptoms which can have a major impact on patients with PD but may not be measured by other more general instruments (Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995). Factor analyses of the PDQ-39 suggest
that there are eight discrete scales that measure (a) Mobility, (b) Activities of Daily Living, (c) Emotional Well-Being, (d) Stigma, (e) Social Support, (f) Cognitions, (g) Communication, and (h) Bodily Discomfort. The PDQ-39 is a self-report measure that is brief and simple in format and can be used in a wide range of health-related settings. As reported in the original development and validation study of the scale by Peto et al. (1995), test-retest reliability for most subscales ranged from .80 to .94, which is considered to be acceptable. The exception was the Social Support subscale which had a Cronbach’s α of .68 (Peto et al., 1995). In a separate examination, Marinus, Ramaker, Van Hilten & Stiggelbout, (2002) also found test-retest reliability problems with the Social Support subscale having a correlation below 0.7 ($r = .68$). The researchers reported that with a sample ($N = 167$) who were retested within three to six days, correlations ($r$) for all the PDQ-39 subscales ranged from .68 to .94 (Marinus et al.) Construct validity was examined by comparing the PDQ-39 factors with the SF-36 subscales with correlations ranging from .34 to .80 (Peto et al., 1995). Marinus et al. found that the PDQ-39 differed from other PD QOL measures in that it includes Cognitions, Communications, and Stigma subscales that measure these domains. Content validity of the PDQ-39 was examined by Marinus et al. who found that over half of the items related to physical features such as walking, motor symptoms and activities. As well, Marinus et al. found that the scale content assesses self-care in detail. Each dimension is scored from 0 to 100 with lower scores indicating better perceived health status.

Subsequent examination of the PDQ-39 found that five subscales were adequate for measuring change in PD patients based upon significant correlations with other measures of health status (Peto, Jenkinson, & Fitzpatrick, 1998). These subscales
included: (a) Mobility, (b) Activities of Daily Living, (c) Emotional Well-being, (d) Stigma, and (e) Social Support. Harrison, Preston, and Blunt (2000) also examined sensitivity to change in the PDQ-39. Measuring a cohort of 67 PD outpatients at baseline, 6, 12, and 18 months, they found that the PDQ-39 summary scale was highly sensitive in detecting a significant \( p < .0001 \) decline in QOL among patients over time. Specifically, they found declines in Mobility, Activities of Daily Living, Social Support, and Stigma subscales contributing to the overall summary index decline. Harrison et al. concluded that the PDQ-39 is an effective tool in measuring symptom change in PD patients and could be helpful in examining possible links between efficacy and effectiveness of PD treatments.

Peto, Jenkinson and Fitzpatrick (2001) addressed the issue of what statistically significant differences in the PDQ-39 could clinically or subjectively mean. Measuring a group of Parkison’s Society members who reported worsening health over a six month period, they found significant \( p < .05 \) differences in the overall summary index score and six out of eight subscales. These subscales include: (a) Mobility, (b) Activities of Daily Living, (c) Emotional Well-being, (d) Stigma, (e) Social Support, and (f) Communication. Changes in Bodily Discomfort and Cognitions were found to be non-significant. Comparing the mean scores at baseline and six month measurement, the authors determined how much of a change in the PDQ-39, between 0 and 100, was indicative of clinically significant change. These values varied between 1.6 to 11.4 for all the subscales and the overall scale. The PDQ-39 has been used to assess QOL in roughly ten prior studies examining QOL of PD patients receiving bilateral STN DBS surgery as discussed in Chapter 2.
Data Analyses

Initially, a Hierarchical Linear Modeling (HLM) or multilevel mixed model of individual change was used to examine potential change in QOL over time. It was hoped that a two level model could be used in which Level 1 modeled time points while Level 2 modeled growth across participants (Radenbush & Bryk, 2002). If successful, this type of analysis could also allow for inclusion of predictors such as age and disease duration. An advantage of attempting this data analysis was that it could involve data modeling that goes beyond examining a linear trend. Based upon the research questions, it is possible that the trajectories of gains and losses are not linear but could be non-linear, indicating initial increases in QOL related to improvement in motor symptoms and then declines over time as the disease continues to progress.

Before data collection began at this follow-up, cursory review of the data set suggested difficulties with missing data. Unfortunately, there was some missing data due to problems with data collection up to 42 months in that some original copies of the QOL questionnaires were sent to an incorrect address and were never recovered. Due to the relatively small sample size (N = 52) and an attempt to avoid additional data loss due to listwise deletion, or deletion of cases due to any missing value, an HLM model was attempted so incomplete cases could be included in the data analysis (Bryk & Radenbush, 1987; Singer & Willlett, 2003). As is common in multivariate data sets, there were few complete cases. Multiple imputation was considered as an appropriate manner for dealing with the missing data in this repeated measures longitudinal data set (Schafer, 1997). However, this consideration was dropped once it was determined that easily accessible software was not available for a longitudinal data set.
Using SAS version 9.1.3, the Mixed procedure (PROC MIXED) was used to attempt the multilevel data model. The typical approach to analyzing data with this method is to initially create simpler models such as examining variation in QOL across multiple occasions of measurement (Radenbush & Bryk, 2002; Singer, 2002; Singer & Willett, 2003). With statistical significance found in these simpler models and with the data model adequately fitting the data, analyses would have proceeded sequentially (Rabenbush & Bryk; Singer, 1998) with a more complex model, allowing an exploration of changes in QOL over time also termed a growth model (Singer, 2002). Non-linear change can be explored within the growth model (Singer & Willett). Once an adequate growth model is found to explain the data, predictors or person-level covariates, such as age and disease duration, could have been added to explain whether variation or differing trajectories of change were related to the predictors (Singer, 2002; Singer & Willett).

Unfortunately, there was not enough power in the sample to complete more complex modeling of the data set. Due to the design of the data analyses, the three research questions followed the sequential multilevel modeling steps described above. It was anticipated that the first research question involving trajectories of QOL change over time would be examined by the growth model. The second and third research questions regarding the relationship between covariates, age and disease duration, and differing QOL trajectories required adequate modeling of the growth model. As a result, non-significance of the growth model and the first research question did not allow an examination of the second and third research questions. Consequentially, a supplemental analysis was undertaken in an attempt to adequately explain the data.
SPSS 15.0 for Windows was utilized to perform the supplemental analyses. These analyses, or data screening, included examination of missing data, outliers, linearity, homoscedasticity and normality among the variables of interest (Tabachnick & Fidell, 2007). Additionally, SPSS 15.0 was used to perform the linear regression analyses and the creation of individual empirical growth plots (Singer & Willett, 2003).

In order to answer the first research question regarding the trajectory of QOL change from pre-surgical measurement to present follow-up, a supplemental linear regression analysis was conducted. The PDQ-39 summary index and the eight subscales were used as outcome variables. Time individually calculated for each participant served as the independent variable (Singer & Willett, 2003). A linear regression analysis was selected to reveal potentially significant relationships between time and QOL. If a statistically significant relationship was found, individual empirical growth plots or a temporally sequenced graph of a participant’s growth record was created (Singer & Willett) to provide preliminary evidence of a potential trajectory of change.

Examination of the second research question involving age as a predictor of differing QOL change trajectories proceeded with a supplemental linear regression analysis. As in the first question, the PDQ-39 summary index and the eight subscales were used as outcome variables. Participants’ age was utilized as a predictor variable. If a statistically significant relationship was found, individual empirical growth plots were created for one participant considered suffering from young-onset PD, younger than age 40 (Schrag et al., 1998) at time of intervention, and one participant considered suffering from older-onset PD, older than age 40 (Schrag et al., 2003) when receiving DBS.
Empirical growth plots were compared to provide preliminary evidence of differing change over time due to age.

Analysis related to the third question of whether disease duration is predictive of differing trajectories of QOL change was undertaken using the linear regression function in SPSS 15.0. QOL measured by the PDQ-39 was used as dependent variables. Disease duration served as the independent variable. Statistically significant correlations between disease duration and QOL were investigated further with individual empirical growth plots. One participant considered to have shorter disease duration under five years (Lang et al., 2006) was compared with a participant with longer disease duration, higher than the average 12 to 15 year disease duration seen among PD patients receiving STN DBS (Lang et al.). This comparison provided preliminary evidence for differing trajectories based on disease duration.
Chapter 4

Results

*Data Collection*

A list of past participants was compiled in May 2008 prior to a visit to the Center for Movement Disorders Surgery, Columbia University and sent to a nurse familiar with the PD patients in this cohort. Because she sees the patients for return follow-up visits, the nurse was able to identify patients who appeared capable of answering the questionnaire. Those known to be deceased or to have developed dementia were excluded from the list of potential participants. Addresses and phone numbers were obtained from the Practice Plan Manager, who further confirmed the status of patients. A total of 45 potential participants were identified. The neurologist assisted in development of the recruitment letter, personalizing it to reflect the doctor-patient relationship between him and the patients. Furthermore, he requested that potential participants become involved in the study.

After receiving IRB approval from the University of Denver and Columbia University Medical Center, data collection began on September 7, 2008 with questionnaire packets sent to the 45 potential participants. After this first round of data collection, ten completed questionnaires were returned. Two potential participants returned the response postcard indicating that they were not interested in participating. Three former participants’ wives contacted the investigator via telephone, return of the questionnaire packet, and a postcard to indicate that their husbands had passed away.
Two packets were returned by the post office indicating that they were “unforwardable.” After checking with the Practice Plan Administrator, it was determined that no further addresses were able to be obtained for these potential participants. After the first round of data collection, 17 of the 45 participants had been accounted for.

A second round of data collection began on October 6, 2008 with questionnaire packets sent to the 28 remaining potential participants. Two completed questionnaires were returned. One was returned as “not forwardable” by the post office. One participant refused participation in the study. One survey was returned by a spouse indicating that the potential participant had passed away. A second spouse emailed the study and indicated that her husband had passed away. The second round of data collection accounted for an additional six participants and overall 23 participants.

A follow-up phone call was made by the investigator to the last known phone numbers provided by the Center for Movement Disorders Surgery, Columbia University, approximately two weeks after the second mailing of the questionnaire packets. One completed survey was returned. Two spouse’s of potential participants contacted the study uncertain of how to proceed. One potential participant’s wife contacted the investigator via phone and stated that she was uncertain whether he would be able to complete the questionnaire competently. She requested that Dr. Ford be contacted to recommend a course of action. A consensus between Drs. McRae and Ford was reached and it was decided that due to the demented condition of her husband, it was requested that she fill out the form to the best of her ability. This questionnaire was received by the investigator and appeared to be adequately filled out. Another potential participant’s wife contacted the investigator by email and reported that she was unhappy about the results of
the surgery and that her husband suffered from dementia and was in a total care nursing home. She was encouraged to fill out the questionnaire on his behalf. This was also received and appeared to be adequately completed. After the follow-up phone call, a total of three additional participants were accounted for.

Overall, there was a 58% response rate to the 45 questionnaires sent with 26 participants replying in some manner to the questionnaire. 16 completed questionnaires (36%) were returned. 3 potential participants refused participation. 5 potential participants were determined to be deceased. 3 questionnaire packets were returned as “not forwardable” by the post office.

Of the 16 responses received for this seven and a half year average follow-up assessment, sample demographics are displayed in Table 1. At pre-surgical measurement, out of 52 potential participants, 28 participants were assessed.
Table 1

Demographics by Wave of Measurement

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<th>Pre-Surgical Measurement</th>
<th>7.5 Year Measurement</th>
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<tr>
<td>Missing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Disease Duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.05</td>
<td>20.57</td>
</tr>
<tr>
<td>SD</td>
<td>5.85</td>
<td>5.68</td>
</tr>
<tr>
<td>Range</td>
<td>2-29</td>
<td>12-28</td>
</tr>
<tr>
<td>Missing</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Time - Years since DBS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>N/A</td>
<td>7.58</td>
</tr>
<tr>
<td>SD</td>
<td>N/A</td>
<td>1.30</td>
</tr>
<tr>
<td>Range</td>
<td>N/A</td>
<td>5.23-8.98</td>
</tr>
</tbody>
</table>

It is possible that missing values for Age and Disease Duration could have been collected from the Neurological Institute at Columbia Presbyterian Medical Center. However, due to time constraints and potential administrative difficulties, these additional data were not collected.

Data Screening –Missing Data

Tabachnick and Fidell (2007) stated that missing data is one of the most pervasive problems in data analysis. In particular, the pattern of missing data is important in
determining the generalizability of results. Oftentimes, a missing data pattern characterized as missing completely at random (MCAR) is hoped for because the pattern is thought to be completely unpredictable and therefore not related to dependent and independent variables. Other patterns such as missing at random (MAR) occur when the pattern is predictable from other values and is considered ignorable because it is unrelated to the outcome variable. A pattern called missing not at random (MNAR) occurs when the missing data pattern is related to the dependent variable and cannot be ignored.

Schafer and Graham (2002) described missing data in longitudinal studies where participants may present for some waves of data collection and not for others, calling this wave non-response. A special case of wave non-response is attrition, where participants leave and do not return to the study. Schafer and Graham also stated that it is not uncommon for subjects to be absent from one wave and then reappear in another. Within this data set, there are patterns of missing data that relate to wave non-response or unit non-response and missing data patterns for observed measurements during waves of data collection or item non-response. The approach to examining patterns of missing data for this longitudinal data set involved looking at patterns of wave non-response and item non-response.

Little (1995) recommended that one should collect as much information as possible regarding the reasons for dropout and incorporate this information in the data analysis. Sources of wave non-response and item non-response appear to involve random and non-random factors within the existing data set. During previous waves of data collection, random factors such as administrative difficulties resulted in missing data with
completed questionnaires sent from Columbia University Medical Center to the wrong address at the University of Denver as well as questionnaires that were not copied in their entirety resulting in partial data collection. For the current wave of data collection, efforts were made to reduce these potential sources of wave and item non-response. These efforts involved: (a) having the questionnaire sent directly to the researcher instead of to Columbia University, (b) the researcher being involved in the photocopying process, and (c) clarifying directions placed in the questionnaire to increase the chances that willing participants would fill out the questionnaire in its entirety. However, there was still item non-response in questionnaires that were filled out by participant’s wives with questions such as whether the participant lacked support from their spouse or partner. It is likely that MAR in the existing data set may relate in part to these random factors. However, there are non-random factors that may contribute to a MNAR pattern of missing data, especially in regards to attrition likely due to the progression of PD.

Prior to this seven and a half year follow-up of the cohort, the data set included a total of eight potential measurements of participants involving measurement pre-surgically, at three months, six months, 12 months, 18 months, 24 months, 36 months, and 42 months. Given a 36% response rate of usable data at this wave of measurement, roughly 7.5 years or 90 months after DBS surgery, it is likely that overall wave nonresponse was related to attrition due to disease progression, cognitive impairment or death. If the pattern of missing data is MNAR, it is considered related to the dependent variable, in this case quality of life, and cannot be ignored. Graham, Cumsille, and Elek-Fisk (2003) stated that when data is MNAR, the causes of missingness are correlated with the variables containing the missing data. Thus, the cause has not been measured.
According to Collins, Schaefer, and Kam (2001), this can result in biased parameter estimates, inflated type I and type II error rates, and degrade confidence intervals. Unfortunately, all of this resulted in an increased risk of reaching incorrect conclusions.

Nonignorable missing data raises unique statistical modeling issues such as those reviewed by Little (1995) involving software for analyzing unbalanced longitudinal data such as SAS Proc Mixed and utilization of a covariate that would be informative and predictive of missing data. Unfortunately, utilization of these techniques generally failed due to power issues related to the small sample size. After reviewing other longitudinal studies examining the quality of life in PD patients who received DBS such as Troster et al. (2003), none appear to have examined the issue of missing data. It is likely that when studying cohorts of PD patients who received DBS over similar periods of time, roughly seven and a half years, similar issues would be found in other longitudinal studies. Although this study was unable to address the issue of non-ignorable missing data as it relates to wave non-response, it is probable that all longitudinal studies examining QOL after DBS with small sample sizes would suffer from similar limitations.

In order to test for patterns of missing data related to item non-response for observed waves of data collection, the Missing Values Analysis (MVA) was completed utilizing SPSS 15.0. Variables of interest selected for missing values analysis involved Gender, Age, Time in days since surgery, Disease Duration, Hoehn and Yahr Stage of Disease Scale rating, Schwab and England Activities of Daily Living Scale rating, overall quality of life as measured by total score on the PDQ-39, and the eight subscales of the PDQ-39: (a) mobility, (b) activities of daily living (ADL), (c) emotional well-being (d) stigma, (e) social support, (f) cognitions, (g) communication, and (h) bodily discomfort.
This analysis was performed with the overall sample that included all participants measured at all nine waves of data collection with each observation treated as an uncorrelated observation and included the sample collected at roughly 7.5 year follow-up.

For the overall sample, the percentage of missing data in the overall sample is displayed in Table 2.

Table 2

Missing Data Percentages in Overall Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>2.0%</td>
</tr>
<tr>
<td>Age</td>
<td>7.9%</td>
</tr>
<tr>
<td><strong>Parkinson's Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>45.5%</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>19.8%</td>
</tr>
<tr>
<td>Schwab and England</td>
<td>6.9%</td>
</tr>
<tr>
<td><strong>PDQ-39</strong></td>
<td></td>
</tr>
<tr>
<td>Overall Quality of Life</td>
<td>13.9%</td>
</tr>
<tr>
<td>Mobility</td>
<td>8.9%</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>3.0%</td>
</tr>
<tr>
<td>Emotional Well-Being</td>
<td>5.9%</td>
</tr>
<tr>
<td>Stigma</td>
<td>1.0%</td>
</tr>
<tr>
<td>Social Support</td>
<td>6.9%</td>
</tr>
<tr>
<td>Cognitions</td>
<td>3.0%</td>
</tr>
<tr>
<td>Communication</td>
<td>4.0%</td>
</tr>
<tr>
<td>Bodily Discomfort</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

According to Tabachnick and Fidell (2007), 5% of missing data in a random pattern from a large data set results in generally less serious missing data problems. As shown in the Table 2, missing data ranged from 1% to 45.5% with the variables of interest in the overall sample. In particular, there is a concerning number of missing data points above 5% among the potential predictor variables such as Disease Duration with 45.5% missing.
and Age with 7.9% missing. Additionally, over 5% of the data were missing in the outcome variable, overall quality of life as measured by the PDQ-39, which had 13.9% missing data. As well, there was over 5% missing data in three (Mobility, Emotional Well-Being, and Social Support) of the eight subscales with the percentage of missing data among the subscales ranging from 1% on the Stigma subscale to 8.9% on the Mobility subscale. The Quality of Life scale is a measure based composed of eight subscales; thus, if any response on the PDQ-39 is missing, the overall aggregate QOL score is not able to be calculated resulting in the much higher percentage of missing data in the PDQ-39 summary index score.

Tabachnick and Fidell (2007) explained that data missing from a small to moderately sized sample such as this one can result in serious problems. This is due to the large impact one missing observation can have upon the overall percentage of missing data. Table 3 displays the percentage of missing data for this wave of data collection, roughly seven and a half year follow-up. The total sample size was very small with 16 responses. As shown in Table 3, one missing observation resulted in a 6.3% missing data and two observations a 12.5% level of missing data.
Table 3

**Missing Data Percentages at 7.5 Year Follow-up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percentage</th>
<th># of Missing Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Age</td>
<td>12.5%</td>
<td>2</td>
</tr>
<tr>
<td><strong>Parkinson's Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>56.3%</td>
<td>9</td>
</tr>
<tr>
<td>Hoehn and Yahr</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Schwab and England</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td><strong>PDQ-39</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Quality of Life</td>
<td>6.3%</td>
<td>1</td>
</tr>
<tr>
<td>Mobility</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Emotional Well-Being</td>
<td>6.3%</td>
<td>1</td>
</tr>
<tr>
<td>Stigma</td>
<td>6.3%</td>
<td>1</td>
</tr>
<tr>
<td>Social Support</td>
<td>6.3%</td>
<td>1</td>
</tr>
<tr>
<td>Cognitions</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Communication</td>
<td>0.0%</td>
<td>0</td>
</tr>
<tr>
<td>Bodily Discomfort</td>
<td>0.0%</td>
<td>0</td>
</tr>
</tbody>
</table>

At present follow-up, there were concerning percentages of missing data for predictor variables, 56.3% for Disease Duration and 12.5% for age. For the PDQ-39, there were missing data (6.3%) in the overall measure of QOL and three of the eight subscales.

According to Tabachnick and Fidell (2007), the next step in the missing data analysis involved constructing a dummy variable consisting of two groups of cases with non-missing values and cases with missing values. An ANOVA of mean differences is run between the two groups. The SPSS 15.0 Missing Value Analysis (MVA) analysis performed this ANOVA with all the variables of interest at a more stringent percentage of missing data (1%) than the 5% recommended by Tabachnick and Fidell, given that the
data set is somewhat small taken as a whole and also at 7.5 year follow-up. Tabachnick and Fidell further stated that if the pattern of missing data is predictable from other variables in the data set such as independent variables, then MAR is suggested and the pattern of missing data can be considered to be ignorable. However, if the pattern of missing data relates to the dependent variable or outcome measure, they suggest examining the effect size of these differences to see if they are potentially statistically significant but realistically meaningless.

There were several independent variables that were significantly related to the pattern of missing data in the overall outcome variable and subscales of the PDQ-39 (see Table 4).

Table 4

*Missing Data ANOVA in Overall Sample*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missingness Variable</th>
<th>Significance</th>
<th>Effect Size ($\eta^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Emotional Well Being</td>
<td>$p \leq .01$</td>
<td>.053</td>
</tr>
<tr>
<td>Gender</td>
<td>Overall Quality of Life</td>
<td>$p \leq .01$</td>
<td>.025</td>
</tr>
<tr>
<td>Schwab and England</td>
<td>Bodily Discomfort</td>
<td>$p \leq .01$</td>
<td>.203</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>Emotional Well Being</td>
<td>$p \leq .01$</td>
<td>.428</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>Social Support</td>
<td>$p \leq .01$</td>
<td>.357</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>Quality of Life</td>
<td>$p \leq .01$</td>
<td>.468</td>
</tr>
<tr>
<td>Dependent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mobility Subscale</td>
<td>Disease Duration</td>
<td>$p \leq .05$</td>
<td>.617</td>
</tr>
</tbody>
</table>

Gender was significantly predictive of the pattern of missing data in the overall measure of Quality of Life ($p \leq .01$) and the subscale Emotional Well Being ($p \leq .01$). The Schwab and England Activities of Daily Living Scale significantly predicted ($p \leq .01$)
missingness in the PDQ-39 Bodily Discomfort subscale. Disease Duration significantly predicted \((p \leq .01)\) missing data in Emotional Well Being and Social Support subscales, as well as the overall measure of Quality of Life as measured by the PDQ-39 Summary Index score. When using stringent type II error criteria at the \((p \leq .01)\) significance level, these findings suggest that the missing data in the overall sample can be characterized as MAR (missing at random) and thus, ignorable. However, when using less stringent criteria \((p \leq .05)\), the missing data analysis is suggestive of a pattern that was MNAR (missing not at random). Furthermore, this missing data pattern was related to the outcome measure. This suggests that there is a systematic relationship of missing data between the PDQ-39 subscale Mobility and Disease Duration. According to Tabachnick and Fidell, this significant t-test implies that the data set has a pattern of missingness that is missing not at random (MNAR) or non-ignorable. Following Tabachnick and Fidell’s recommendation to examine the effect size \(\eta^2\), the SPSS 15.0 Compare Means function was used to produce an estimate. Based upon Cohen’s guidelines for magnitude of effect sizes in behavioral science studies: (a) small \(\eta^2=.01\), (b) medium \(\eta^2=.09\), and large \(\eta^2=.25\) (as cited in Tabachnick & Fidell, 2007), gender related missingness had a small effect size \(\eta^2 < .01\). The S&E effect size \(\eta^2=.20\) was closer to a large effect size and thus estimated to be large. Disease Duration and the PDQ-39 Mobility subscale also had large effect sizes \(\eta^2 > .25\). This implied that the impact of missingness was significant and needed to be addressed with a missing data method such as multiple imputation.

Using SPSS 15.0, a missing variable analysis was conducted on the present, 7.5 year follow-up sample. The pattern of missing data of the independent variable, age, was found to be significantly related \((p \leq .01)\) to the Social Support subscale of the PDQ-39
(see Table 5). This finding implies MAR. However, patterns of missing data on two subscales of PDQ-39, Social Support and Bodily Discomfort, were found to have a systematic relationship with each other suggesting MNAR by the dependent variable. Using the SPSS 15.0 Compare Means function, the effect size ($\eta^2$) was estimated suggesting large effects ($\eta^2 > .25$) for both age and the PDQ-39 Social Support subscale patterns of missingness.

Table 5

**Missing Data ANOVA at 7.5 year follow-up**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missingness Variable</th>
<th>Significance</th>
<th>Effect Size ($\eta^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Social Support</td>
<td>$p \leq .01$</td>
<td>.980</td>
</tr>
<tr>
<td><strong>Dependent</strong></td>
<td>Social Support</td>
<td>$p \leq .01$</td>
<td>.698</td>
</tr>
</tbody>
</table>

Based upon the results of the preceding missing data analyses, Collins, Schafer and Kam (2001) stated that the implications of this pattern of missingness can potentially introduce bias into the quality of life data of PD patients measured in this cohort. In the overall sample, it is possible that participants with longer Disease Duration may not have answered some of the Mobility items on the questionnaire. However, this was speculation. Nevertheless, a potentially interesting finding in that increased mobility is thought to be one of the benefits of DBS surgery as well as a reduction in dopaminergic medication dosage. At current follow-up, a relationship was found between missing responses on the PDQ-39 Social Support subscale and the PDQ-39 Bodily Discomfort
subscale. Once again, this finding pointed to evidence of non-randomness in the pattern of missing data (Tabachnick & Fidell, 2007) and suggested that the cause of missingness had not been measured (Graham et al. 2003). Tabachnick and Fidell stated that although the decision regarding how to deal with missing data is important, the decision is made from among bad alternatives. Given that several of the patterns of missing are statistically significant with large effects sizes, an attempt at utilizing multiple imputation was made to create a complete imputed data set. It was hoped that two analyses could be made, one with missing data and one without missing data so that the results could be compared (Tabachnick & Fidell; D. Russell, personal communication, December 12, 2008).

Tabachnick and Fidell stated that this is particularly important with small data sets and if the results are similar, one can have confidence in them.

**Univariate Outliers**

An exploration of potential outliers was performed utilizing SPSS 15.0 to determine if there were any cases with extreme values that could unduly skew the results of the overall data analysis. Tabachnick and Fidell (2007) suggested that the examination of univariate outliers proceed first as opposed to multivariate outliers due the increased ease in detecting univariate outliers. The exploration began by including all variables of interest from the overall sample: (a) Age, (b) Disease Duration, (c) Gender, (d) Hoehn and Yahr Stage of Disease Scale rating (H&Y), (e) Schwab and England Activities of Daily Living Scale rating (S&E), and (f) overall quality of life as measured by the summary index score on the PDQ-39. Additionally, the eight subscales of the PDQ-39 were also included: (a) Mobility, (b) Activities of daily living (ADL), (c) Emotional Well Being, (d) Stigma, (e) Social Support, (f) Cognitions, (g) Communication, and (h) Bodily
Discomfort. Standardized scores were obtained using SPSS 15.0 Descriptives and checking the box to “save standardized values as variables.” Z scores were plotted using the SPSS Explore function with box plots. Five potential univariate outliers were identified in the overall sample by examining box plots with results displayed in Table 6.

Table 6

*Outliers in Overall Sample*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Outliers</th>
<th>Participant ID</th>
<th>Measurement Occasion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Independent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>1</td>
<td>330</td>
<td>Pre-surgical</td>
</tr>
<tr>
<td><strong>Dependent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emotional Well-Being</td>
<td>1</td>
<td>301</td>
<td>Pre-surgical</td>
</tr>
<tr>
<td>Stigma</td>
<td>1</td>
<td>301</td>
<td>Pre-surgical</td>
</tr>
<tr>
<td>Social Support</td>
<td>1</td>
<td>302</td>
<td>Pre-surgical</td>
</tr>
<tr>
<td>Overall Quality of Life</td>
<td>1</td>
<td>301</td>
<td>Pre-surgical</td>
</tr>
</tbody>
</table>

In terms of independent variables, participant 330 had one potential outlier, age. Among the dependent variables, Participant 301 appeared to have the most potentially outlying scores on the Emotional Well Being, Stigma subscales, as well as overall QOL measured by the PDQ-39 Summary Index score at pre-surgical measurement. Participant 302 had one potentially outlying score at baseline measurement involving the PDQ-39 Social Support subscale.

Tabachnick and Fidell (2007) proposed four factors that contribute to the presence of outliers: (a) incorrect data entry, (b) failure to specify missing codes, (c) participants not being a member of the intended population sampled, and (d) the distribution of the variable has more extreme values than a normal distribution. In terms of incorrect data
entry, the original questionnaires for participants 301 and 302 were reviewed and their PDQ-39 scores were verified as being entered correctly into the database. Independent variable outliers generally related to demographics and were confirmed as being correct. Participant 330 was one of the youngest members of the population sampled, receiving DBS in their early 30’s, and accounting for the extreme value on age.

In order to ensure that missing data codes were specified, the database was re-created, despite the existence of data sets which included all longitudinal data up to 7.5 year measurement, to ensure that all missing data were coded as missing. Although there certainly could be errors in this process, the researcher is fairly confident that all missing data were coded as missing.

In regard to participants not being part of the intended population, inclusion and exclusion criteria for recipients of DBS surgery were determined by the Center for Movement Disorders Surgery team at the Neurological Institute at Columbia University Medical Center. Criteria included existence of idiopathic Parkinson’s Disease and the presence of disabling motor fluctuations despite optimal medical management (Ford et al., 2004). Thus, it is highly likely that participants are members of the intended population.

The fourth potential factor identified by Tabachnick and Fidell, (2007) is that the population may have more extreme values than a normal distribution. An examination of possible factors leading to extreme pre-surgical QOL subscale and summary index scores for participants 301 and 302 are being younger, both were in their 40’s, and having a younger age of PD onset. These factors were identified by Voon et al. (2008) as being significantly associated with attempted suicides in a multi-center study examining PD
patients who received STN DBS. Additionally, both participants were not sampled at this follow-up due to death so it is likely that they were suffering from low QOL pre-surgically. Higher scorers on the PDQ-39 indicate more difficulties related to QOL, and both participants never responded to subsequent follow-ups suggesting that their QOL may not have improved.

**Univariate Normality**

According to Tabachnick and Fidell (2007), multivariate normality can be partially confirmed through an examination of univariate normality, linearity, and homoscedasticity. Violations of normality may influence the robustness of significance tests leading researchers to incorrectly reject the null hypothesis. Univariate normality was examined to determine whether transformations were appropriate and also whether to test for multivariate normality. Skewness and Kurtosis were checked using SPSS 15.0 Frequencies function. Tabachnick and Fidell recommended screening on continuous variables. Continuous variables of interest included the standardized scores for: (a) Age, (b) Time since intervention in days, (c) Disease Duration, (d) Schwab and England Activities of Daily Living Scale rating, (e) overall quality of life as measured by total score on the PDQ-39. Additionally, the PDQ-39 subscales: (a) Mobility, (b) Activities of Daily Living (ADL), (c) Emotional Well Being (d) Stigma, (e) Social Support, (f) Cognitions, (g) Communication, and (h) Bodily Discomfort were also screened.

Tabachnick and Fidell stated that when a distribution is normal the values of skewness and kurtosis are zero. Table 7 displays the SPSS 15.0 output for skewness and kurtosis based on the z-score for all potential variables of interest. In order to test whether these values vary significantly from zero, Tabachnick and Fidell suggested calculation of z-
scores by dividing the skewness value over the standard error of skewness. The same procedure was used to calculate $z$-scores for kurtosis. These $z$-scores are compared with a $z$-table. Tabachnick and Fidell recommended the use of conservative statistical significance levels $p \leq .01$ or $p \leq .001$ to evaluate the significance of skewness and kurtosis with small samples. They stated that this is because the standard of error of both skewness and kurtosis decrease with larger samples, thus minor deviations from normality are likely to reject the null. Small samples are less prone to minor deviations, creating statistically significant deviations from normality. Thus, significance at the $p \leq .01$ level was used to determine significant detractions from normality with a $z$-score $\leq +/- 2.33$.

Table 7

*Univariate Normality in Overall Sample*

<table>
<thead>
<tr>
<th>Continuous Variable</th>
<th>Skewness</th>
<th>Z-Score</th>
<th>Kurtosis</th>
<th>Z-Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-.92</td>
<td>-3.54</td>
<td>.95</td>
<td>1.86</td>
</tr>
<tr>
<td><strong>Parkinson's Disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease Duration</td>
<td>.60</td>
<td>1.78</td>
<td>-.010</td>
<td>-.02</td>
</tr>
<tr>
<td>Schwab and England</td>
<td>-.60</td>
<td>-1.76</td>
<td>-.34</td>
<td>-.49</td>
</tr>
<tr>
<td><strong>Time – Days Since Intervention</strong></td>
<td>1.39</td>
<td>5.54</td>
<td>.85</td>
<td>1.70</td>
</tr>
<tr>
<td><strong>PDQ-39</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Quality of Life</td>
<td>.63</td>
<td>2.33</td>
<td>.46</td>
<td>.87</td>
</tr>
<tr>
<td>Mobility</td>
<td>-.11</td>
<td>-.42</td>
<td>-.65</td>
<td>-1.25</td>
</tr>
<tr>
<td>Activities of Daily Living</td>
<td>.79</td>
<td>3.16</td>
<td>-.02</td>
<td>-.04</td>
</tr>
<tr>
<td>Emotional Well-Being</td>
<td>.25</td>
<td>.96</td>
<td>-.47</td>
<td>-.92</td>
</tr>
<tr>
<td>Stigma</td>
<td>.64</td>
<td>2.56</td>
<td>-.73</td>
<td>-1.46</td>
</tr>
<tr>
<td>Social Support</td>
<td>.92</td>
<td>3.54</td>
<td>.13</td>
<td>.25</td>
</tr>
<tr>
<td>Cognitions</td>
<td>.34</td>
<td>1.40</td>
<td>-.05</td>
<td>-.10</td>
</tr>
<tr>
<td>Communication</td>
<td>.20</td>
<td>.80</td>
<td>-.55</td>
<td>-1.10</td>
</tr>
<tr>
<td>Bodily Discomfort</td>
<td>.34</td>
<td>1.36</td>
<td>-.51</td>
<td>-1.02</td>
</tr>
</tbody>
</table>
Among potential independent continuous variables, age was significantly \((p \leq .01)\) negatively skewed, which is an expected finding given that Parkinson’s disease tends to afflict older adults and is likely a characteristic departure from normality among many cohorts of PD patients who received DBS surgery worldwide. Time was significantly \((p \leq .01)\) positively skewed. Factors influencing this finding likely related to a greater number of participants being measured pre-surgically reflecting motivation for the surgery and as time went on, loss of participants due to disease progression or attrition.

In terms of continuous outcome variables, overall QOL measured by the PDQ-39 summary index was positively skewed \((p \leq .01)\). This could reflect a response bias among participants in that those who were doing better in terms of QOL (a lower score reflects better QOL), tended to respond. Among the PDQ-39 subscales, three were positively skewed \((p \leq .01)\): (a) Activities of Daily Living (ADL), (b) Social Support, and (c) Stigma. Positive skew in PDQ-39 ADL and Stigma subscales could have been related to DBS surgery where recipients have reported improved motor functioning (Krack et al. 2003; Schupbach et al. 2005).

**Linearity**

Tabachnick and Fidell (2007) stated that the linearity assumption involves examining whether a straight line relationship exists between two variables. This is important because a Pearson correlation captures linear relationships and if there is a significant non-linear relationship among variables, it is not captured in the analysis. Analysis of linearity is also important in helping to predict whether there is a potential trajectory among the variables of interest in this study. Tabachnick and Fidell explained that at times the relationship between variables may not be linear. Furthermore, they
stated that linearity is typically assessed by examining bivariate scatterplots between pairs of variables. If linearity is present, the scatterplot will be oval-shaped. However, they indicated that examining bivariate scatterplots is like “reading tea leaves,” especially with small samples, which is certainly the case with this study. They recommend using skewness statistics from the normality analysis to determine which variables were likely to depart from linearity. Using these criteria, the variables with significant skewness ($p \leq .01$) that potentially needed to be examined among the independent variables were age and time. Although time was typically measured in days for many analyses in this study, time was graphed as days and years. Since the bivariate scatterplots were identical, time was expressed as years for easier examination. For the dependent variables, four possible PDQ-39 outcome measures could have been examined: (a) the overall Quality of Life summary index, (b) the Activities of Daily Living subscale, (c) the Stigma subscale, (d) the Social Support subscale. In order to examine these variables with bivariate scatter plots, two variables were chosen and plotted. Because all possible combinations of variable pairs among all six possible variable would have resulted in 36 potential scatter plots to examine, Tabachnick and Fidell further suggested considering pairs of variables that may have true non-linearity. Thus, the bivariate relationships selected for comparison were based upon potential relationships of interest: (a) time and overall QOL measured by the PDQ-39 summary index, (b) age and the PDQ-39 summary index, (c) age and the PDQ-39 Stigma subscale. Figures 1 displays the SPSS 15.0 output using the Scatter/Dot function to examine the potential linear relationship between Time and PDQ-39 summary index measuring overall QOL.
As stated previously, an oval shape in the bivariate scatterplot suggests linearity. It appears that the relationship between Time and Overall QOL may not be linear as shown in Figure 1. Furthermore, Figure 1 suggested a weak relationship between the variables.

A bivariate scatterplot was created for Age and Overall QOL. Results displayed in Figure 2 suggested the data are non-linear and had a weak relationship between each other.
Figure 2

Linearity Bivariate Scatterplot: QOL by Age

The final examination of linearity involved examining Age and the PDQ-39 Stigma subscale displayed in Figure 3 because the variables had a weak relationship between each other.
Homoscedasticity

According to Tabachnick and Fidell (2007), the assumption of homoscedasticity, or homogeneity of variance, presumes that the variability in scores for one continuous variable is nearly the same as the variability of another continuous variable. In essence, the relationships between variables are consistent in variability across all levels of the
variables. Homoscedasticity was evaluated by examining bivariate scatterplots. If homoscedasticity is present, the scatterplot is generally the same width across all values of the variables with some bulging towards the middle. Therefore, heteroscedasticity, or lack of homogeneity, is evident when there is no consistent width in the scatterplot.

Referring to the scatterplots in Figures 1, 2 and 3, among all three variable pairs plotted, heteroscedasticity appeared present due to lack of consistent width. Tabachnick and Fidell stated that heteroscedasticity is not fatal in that it does not invalidate an analysis with ungrouped data, but can weaken it. They explained that the linear relationship between variables may have been captured by the analysis, but that predictability is improved when heteroscedasticity is accounted for. In the case of this analysis, it is possible that lack of homogeneity of variance resulted from overall QOL and Stigma being better predicted by a multivariate approach.

**Variable Transformations**

Tabachnick and Fidell (2007) stated that although data transformations are solutions to outliers and deviations from normality, linearity, and homoscedasticity, they do not recommend their automatic use for all violations. They explained that data analysis results from transformed variables can be difficult to interpret, especially if the variables are in commonly understood units. For example, in this study a transformation of the variable age that has a moderate positive skew could be transformed by its square root; however, the square root of age would be difficult to interpret. The authors do recommend transforming variables when the scale of a variable is somewhat arbitrary. Although the PDQ-39 scores appear somewhat arbitrary at first glance, Jenkinson, Fitzpatrick and Peto (1998) stated that a score of 0 equates to “no problem at all” whereas
a score of 100 equals a “maximum level of problem.” It seemed difficult to interpret the meaning of the scores between these ranges; for example, the difference between a score of 80 compared to a score of 90. During the development of the PDQ-39, the instrument was found to be consistent with existing clinical measures such as the Hoehn and Yahr Stage of Disease scale with mean scores of the subscales corresponding to stages on the Hoehn and Yahr scale. Harrison, Preston, and Blunt (2000) found the PDQ-39 was able to significantly \( p < .0001 \) measure decline among 67 PD outpatients. Peto, Jenkinson, and Fitzpatrick (2001) also determined minimally important differences in the PDQ-39 subscales, reporting values for the smallest score changes thought to be subjectively meaningful to PD patients. Given these findings, it was decided that none of the variables could be transformed without losing their interpretive quality. Thus, none of the variables were transformed.

**Multivariate Outliers**

According to Tabachnick and Fidell (2007), the examination of potential multivariate outliers among continuous variables ensues once univariate outliers have been examined and the decision to transform variables has been made. Multivariate outliers are instances of unusual combinations of scores based upon two or more variables. They recommended the use of Mahalanobis distance that typically examines the distance of a data point from a centroid. However, they cautioned that recent research has suggested that these methods are not completely reliable. Therefore, results need to be examined cautiously. These potential outliers involved all continuous variables of interest: (a) Age, (b) Time since intervention in days, (c) Disease Duration, (d) Schwab and England Activities of Daily Living Scale rating, and (e) overall quality of life as
measured by total score on the PDQ-39. Additionally, the eight subscales of the PDQ-39: (a) Mobility, (b) Activities of Daily Living (ADL), (c) Emotional Well Being (d) Stigma, (e) Social Support, (f) Cognitions, (g) Communication, and (h) Bodily Discomfort were also included in the multivariate outlier examination. The SPSS 15.0 Regression function was utilized to create Mahalanobis distance values. As suggested by Tabachnick and Fidell, the SPSS 15.0 Residuals subcommand was used to print out cases with the highest ten Mahalanobis distance values. Table 8 displays the SPSS output.

Table 8
Largest Mahalanobis Distance

<table>
<thead>
<tr>
<th>Ranking of Largest Mahal. Distance</th>
<th>Participant ID</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>341</td>
<td>22.37</td>
</tr>
<tr>
<td>2</td>
<td>301</td>
<td>22.01</td>
</tr>
<tr>
<td>3</td>
<td>350</td>
<td>21.86</td>
</tr>
<tr>
<td>4</td>
<td>330</td>
<td>21.79</td>
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<tr>
<td>5</td>
<td>326</td>
<td>20.46</td>
</tr>
<tr>
<td>6</td>
<td>341</td>
<td>19.41</td>
</tr>
<tr>
<td>7</td>
<td>319</td>
<td>19.40</td>
</tr>
<tr>
<td>8</td>
<td>307</td>
<td>18.81</td>
</tr>
<tr>
<td>9</td>
<td>354</td>
<td>18.46</td>
</tr>
<tr>
<td>10</td>
<td>325</td>
<td>17.78</td>
</tr>
</tbody>
</table>

Tabachnick and Fidell recommended using a conservative probability estimate ($p < .001$) for the Chi Square ($\chi^2$) value to indicate whether a case is a statistically significant outlier. The degrees of freedom ($df = 13$) for the Chi Square ($\chi^2$) value is usually equivalent to the number of continuous variables of interest. Examining critical values of Chi Square ($\chi^2$) value from a table available at the back of most statistics texts, in this case Tabachnick and Fidell’s text, the critical Chi Square ($\chi^2$) value Mahalanobis
distance for 13 degrees of freedom (\(df = 13\)) and a statistical significance level (\(p < .001\)) equaled 34.53. Because there was multicollinearity between the overall PDQ-39 Summary Index score and the eight subscales that produce the aggregate index score, a more stringent test using 12 degrees of freedom (\(df = 12\)) yielded a critical Chi Square (\(\chi^2\)) value of 31.26. Comparing the highest values in Table 8, none of the Mahalanobis distance values reached statistical significant (\(p < .001\)) and suggested no multivariate outliers among the continuous variables of interest in the data set.

Data Screening – Summary

Overall, the data screening analysis suggested the data set had difficulties with missing data that potentially affected the generalizability of results from this study. There was a wide range of missingness ranging between 1 – 46% among the variables of interest. Random factors contributing to missingness were likely to involve disease progression, age-related cognitive decline, or dissatisfaction with surgical outcome. Additionally, missingness could have related to non-random factors such as difficulties with data collection and not overcoming administrative issues such as contacting staff at the Neurological Institute at Columbia University Medical Center for Age and Disease Duration. Given that the data set was small (\(n = 16\)) for this period of follow-up, the percentage of missing data was problematic because the impact of one missing value increased the percentage of missing data to about 6%, a potentially concerning level of missing data.

The pattern of missingness was Missing Not At Random (MNAR), suggesting the pattern was related to the dependent variable, QOL as measured by the PDQ-39. In the overall sample, analyses suggested a systematic relationship of missing data between the
PDQ-39 Mobility subscale and Disease Duration that was significant ($p < .05$) and had a large effect size ($\eta > .25$). Examining missingness at this measurement, Social Support and Bodily Discomfort PDQ-39 subscales were found to have a systematic relationship with each other that was significant ($p < .01$) and had a large effect size ($\eta^2 > .25$). MNAR resulted in potentially biased parameter estimates, inflated Type I and Type II error rates, degraded confidence intervals, and overall, an increased risk of reaching incorrect conclusions resulting from bias in the data set (Collins et al., 2001). It is possible that other studies following cohorts of PD patients who received DBS for up to seven and a half years may suffer from similar limitations and potential biases.

An analysis of univariate outliers revealed that two participants had outlier scores on subscales of the dependent variable, QOL as measured by the PDQ-39. At time of measurement, both of these participants were in their 40’s and suffered from early onset of PD which could account for their extreme scores.

Several continuous variables violated the assumption of univariate normality, resulting in significant positive and negative skewness as well as negative kurtosis. These included: (a) age, (b) time, (c) the PDQ-39 Summary Index, and three PDQ-39 subscales: Activities of Daily Living, Social Support, and Stigma. Some of these violations could potentially be explained by the longitudinal design of the study and the sample. We would expect to see skewness of age and time. Despite six variables of interest violating normality, a decision was made not to transform the variables’ distributions due to the difficulty in interpreting any significant results of variables that were measured in commonly used scales of measurement.
Variables that showed evidence of being non-normal were examined for linearity among relationships of interest. It appeared that the variables were not related to each other.

Homogeneity of variance, or homoscedasticity, was examined among these same variables in the relationships stated above and this assumption was violated. This finding potentially weakens the analysis but does not invalidate it. Significant multivariate outliers were not found when examining Mahalanobis distance among the variables of interest.

Thus, preliminary data screening suggested that the data set has a high degree of missing data which is missing not at random (MNAR), with the existence of univariate outliers, and violations of the assumptions of normality, linearity, and homoscedasticity. However, it is likely that other studies that follow cohorts of PD patients who received DBS at 7.5 year follow-up may suffer from similar data set difficulties in that some of these “weaknesses” are inherent in the population and are likely common limitations when following a cohort for this extended period of follow-up.

*Trajectory of Change Over Time*

Non-significant change over time was found in the overall sample using SPSS 15.0 with a linear regression model. Table 9 displays the results of the overall inferential test. Findings were non-significant, suggesting that we cannot reject the null hypothesis that the correlation between the IV, time represented in days, and the DV, overall quality of life as measured by the PDQ-39, was zero.
Table 9

Regression Inferential Test: Time and QOL

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>60.319</td>
<td>1</td>
<td>60.319</td>
<td>0.467</td>
<td>.496(a)</td>
</tr>
<tr>
<td>Residual</td>
<td>10985.789</td>
<td>85</td>
<td>129.245</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11046.107</td>
<td>86</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Predictors: (Constant), Days_corrected
b Dependent Variable: QOL

Non-significance of the inferential test suggests that we cannot interpret the beta weights of the regression coefficients because they are essentially meaningless. This suggested that change over time was non-significant for changes in the QOL from pre-surgical evaluation to seven and a half year follow-up. However, when conducting an exploratory analysis of the data by creating an empirical growth plot, described by Singer and Willett (2003) as a temporally sequenced graph of a participant’s empirical growth record, curvilinear change is suggested, as seen in Figure 4, which was created using the Chart Builder function in SPSS 15.0. This plot represented the change across time for one participant who had four data points or occasions of measurement including pre-surgical measurement and measurement at this follow-up. Other characteristics of this participant involved being slightly older than the 40 to 60 year old average DBS recipient (Lang et al., 2006) but within the average disease duration of 12 to 14 years (Lang et al.) at intervention. When measured at this follow-up, the participant had one of the highest multivariate outlier values of Mahalanobis distance. However, this value was non-significant.
Willett (1997) stated that modeling non-linear change requires more complex mathematical models with additional waves of data needed so that the model can ultimately fit. He further suggested that non-linear growth models require at least five waves of data. As seen in Table 10, this data set only contained one participant with five waves of data, and this participant did not have pre-surgical data; thus, baseline level of
QOL was not established. For the overall sample, including all waves of measurement, the number of observations ranged from one to five.

Table 10

Sample Size by Measurement Occasions

<table>
<thead>
<tr>
<th>Measurement Occasions</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>51</strong></td>
</tr>
</tbody>
</table>

In the overall sample, 20 participants had one occasion of measurement, 17 had two occasions, 11 had three, two had four and one had five occasions of measurement. Singer and Willett (2003) stated that there can be problems with modeling change if a large number of participants have too few waves of measurement. In this sample, nearly 73% (37 participants) of the sample had one and two waves of measurement which is inadequate for measuring a growth model. Roughly 6% of the participants had four or more waves of measurement, giving any potential non-linear analysis a sample size of three. Although the individual empirical growth plot (Figure 4) suggests the existence of curvilinear change among participants in the sample, it is difficult to determine if this range of change is significant both statistically and/or clinically. According to Crosbie (1993), visual inference of single subject data can be potentially overly lenient and statistical procedures are technically demanding and require more observations than typically obtained. From a clinical perspective, Peto, Jenkinson and Fitzpatrick (2001), the creators of the PDQ-39, provided some guidelines. They examined the smallest
change between PDQ-39 scores that were subjectively meaningful to a sample of 800 members of the Parkinson’s Disease Society in the UK. They found that minimally important differences depended on the subscale. For the PDQ-39 Summary Index or overall QOL score, a change of 1.6 points was found to represent clinically significant change. In Figure 4, the participant had a pre-surgical QOL score of 62.05 that had improved to 49.47 at first measurement at 24.3 months or approximately two years. Using Peto, Jenkinson and Fitzpatrick’s (2001) criteria, this change of about 12 points was thought to be clinically significant. Figure 4 also displayed a sustained difference of 3.59 between baseline measurement and this measurement, 105 months or roughly nine years, that was also considered clinically significant. Another method of confirmation of clinically significant QOL change could have involved clinical interviews with participants. However, this method of investigation was not utilized in this study. Thus, the empirical growth plot for one participant (Figure 4) suggested curvilinear change which the study is unable to model given the limitations of the data set and the requirements of a larger sample of participants measured at three to four occasions of measurement needed to perform this mathematically complex HLM model.

Rationale for HLM Model

The proposed analysis involved multilevel modeling with the use of SAS Proc Mixed under SAS version 9.1.3. For this cohort of PD patients who received DBS surgery at the Center for Movement Disorders Surgery at Columbia Presbyterian Medical Center in New York, New York, there were a potential maximum of nine longitudinal measurements for all participants. These waves of measurement include pre-surgical and eight possible measurements post-surgically at 3, 6, 12, 18, 24, 36, 42 months and current
assessment, nearly an average of 91 month follow-up or approximately seven and a half years. Given the possibility of up to nine waves of measurement, it seemed possible to use Hierarchical Linear Modeling (HLM) to examine this repeated measures data set. This method was chosen instead of a repeated measures analysis of variance (ANOVA) due to the potential of the data set being unbalanced, meaning all participants did not have the same number of repeated observations. According to Kenny, Bolger, and Kashy (2002), the greatest limitation of using repeated measures ANOVA is the requirement for balanced data or the need for all participants to have the same number of observations. Kenny et al. explained that data sets in repeated measures designs are often not balanced due to missing observations from some participants and the nature of the research design. These reasons appear to be the case with the present data set. Given that the study attempted to collect data from participants who suffer from a neurodegenerative disease, it was likely that there would be missing data, especially with participants whose disease processes may be moving at different rates. Those participants with a faster disease process rate may have had fewer observations than those with a slower disease process. In addition, Kenny et al. explained that even if the number of observations were equal among participants, the distribution of each predictor variable, continuous and categorical, needed to be the same for each participant. For example if the Hoehn and Yahr were used as a predictor, there would need to be the same number of observations in each category for each person (Kenny et al.). This assumption was highly unlikely with this sample. Kenny et al. further argued that HLM models provide a potential solution to the limitations of repeated measures ANOVA, in particular being able to handle unbalanced designs and designs with continuous variables.
In addition to overcoming the restrictions of repeated measures ANOVA, HLM models can be appropriate for measuring change. Willett (1997) stated that the measurement of change is important in psychology when people change in interesting ways. In this case, this study attempted to measure potential change as the result of DBS surgery. Willett explained that change can be documented by repeatedly measuring each person over extended periods of time. A sample of people followed carefully over time with multiple waves of data collected at sensibly spaced intervals is recommended. Willett’s definition of “sensible” depends on the hypothesized trajectory of change. He stated that if the variable of interest is changing steadily and smoothly over time, three to four widely spaced measurements per participant could be sufficient to capture the shape and direction of change. Willett proposed that if the trajectory of change is complex, many more closely spaced measurements may be required. The difficulty appeared to be sufficiently hypothesizing the change and knowing when to begin making more closely spaced measurements, that is, knowing when change becomes more complex.

Singer and Willett (2003) further proposed that HLM modeling can adequately handle design issues intrinsic to a longitudinal study resulting in more complex data sets such as irregularly spaced waves of data collection, number of observations per participant, and variation in spacing of waves across participants. They explained that participants in a longitudinal study can have their own data collection schedule with the number of waves varying without limit between individuals. Given this flexibility, HLM appeared to be an appropriate tool for data analysis.

Unfortunately, the researcher did not examine the total number of observed measurements per participant in the existing data set that included waves of measurement.
from pre-surgical evaluation to 42 month follow-up. If the researcher had, the dissertation proposal involving the examination of a potential trajectory, non-linear, change would not have been proposed. It was not until data had been collected at the current follow-up and the data set was converted from a person-level data set to a person-period data set that it became obvious that there may not have been enough observations to model non-linear change. Singer (2002) explained that a person-level data set involves each participant having one record and that multiple variables are used to record data for each occasion of measurement. In contrast, in a person-period data set each participant has multiple records with a record for each occasion of measurement. Once this conversion was completed after data collection, it became apparent that there were fewer waves of measurement per participant than anticipated. Nevertheless, an attempt was made to complete the SAS PROC MIXED analysis.

SAS Proc Mixed Analysis

The SAS PROC MIXED analysis was conducted using SAS version 9.1.3 and followed analyses suggested by Singer and Willett (2003) and Singer (2002). SAS data sets were prepared and issues related to SAS programming such as entering missing data, properly calculating dates, properly displaying output in MS Word and other basic issues were learned by consulting Cody’s (2007) SAS programming text. Principles learned from Cody’s text were applied during the SAS analysis. Additionally, a SAS website titled “Resources to help you learn and use SAS” (University of California, Los Angeles, Academic Technology Services, Statistical Consulting Group, n.d.) was invaluable and assisted the researcher in learning other SAS basics.
Singer described the first step of the individual growth model as creating a person-period data set. The current data set was formatted at what she described as a person-level data set where each person has one record and there are multiple variables to record data at each measurement occasion. Conversion to a person-period data set involved changing the data so that each person had multiple records with each record representing an occasion of measurement. Additionally, this data set format is needed for SAS PROC MIXED to analyze an individual growth model. Singer and Willett noted that although longitudinal studies seek to measure participants on an identical set of occasions, the reality is that actual measurement occasions end up differing. Thus, all participants ultimately have their own data collection schedule and multilevel modeling via SAS PROC MIXED is able to handle this variation in measurement. Singer and Willett argued that using participants’ unique data collection schedules to represent the metric time produces more precise trajectories. For this study, periods of measurement were determined by calculating the number of days since surgery; once the days had been calculated, that number was divided by 30 to calculate the number of months since DBS surgery. Number of years since DBS surgery was calculated by dividing by 12. For descriptive statistics of the metric used for time, Time - Years since DBS, see Table 1. Singer and Willett stated that once the spacing of waves is allowed to vary across individuals, allowing the number of measurements to vary as well is a small step called an “unbalanced” data set. This was the case in this study with Table 10 displaying the variability in the number of measurement occasions across the overall sample.
Singer (2002) recommended beginning the analysis with an unconditional means model in which the variation of quality of life (PDQ-39) is explored across multiple occasions of measurement. She explained that this can be represented by equation 1:

\[ Y_{ij} = \mu + \alpha_j + r_{ij} \]  

(1)

\(Y_{ij}\) represents the value of quality of life for individual \(j\) on the \(i^{th}\) occasion of measurement. Singer further stated that this model does not measure the systematic variation in QOL over time but simply the extent to which QOL varies. In equation 1.1, \(\mu\) represents the grand mean of QOL across individuals and occasions of measurement, \(\alpha_j\) signifies the deviation of individual \(j\) from the grand mean, and \(r_{ij}\) represents random error associated with individual \(j\) on the \(i^{th}\) occasion of measurement. Table 11 displays the SAS PROC MIXED output of the unconditional means model.

**Table 11**

SAS PROC MIXED: Unconditional Means Model

<table>
<thead>
<tr>
<th>Iteration History</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iteration</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>
According to Singer, the minimum number of iterations for PROC MIXED is two, with longer convergence occurring for data sets that include missing data and are unbalanced. For this data set, convergence occurred in three iterations, which seems acceptable. In examining the “Solution for Fixed Effects,” the estimate of 55.76 tells us that the average participant had an average QOL score of 55.76 across all occasions of measurement.

Singer explained that if all participants in the sample were measured on equal numbers of occasions, the estimate would represent the average score for all participants in the sample or the grand mean, \( \mu \), in equation 1. However, since the sample in this study
involved participants measured at differing numbers of occasions, Singer stated that this estimate becomes an average of person-level averages and is no longer the average of individual scores. In essence, the estimate is the mean of the average scores for each unique participant with their unique data collection schedules. The “Covariance Parameter Estimates” revealed the random effects estimates of 75.14, representing the variation that occurs between persons, and 58.97 representing the variation occurring within persons. In addition, according to the $z$-test, both appear to differ significantly from 0. This suggests that there is significant variation between participants in QOL across time and that participants in this study differed significantly in QOL over time. Given the outcome of this unconditional means model, results suggested that it would be worthwhile to try the next model, the unconditional linear growth model.

According to Singer (2002), the next model, the unconditional linear growth model, allowed examination of systematic changes in QOL over time and is represented by equation 2.

$$Y_{ij} = \pi_{0j} + \pi_{1j}(\text{time})_{ij} + r_{ij}$$

Singer stated that this model differs from the unconditional means model in three ways. First, the model includes the variable, time, to represent systematic linear change in QOL over time, adding a fixed effect and allowing the postulation that participants’ value of QOL varies linearly over time; in essence, the examination of intercept. Second, an
additional random effect is added to the model which hypothesized the rate of growth or change in QOL varied across individuals, also called “slope.” Finally, as a result of allowing the slopes and intercepts to vary across individuals and by producing a covariance matrix, the model allowed examination of the function of the correlation between intercepts and slopes. For this study, the unconditional linear growth model began to address the hypothesis that there is a trajectory of change in QOL of PD patients who received DBS and appeared to be an appropriate analysis for attempting to answer the hypotheses of this study. However, Singer raised the issue of re-centering the time predictor so that the intercept describes the value of QOL at a meaningful point in time. Singer and Willett (2003) addressed this issue more thoroughly by discussing other methods of centering the time variable depending on the focus of the analysis. Generally, the focus of re-centering time involves having the intercept correspond with a participant’s true initial status. In the case of this study, true initial status involved participants’ QOL at pre-surgical measurement. Singer and Willett suggested selecting a sensible initial starting point that involved selecting an intercept that is meaningful for the process the study is seeking to examine. By selecting different intercepts, the anchor point of the trajectory changes resulted in a change of the parameter estimates for intercept and its interpretation. In particular, this involved looking at a different elevation of the anchor point of change over time. Thus, re-centered time at the end point of the study allowed examination of the final status of participants’ QOL. This is of interest because the study sought to examine a trajectory of change over time that was ultimately interested in QOL outcome at long-term follow-up. Thus, Singer and Willett suggested taking the value for time and subtracting it from the longest measurement for time in the
study. Examining the variable for time, Time - Years since DBS, in Table 1, the longest time length was 8.98 years. The time variable was centered on final status by subtracting each value for time from 8.98. Results of the unconditional linear growth model are displayed in Table 12.

Table 12
SAS PROC MIXED: Unconditional Linear Growth Model

<table>
<thead>
<tr>
<th>Iteration History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iteration</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

Convergence criteria met.

<table>
<thead>
<tr>
<th>Covariance Parameter Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cov Parm</td>
</tr>
<tr>
<td>UN(1,1)</td>
</tr>
<tr>
<td>UN(2,1)</td>
</tr>
<tr>
<td>UN(2,2)</td>
</tr>
<tr>
<td>Residual</td>
</tr>
</tbody>
</table>
Table 12 (continued)

SAS PROC MIXED: Unconditional Linear Growth Model

<table>
<thead>
<tr>
<th>Fit Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2 Res Log Likelihood</td>
</tr>
<tr>
<td>AIC (smaller is better)</td>
</tr>
<tr>
<td>AICC (smaller is better)</td>
</tr>
<tr>
<td>BIC (smaller is better)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Null Model Likelihood Ratio Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>DF</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Solution for Fixed Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Intercept</td>
</tr>
<tr>
<td>TimeC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type 3 Tests of Fixed Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>TimeC</td>
</tr>
</tbody>
</table>

The output indicated that the model converged in six iterations which was acceptable. Examining the fixed effects under the “Solution for Fixed Effects” section, it was found that the value for “Intercept” indicated that the average QOL at final status, in this case at roughly 7.5 year follow-up, was 60.82. The average estimate of slope or average rate of growth is .75 across participants. From these results, the average person ended the study with a QOL score of 60.82 which, using a linear model to conceptualize change, lost an
average of .75 per occasion of measurement. The ending status of participants in the study was significant if different from zero ($p \leq .01$); however, the average rate of change was non-significant ($p \leq .01$). Examining the random effects under the “Covariance Parameter Estimates” section, 98.25 indicated the variability in end status; however, there was a problem with the parameter estimate of the variability in growth rates with an estimate of 6.92E-16. Upon examination of the SAS 9.1.3 log file, an error message was found and is shown in Table 13.

Table 13

SAS Log File Output Unconditional Growth Model

NOTE: Estimated G matrix is not positive definite.

The SAS online Customer Support Database (SAS Institute Incorporated, 2009) was referred to and it was suggested that the variable used in the Random statement, in this case “time,” was estimated to be zero. It was recommended that it be removed from the model. Given that the unconditional means model found significant variation between participants in QOL across time and that participants in this study differed significantly in QOL over time, this was an interesting finding which suggested that the variance of time was essentially the same across all occasions of measurement. Tabachnick and Fidell (2007) recommended that when using HLM modeling to examine repeated measures data, investigators are often dealing with large, complex data models which can be unstable. They suggested that even small models with a few predictors such as the unconditional linear growth model grow quickly and that large samples are needed to estimate only a few predictors. Eliason’s study (as cited in Tabachnick and Fidell, 2007)
suggested that a sample size of at least 60 is needed even when merely five or fewer parameters are estimated. In this analysis with a sample size of 51 participants with usable data in the overall sample, three parameter estimates were successful in the unconditional means model. The unconditional linear growth model would have pushed the small data set to estimate up to five additional parameters. It is likely that the small data set was unable to support the statistical analysis. Singer and Willett (2003) addressed this issue when using unbalanced data sets, explaining that severe unbalance or too few participants with enough waves of data can result in a lack of convergence or being unable to estimate one or more variance components. Although they offered no clear guidelines on the sample size, or the number of participants needed to have three or more occasions of measurement, Table 10 shows that in this sample there are 14 participants who have three or more occasions of measurement. Singer and Willett described this type of population parameter estimate, “Estimated G matrix is not positive definite,” as reaching a boundary constraint in which the variance component of growth rates is estimated to be zero or negative. They recommended simplification of the model as a possible remedy. Unfortunately, because the study sought to use more complex data models to explain a trajectory of change over time, this left the data analysis at an impasse.

Singer and Willett (2003) provided an example in which recentering of time could potentially lead to a simpler level-1 model by using a centering constant that eliminates the need for an explicit intercept parameter, but instead, used parameters that represent an initial and final status. Although this type of analysis does not provide much information
regarding the trajectory of change, it did potentially allow the hypothesis testing of time as a predictor of QOL. In this model, time is recentered following equation 3.

$$\frac{\text{Maximum time} - \text{TIME}_{ij}}{\text{Max time} - \text{Minimum time}}$$

(3)

The SAS PROC MIXED output is displayed in Table 14.
Table 14

SAS PROC MIXED: Re-centered Time Level 1 Model

<table>
<thead>
<tr>
<th>Iteration</th>
<th>Evaluations</th>
<th>-2 Res Log Like</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>654.10217440</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>930.53802772</td>
<td>0.00012734</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>905.95222576</td>
<td>0.00042399</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>881.32953528</td>
<td>0.00141540</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>856.70525312</td>
<td>0.00472553</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>832.08093204</td>
<td>0.01571198</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>807.42328740</td>
<td>0.05039119</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>785.79864192</td>
<td>0.04754761</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>781.73726776</td>
<td>0.01780274</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>764.97067911</td>
<td>0.56933337</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>748.91165169</td>
<td>14.65609876</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>736.49839147</td>
<td>522.03084986</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
<td>722.78993752</td>
<td>369.92548497</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>711.10793642</td>
<td>380.39200171</td>
</tr>
<tr>
<td>14</td>
<td>3</td>
<td>698.16740117</td>
<td>.</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>687.41699317</td>
<td>.</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>683.95365520</td>
<td>.</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>677.7251206</td>
<td>.</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>671.33186353</td>
<td>.</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>662.44927726</td>
<td>.</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>650.15300316</td>
<td>.</td>
</tr>
<tr>
<td>21</td>
<td>2</td>
<td>641.66177402</td>
<td>.</td>
</tr>
<tr>
<td>22</td>
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<td>635.86658080</td>
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<tr>
<td>23</td>
<td>1</td>
<td>634.92049778</td>
<td>.</td>
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<tr>
<td>24</td>
<td>1</td>
<td>634.78088220</td>
<td>.</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
<td>634.77616574</td>
<td>0.00000003</td>
</tr>
<tr>
<td>26</td>
<td>1</td>
<td>634.77615839</td>
<td>0.00000000</td>
</tr>
</tbody>
</table>
Table 14 (continued)

SAS PROC MIXED: Re-centered Time Level 1 Model

Convergence criteria met.

Covariance Parameter Estimates

<table>
<thead>
<tr>
<th>Cov Parm</th>
<th>Subject</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Z Value</th>
<th>Pr Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>UN(1,1)</td>
<td>ID</td>
<td>273.11</td>
<td>763.48</td>
<td>0.36</td>
<td>0.3603</td>
</tr>
<tr>
<td>UN(2,1)</td>
<td>ID</td>
<td>-10.8691</td>
<td>43.7598</td>
<td>-0.25</td>
<td>0.8038</td>
</tr>
<tr>
<td>UN(2,2)</td>
<td>ID</td>
<td>0</td>
<td>.</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Residual</td>
<td></td>
<td>52.8889</td>
<td>11.8966</td>
<td>4.45</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Fit Statistics

| -2 Res Log Likelihood | 634.8 |
| AIC (smaller is better) | 640.8 |
| AICC (smaller is better) | 641.1 |
| BIC (smaller is better) | 646.5 |

Null Model Likelihood Ratio Test

<table>
<thead>
<tr>
<th>DF</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>19.33</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Solution for Fixed Effects

| Effect | Estimate | Standard Error | DF | t Value | Pr > |t| |
|--------|----------|----------------|----|---------|------|---|
| Intercept | 114.46   | 28.0668        | 42 | 4.08    | 0.0002 |
| TimeR   | -6.7197  | 3.1947         | 42 | -2.10   | 0.0415 |
Unfortunately, under the “Covariance Parameter Estimates” section of the output “UN (2,2) the variability in growth rates estimate was zero. Additionally, the analysis ran into the same boundary constraint issue, “Estimated G matrix is not positive definite,” with the identical error message in the log file as in Table 10.3. This suggested that the data set was inadequate to perform the unconditional linear growth model.

Multiple imputation as outlined by Schafer (2001) using the EM algorithm, was considered as a means of imputing a complete data set to run within SAS PROC MIXED. Unfortunately, the standalone windows version of the software called PAN, designed to impute what Schaefer called multivariate panel data, or more than one variable measured for individuals at multiple time points, was not available. Therefore, this method of possible analysis of the data set was abandoned.

Non-Linear Change

Given the evidence for a non-linear trend presented by the empirical growth plot in Figure 4, it appeared that QOL may have improved for a certain period of time followed by a gradual decline which returned participants to pre-surgical levels of QOL. Unfortunately, the data models needed to test non-linear change are even more complex than the unconditional growth model which failed, likely due to the overall small sample
size and lack of participants with three or more occasions of measurement. Singer and Willett (2003) stated that in order to hypothesize a nonlinear trajectory of change, one needs to hypothesize both why and when a shift in trajectory may occur. This idea suggests that more frequent follow-up might have been appropriate for this study because a roughly 50 month lapse in QOL measurement between 42 month follow-up and 90 month follow-up should not have occurred if the purpose of the study was to potentially capture data about participants’ QOL during a hypothesized shift. Willett (1997) recommended collecting at least one more wave of data than there are individual growth parameters. In general, linear growth models require at least three waves of data. Nonlinear models require at least five occasions of measurement. For this data set, there was only one participant who was measured for five waves of data collection, as seen in Table 10.

*Unconditional Means Model by Group*

Uncertain how to proceed with the data analysis, the dissertation committee was consulted, and the chair recommended contacting a statistical consultant. Dr. Daniel Russell (personal communication, December 12, 2008) at Iowa State University was contacted and he suggested that the study adopt a much simpler data analysis approach given the limitations of the data set. Given the relatively small sample size, he suggested dividing the sample into two groups and running an unconditional means mixed model analysis. The first group with a pre-surgical and a post-surgical measurement at any time point between three and 42 months (pre-post) and the second group with post-surgical follow-up and 7.5 year follow-up (post-7.5 year follow-up). Dr. Russell stated that if there were no differences then we could make generalizations about the entire sample.
Unfortunately, there were differences between the groups with output for both groups displayed in Table 15.

Table 15

SAS PROC MIXED: Unconditional Means Model by Group

PROC MIXED: PRE POST Group

<table>
<thead>
<tr>
<th>Cov Parm</th>
<th>Subject</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Z Value</th>
<th>Pr Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept ID</td>
<td>10.3598</td>
<td>22.8916</td>
<td>0.45</td>
<td>0.3254</td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>79.2819</td>
<td>28.4337</td>
<td>2.79</td>
<td>0.0026</td>
<td></td>
</tr>
</tbody>
</table>

Solution for Fixed Effects

| Effect | Estimate | Standard Error | DF | t Value | Pr > |t| |
|--------|----------|----------------|----|---------|-------|
| Intercept | 53.2001 | 1.9663 | 11 | 27.06 | <.0001 |

PROC MIXED: POST 7.5 Year Follow-up Group

<table>
<thead>
<tr>
<th>Cov Parm</th>
<th>Subject</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Z Value</th>
<th>Pr Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept ID</td>
<td>100.68</td>
<td>44.0526</td>
<td>2.29</td>
<td>0.0111</td>
<td></td>
</tr>
<tr>
<td>Residual</td>
<td>38.8840</td>
<td>11.1623</td>
<td>3.48</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

Solution for Fixed Effects

| Effect | Estimate | Standard Error | DF | t Value | Pr > |t| |
|--------|----------|----------------|----|---------|-------|
| Intercept | 54.1786 | 2.7948 | 14 | 19.39 | <.0001 |
Examining the “Intercept” term for each unconditional means model under the “Covariance Parameter Estimates” for each group’s analysis, there were differences in the significance level of the intercept term, suggesting that the Pre-Post group had non-significant variation ($p = .33$) in QOL over time. In contrast, the Post-7.5 year group intercept term was significant ($p < .05$), suggesting significant variation in QOL over time. Although Singer (2002) noted that the validity of these tests can be questionable with small sample sizes, results appeared to suggest that there were significant differences between the two groups.

*Supplemental Analysis- Linear Regression*

Dr. Russell (personal communication, March 11, 2009) was re-consulted and given the small sample size and the generally small number of observations, (generally less than three per participant in the overall sample), he suggested that a between subjects data set be created in which all observations were considered independent. That is, instead of using a person-period data set in which the number of occurrences of observations is noted and modeled, each occurrence is treated as an independent observation. In order to achieve this, the person-period data set was utilized with an additional number added to the participant ID. For example, if there were three observations for participant 327, they were re-coded as 3270, 3271, and 3272. Dr. Russell further suggested that time be treated in a more precise manner by computing the exact number of days since surgery. In essence, this eliminated any structure to the occurrence of observations and allowed all participants to have their own unique data collection schedule. With these adjustments to the data set, Dr. Russell recommended that a linear regression analysis with QOL score as the dependent variable be performed with
predictors such as Time, Age, and Disease Duration. Dr. Russell cautioned that this type of analysis could be subject to positive bias with an increased likelihood of finding a significant relationship but stated that there would be no impact upon the form of the relationship between the variables. Tabachnick and Fidell (2007) stated that the goal of a linear regression is to investigate a relationship between a dependent variable (DV) and an independent variable (IV). In particular, they stressed that regression is used to predict a score on one variable from a score on the other. Bivariate linear regression attempts to determine whether the DV is predicted from the IV and whether the relationship fits a straight line. In this case, the individual variation of Time since DBS surgery, Age, and Disease Duration were used to predict QOL. Given that the hypothesized relationship is non-linear as displayed in Figure 4, attempts were also made to determine whether quadratic and cubic coefficients fit the regression line.

Preliminary Analysis of Between Subjects Data Set

The between subjects data set was examined using SPSS 15.0 to calculate the overall number of total observations. This resulted in a sample size of 103, or 103 total observations of the sample from pre-surgical assessment to 7.5 year follow-up (Table 13). This approach presented a potentially more robust sample size by which to examine predictors such as Time, Age, and Disease Duration as well as examine overall QOL and the subscales of the PDQ-39. Descriptive statistics for Age and Disease Duration were previously examined grouped by wave of measurement in Table 1. Descriptive statistics based on the present approach are reported in Table 16. For clarity, Time was expressed in years.
Table 16

*Demographics in Overall between Subjects Sample*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sample Size</th>
<th>Age</th>
<th>Disease Duration</th>
<th>Time – Years since DBS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean: 57.93</td>
<td>Mean: 14.93</td>
<td>Mean: 2.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD: 11.24</td>
<td>SD: 6.19</td>
<td>SD: 2.59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range: 31 - 78</td>
<td>Range: 2 - 31</td>
<td>Range: 0 – 8.975</td>
</tr>
</tbody>
</table>

The remaining preliminary analyses such as missing data, normality, and homoscedasticity were unchanged from the overall analyses performed and presented earlier in this paper.

*Change Over Time with PDQ-39 and QOL*

Using the Linear Regression function in SPSS 15.0, Time since DBS was found to be non-predictive of overall quality of life. Tabachnick and Fidell (2007) stated that the overall inferential test in regression determines whether the sample of the score is taken from a population in which the correlation $r$ is zero. This inferential test is displayed in Table 17.
Table 17

Regression Inferential Test: Time and QOL

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>60.319</td>
<td>1</td>
<td>60.319</td>
<td>.467</td>
<td>.496(a)</td>
</tr>
<tr>
<td>Residual</td>
<td>10985.789</td>
<td>85</td>
<td>129.245</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11046.107</td>
<td>86</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Predictors: (Constant), Days_corrected
b Dependent Variable: QOL

Non-significance suggests that time represented as days since DBS surgery is not predictive of QOL as measured by the PDQ-39.

Because the relationship between time and QOL was hypothesized to be non-linear, the SPSS 15.0 Regression Curve Estimation function was utilized to examine the possibility that the regression line could be quadratic or cubic in function and non-linear.

The overall inferential test for these analyses are shown in Tables 18 and 19.

Table 18

Regression Inferential Test: Time squared and QOL

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>66.614</td>
<td>2</td>
<td>33.307</td>
<td>.255</td>
<td>.776</td>
</tr>
<tr>
<td>Residual</td>
<td>10979.493</td>
<td>84</td>
<td>130.708</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11046.107</td>
<td>86</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The independent variable is Days_corrected.

With non-significance suggesting that time squared is not predictive of QOL as measured by the PDQ-39 as well as time cubed as seen in Table 19.
Table 19

Regression Inferential Test: Time cubed and QOL

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>84.367</td>
<td>3</td>
<td>28.122</td>
<td>.213</td>
<td>.887</td>
</tr>
<tr>
<td>Residual</td>
<td>10961.741</td>
<td>83</td>
<td>132.069</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11046.107</td>
<td>86</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The independent variable is Days_corrected.

These results indicated that the predictive value of Time since DBS and QOL is non-significant in terms of available data analysis procedures.

*Change Over Time with PDQ-39 subscales*

A significant linear regression correlation coefficient was found between Time since DBS surgery and the Cognitive Impairment or Cognitions subscale of the PDQ-39. Jenkinson, Fitzpatrick, and Peto (1998) stated that the Cognitions subscale addresses a variety of cognitive problems such as difficulties with concentration and memory. Item content also involves asking about whether patients fall asleep unexpectedly and having bad dreams or hallucinations among the four items. Results of the SPSS 15.0 Linear Regression function are displayed in Table 20.
Table 20

Linear Regression: Time and PDQ-39 Cognitive Impairment Subscale

ANOVA

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>1059.560</td>
<td>1</td>
<td>1059.560</td>
<td>4.489</td>
<td>.037</td>
</tr>
<tr>
<td>Residual</td>
<td>22657.787</td>
<td>96</td>
<td>236.019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23717.347</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Predictors: (Constant), Days_corrected
b Dependent Variable: Cog

Coefficients(a)

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td>B</td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>48.077</td>
<td>2.051</td>
<td>23.439</td>
</tr>
<tr>
<td></td>
<td>Days_corrected</td>
<td>.004</td>
<td>.002</td>
<td>.211</td>
</tr>
</tbody>
</table>

a Dependent Variable: Cog

The inferential test was found to be significant ($p < .05$) and suggested a potentially meaningful correlation between Time and Cognitive impairment. As a result, it was appropriate to examine the correlation coefficient of Time. With a beta weight of .211, it appeared that time accounts for about 4% of the variance in QOL of PDQ-39 Cognitions over time. Thus, for a one unit change in time, each day that passes since DBS, there was a .211 unit increase in QOL related cognitions, measured by the PDQ-39 Cognitions subscale. Because an increase in the score on this subscale is indicative of increasing difficulty, this result suggested that QOL in terms of Cognitive Impairment worsens over time since DBS.
Age and PDQ-39 Stigma Subscale

A significant relationship \((p < .01)\) was found between Age and Stigma QOL. Age was originally measured pre-surgically and then estimated based upon the amount of time passed since surgery because participants’ actual birthdates were not known. Jenkinson et al. (1998) described the Stigma subscale of the PDQ-39 as addressing various social difficulties as a result of suffering from PD, such as feeling the need to conceal evidence of the disease from others. This scale consists of four items. The SPSS 15.0 Linear Regression analysis is displayed in Table 21.

Table 21
Linear Regression: Age and PDQ-39 Stigma Subscale

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>8564.031</td>
<td>1</td>
<td>8564.031</td>
<td>25.228</td>
<td>.000(a)</td>
</tr>
<tr>
<td>Residual</td>
<td>30552.273</td>
<td>90</td>
<td>339.470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>39116.304</td>
<td>91</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Predictors: (Constant), Age
b Dependent Variable: Stigma

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>104.530</td>
<td>12.285</td>
<td>8.509</td>
<td>.000</td>
</tr>
<tr>
<td>Age</td>
<td>-1.002</td>
<td>.199</td>
<td>-.468</td>
<td>-5.023</td>
</tr>
</tbody>
</table>

a Dependent Variable: Stigma

The inferential test was found to be significant \((p < .01)\), and suggested a potentially meaningful correlation between Age and Stigma. The beta weight for Age was negative \((- .468)\), suggesting that as age increased there was a decrease in score, signifying improvement, of perceived stigma associated with PD as measured by the PDQ-39. This
correlation accounted for roughly 22% of the variance in the Stigma subscale, which suggests that PD patients who received DBS had an improvement in QOL relative to Stigma as their age increased. For the overall between subjects sample, out of 103 possible observations for age, ten observations for age were missing and not able to be estimated, or approximately 10% missing data representing seven participants in the overall sample.

As a method of examining this relationship further and providing preliminary evidence for differences in QOL based on age, individual empirical growth plots were created for two participants. The participants were matched on a number of variables based on the limitations of the data set. These included: (a) three occasions of measurement, (b) close proximity of time when measured, (c) both having pre-surgical measurement, and (d) complete PDQ-39 data on the index score and all subscales. One participant was considered to have young-onset PD (Schrag et al., 1998) and received DBS at or before age 40; had the empirical growth plot for this person appears in Figure 5. The second participant had later-onset PD (aged 40 or older) and the growth plot for this individual is displayed in Figure 6.
For this participant who was aged 40 or younger, Stigma appeared to improve at around two years post-surgery and was maintained at this level until the seven and a half year follow-up. For the Stigma subscale, a minimal difference of 5.6 suggests clinical
significance (Peto et al., 2001). Thus, this improvement of five points between pre-
surgical Stigma and the two post-surgical measurements could have borderline clinical
significance.

The individual growth plot for the participant over age 40 shows a different
pattern of change, which is displayed in Figure 6.
There appear to be improvements up to two years post-surgery with a difference in Stigma subscale score of 15. At around five year follow-up, this individual had a 15 point
higher Stigma score compared to pre-surgical levels, suggesting clinically significant worsening beyond the pre-intervention level.

*Disease Duration and PDQ-39 subscales*

Disease Duration was found to be significantly related to several PDQ-39 subscales, including: (a) Emotional Well-Being, (b) Stigma, and (c) Social Support. Disease Duration was assessed for participants pre-surgically by asking how long they had been diagnosed with PD prior to seeking DBS surgery. Because this question was not assessed during subsequent measurement, Disease Duration was estimated by adding the time at which participants were measured pre-surgically, for example at two years, to their originally reported number of years symptomatic with PD at pre-surgical measurement. Surprisingly, Disease Duration was found to be significantly related to several QOL subscales despite quite a bit of missing data; 45.5% in the overall sample as seen in Table 2. The SPSS 15.0 Linear Regression function was used to determine if there was a significant relationship and to calculate the percentage of variance explained by Disease Duration. As in the Age and Stigma analysis, two participants’ empirical plots were created graphing Disease Duration and QOL of the significant subscale. Both selected participants were matched on (a) pre-surgical assessment and (b) three occasions of measurement with one measurement at this follow-up and (c) similar time periods between data collection, two years and three years. Unfortunately, the two participants selected for empirical growth plot comparison differed in Disease Duration. It would have been ideal to select participants with Disease Duration between the average 12-14 years for DBS recipients (Lang et al., 2006). However, none met that particular matching criteria. Thus, a participant with initial Disease Duration of 20 years was selected to
represent longer Disease Duration. Again, ideally, the other’s Disease Duration would have been 5 years or less as recommended by Lang et al. and authors the CAPSIT-PD protocol (Defer, Widner, Marie, Remy & Levivier, 1999). However, none met this matching criteria so a participant with 7 year Disease Duration at surgery was selected for comparison.

Using SPSS 15.0 Linear Regression function, the inferential test for Disease Duration was found to be significant ($p \leq .01$) suggesting a meaningful correlation with the Emotional Well-Being Subscale of the PDQ-39 as shown in Table 22.

Table 22

Linear Regression: Disease Duration and PDQ-39 Emotional Well-Being

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>1819.740</td>
<td>1</td>
<td>1819.740</td>
<td>9.269</td>
<td>.004(a)</td>
</tr>
<tr>
<td>Residual</td>
<td>10012.125</td>
<td>51</td>
<td>196.316</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11831.866</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Predictors: (Constant), Disease Duration

The beta weight for this correlation was negative (-.392) suggesting that as Disease Duration increased, there was a decrease in the Emotional Well-Being score, resulting in improvement in QOL of well-being. Jenkinson et al. (1998) state that the Emotional
Well-Being subscale examines various emotional problems such as feeling depressed or worried about the future. The subscale consists of six items. Disease Duration accounted for roughly 15% of the variance in the Emotional Well-Being subscale. Thus, for a one unit change in Disease Duration, or for each additional year of Disease Duration, a \(-0.392\) change in QOL of Emotional Well-Being occurred, suggesting that the QOL in Emotional Well-Being improved as Disease Duration increased after DBS surgery.

Unfortunately, there was missing data for the shorter Disease Duration participant at pre-surgical measurement so a comparison of individual empirical growth plots was not performed with the Emotional Well-Being subscale.

The inferential test for Disease Duration was also found to be significant \((p < .01)\) and suggested a meaningful correlation with the Stigma Subscale. The SPSS 15.0 results are displayed in Table 23.

Table 23

Linear Regression: Disease Duration and PDQ-39 Stigma Subscale

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Regression</td>
<td>2502.473</td>
<td>1</td>
<td>2502.473</td>
<td>8.090</td>
</tr>
<tr>
<td></td>
<td>Residual</td>
<td>16085.027</td>
<td>52</td>
<td>309.327</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>18587.500</td>
<td>53</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Predictors: (Constant), Disease Duration
b Dependent Variable: Stigma

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>55.771</td>
<td>6.309</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disease Duration</td>
<td>-1.126</td>
<td>.396</td>
<td>-2.844</td>
</tr>
</tbody>
</table>

a Dependent Variable: Stigma
This correlation was negative (-.367) and suggested that as Disease Duration increased QOL in terms of Stigma decreased in score and improved. Disease Duration accounts for 13% of the variance in the change in Stigma.

The Stigma individual empirical growth plot for shorter Disease Duration is displayed in Figure 7 and longer Disease Duration Figure 8.
Figure 7

Individual Empirical Growth Plot: Stigma by 7 Year Disease Duration
Both growth plots indicated improvement when measured at two years. The shorter Disease Duration participant had an improvement of 10 points at two year follow-up. With more than a 5.6 point change, this suggested clinically significant change (Peto et
The longer Disease Duration participant showed an improvement of 15 points at two year follow-up suggesting clinically significant change as well. Between two years and this follow-up, both participants showed increase in scores, indicating a worsening of Stigma over time. The shorter Disease Duration participant had a 5 point difference, at follow-up suggesting borderline clinical improvement beyond the pre-surgical level of Stigma. The longer Disease Duration participant had a 15 point difference suggesting a clinically significant decline beyond pre-surgical assessment.

The inferential test for Disease Duration was also found to be significant ($p < .05$) in regard to the Social Support subscale. Jenkinson et al. (1998) stated that the Social Support subscale measures perceived support from social relationships such as problems in close relationships or not getting support. Results of the SPSS 15.0 output appear in Table 24.

Table 24

Linear Regression: Disease Duration and PDQ-39 Social Support Subscale

<table>
<thead>
<tr>
<th>Model</th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regression</td>
<td>1192.541</td>
<td>1</td>
<td>1192.541</td>
<td>5.532</td>
<td>.023</td>
</tr>
<tr>
<td>Residual</td>
<td>10994.461</td>
<td>51</td>
<td>215.578</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>12187.002</td>
<td>52</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Predictors: (Constant), Disease Duration
b Dependent Variable: SSwP
Table 24 (continued)

Linear Regression: Disease Duration and PDQ-39 Social Support Subscale

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>t</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Std. Error</td>
<td>Beta</td>
<td>B</td>
</tr>
<tr>
<td>(Constant)</td>
<td>45.081</td>
<td>5.312</td>
<td>8.486</td>
<td>.000</td>
</tr>
<tr>
<td>Disease Duration</td>
<td>-.780</td>
<td>.332</td>
<td>-.313</td>
<td>-2.352</td>
</tr>
</tbody>
</table>

a  Dependent Variable: SSwP

Once again, the correlation was negative (-.313) suggesting that as Disease Duration increased, Social Support decreased and improved. Disease Duration accounted for roughly 10% of the variance in Social Support.

The Social Support individual empirical growth plotted for shorter Disease Duration is displayed in Figure 9 and longer Disease Duration in Figure 10.
Figure 9

Individual Empirical Growth Plot: Social Support by 7 Year Disease Duration
Both plots began at relatively low levels, suggesting good social support for both participants that maintain at roughly two years. For the shorter Disease Duration participant, the difference between baseline and this follow-up is 10 points, which does not meet the cutoff of 11.4 points according to Peto et al., 2001, suggesting non-clinically
significant change. The longer Disease Duration difference was even less at 6.67, suggesting non-clinical change.

Summary

Examination of a trajectory of QOL change across time was not obtainable due to restrictions of the data set, in particular, not having a large enough sample size with a sufficient number of observations. The analysis likely experienced a boundary constraint issue where the data analysis was taken as far as possible given the size of total observations beyond four occasions of measurement. Supplemental analyses suggested statistically meaningful relationships between the variables of interest. When a meaningful correlation was found, comparison of empirical growth plots of single subject data ensued. This provided additional preliminary evidence for the three research questions similar to pilot study data (D. Russell, personal communication, March 11, 2009).

The first research question examined whether there was a trajectory of change over time in overall QOL and among any of the PDQ-39 subscales. The results of the linear regression analyses suggested non-significant overall QOL change over time as measured by the PDQ-39 Summary Index. However, with the PDQ-39 Cognitions subscale, findings implied that as time went on after DBS intervention, the subscale score increased suggesting that cognition-related QOL worsened.

In terms of the second research question, whether there were QOL differences between younger and older DBS recipients, age appeared to have a significant relationship with Stigma-related QOL. This relationship suggested improvement in the PDQ-39 Stigma subscale as age increased. Preliminary evidence from individual
In Question Three, which examined differences in QOL related to Disease Duration, significant correlations were revealed between Disease Duration and three PDQ-39 subscales: (a) Emotional Well-Being, (b) Stigma, and (c) Social Support. Results of the linear regression analysis implied that as Disease Duration increased the PDQ-39 Emotional Well-Being subscale score decreased, suggesting that QOL related to emotional problems improved after DBS intervention. Individual empirical growth plots were unobtainable for the PDQ-39 Emotional Well-Being subscale due to missing data. Linear regression analysis between Disease Duration and the PDQ-39 Stigma subscale suggested that Stigma-related QOL seemed to improve as Disease Duration lengthened after DBS intervention. Comparison of individual empirical growth plots provided preliminary evidence that shorter Disease Duration at time of intervention resulted in less clinically significant differences in the Stigma subscale at seven and a half year follow-up. Longer Disease Duration suggested a worsening of stigma related QOL beyond pre-intervention levels. Finally, a significant relationship was found between Disease Duration and the PDQ-39 Social Support subscale. As Disease Duration increased, QOL related to social relationships appeared to worsen. Single-subject empirical growth plots suggested no difference in this worsening over time between shorter and longer Disease Duration.
Chapter 5

Discussion

This study was an attempt to examine QOL in PD patients who received STN DBS at approximately seven and a half years after surgery, to our knowledge, one of the longest follow-up periods in the DBS literature. Although there is evidence to suggest that the benefit of DBS diminishes over time (Montel & Bungener, in press), Krack et al. (2003) and Schupbach et al. (2005) found that DBS motor and disability improvements were maintained at five year follow-up. This study endeavored to add evidence to how long the benefits of DBS are maintained, particularly in terms of QOL. Unfortunately, a trajectory of change over time was unable to be determined due to limitations of the data set. Because proposed analyses were not able to be completed, alternative analyses were performed which yielded preliminary evidence.

As a result of this study, there are some lessons that have been learned in regard to examining change over time. Taken as far as the HLM individual growth model could go, significant variation in overall QOL, as measured by the PDQ-39 Summary Index, was found across multiple occasions of measurement; this finding is worthy of further examination. Preliminary evidence from plotting individual data suggested trajectories of QOL improvement followed by gradual decline that at times approached pre-surgical levels, in essence, a V-shaped trajectory. There is no statistical test for determining if changes in a single-subject growth chart are significant (Crosbie, 1993). In an effort to address this issue, only individual growth plots from statistically significant linear
regression analyses were compared. At best, this yielded evidence similar to pilot study data. Although further analyses from this data set are unlikely to yield substantive empirical evidence, other examinations of a trajectory of change over time could be undertaken with a larger data set.

Results

Time was not predictive of overall QOL as measured by the PDQ-39. However, a significant relationship was found between time and the PDQ-39 Cognitions subscale, suggesting worsening of cognitive problems after DBS intervention. This finding was contrary to other DBS QOL studies reviewed. In particular, Just and Ostergaard (2002) found significant improvement in the PDQ-39 Cognitions subscale six months after DBS intervention. It is likely that the difference between this study and Just and Ostergaard’s study related to the seven year difference in overall follow-up duration. However, this finding was consistent with a meta-analysis of behavioral changes among 1398 advanced PD STN DBS recipients conducted by Temel et al. (2006) which concluded that chronic, cognitive dysfunctions are the most frequently occurring side-effect of STN DBS, occurring in 41% of the PD patients they examined. Temel et al. also noted the variability in the impact of these cognitive changes upon patients. Some patients were impacted heavily by executive functioning difficulties while others experienced only a moderate degree of deterioration in verbal memory. The present study provided preliminary evidence of worsening QOL related to cognitions after DBS intervention at seven and a half year follow-up. Thus, the preliminary findings further suggested that no matter how moderate or severe the cognitive change, DBS appears to have long-term impact. However, it is difficult to separate the effects of DBS intervention from continued
Parkinson’s disease progression which may contribute to the decline in cognition-related QOL.

Age was found to have a significant relationship with Stigma. This finding suggested that as age increased after DBS, Stigma improved. A possible explanation for this finding is sustained motor improvements. Motor symptoms of PD are outwardly visible signs and potentially the most stigmatizing aspect of PD. As a result, sustained motor improvements and reduced dopaminergic drug dosages may contribute to this aspect of QOL. Schrag, Hovris, Morley, Quinn and Jahanshahi, (2003) have suggested that among non-DBS recipients aging may help PD patients come to terms with their disease. Likewise, as DBS recipients in the present study grew older, they may have found PD signs and symptoms to be more acceptable.

Although other QOL studies have found Stigma to improve after DBS at shorter periods of follow-up (Drapier et al., 2005; Lezcano et al., 2004; Martinez-Martin et al., 2002; Patel et al., 2003), none, to our knowledge, have used age under 40 as a predictor of QOL. Comparison of individual growth plots suggested differences between older, aged ≥ 40, and younger patients. Younger patients appeared to improve and maintain their gains in Stigma related QOL at seven and a half year follow-up. However, this improvement did not reach clinical significance. In contrast, older patients appeared to have initial improvement in Stigma lasting two years, followed by gradual decline that worsened beyond pre-surgical levels at seven and a half year follow-up. It is possible that the sustained improvements in Stigma-related to age differences in post-surgical improvement. This finding is consistent with Welter et al. (2002) who found greater percentage improvements and lower disability scores in post-operative clinical outcomes
among younger patients receiving STN DBS. As well, Charles et al. (2002) found that
younger age was predictive of better STN DBS outcome. Younger age could be
predictive of better outcome due to longer periods of sustained improvement in addition
to greater improvement. However, these findings potentially run contrary to Schrag et al.
(2003) who found that Stigma worsened in young-onset PD patients among non-DBS
recipients. It is possible that DBS intervention may make a difference in Stigma among
young-onset PD patients at seven and a half year follow-up.

Disease Duration had significant relationships with several domains of QOL: (a)
Stigma, (b) Emotional Well-Being, and (c) Social Support. A significant relationship was
revealed between Disease Duration and Emotional Well-Being. Results suggested an
improvement in Emotional Well-Being as Disease Duration increased after DBS.
Improvement in Emotional Well-Being after DBS was consistent with similar
improvements found at six month follow-up by Martinez-Martin et al. (2002) and two
year follow-up by Lezcano et al. (2004). Additionally, when comparing DBS recipients
with levodopa managed PD patients, Deuschl et al. (2006) and Weaver et al. (2009) also
found improvement in Emotional Well-Being at six months in DBS recipients. This
study’s findings further suggested that gains are maintained at seven and a half years.
However, the relationship between Disease Duration and Emotional Well-Being was
contrary to Schupbach et al. (2007) who did not find evidence of improvement in this
domain among DBS recipients with disease duration ranging from 5 to 10 years at 18
month follow-up. A potential reason for this difference could be that 18 months was not
long enough to measure long term changes in Emotional Well-Being whereas seven and a
half years sufficiently measured change in this aspect of QOL.
Disease Duration had a significant relationship with Stigma. Stigma related QOL appeared to improve as Disease Duration lengthened after DBS intervention. A comparison of individual growth plots between shorter duration (7 years) and longer duration (20 years) PD participants found improvements in both individuals at two year follow-up. However, at seven and a half year follow-up, the longer duration participant had worse Stigma scores than at baseline. Additionally, the difference appeared to be clinically significant (Peto et al., 1998). This finding suggested that improvements are not maintained in longer Disease Duration PD recipients of DBS and that shorter Disease Duration DBS recipients appeared to maintain their gains at roughly five year follow-up (both participants had received their surgeries approximately five years before follow-up). Stigma has been found to improve in DBS QOL studies (Drapier et al., 2005; Lezcano et al., 2004; Martinez-Martin et al., 2002; Patel et al., 2003) and in studies comparing DBS with best medication treatment (Deuschl et al. 2005; Weaver et al. 2009). Evidence towards recommending the surgery for PD patients with a shorter Disease Duration was provided in a case series by Mesnage et al. (2002) and in a randomized, controlled clinical trial (Schupbach et al., 2007). However, Mesnage et al. did not examine QOL. Schupbach et al. found improvements in Stigma among a group of DBS recipients who had a Disease Duration ranging from 5 to 10 years. Thus, this finding added preliminary evidence that DBS surgery at an earlier disease stage may result in improvements in Stigma-related QOL being maintained for a longer period of time. However, as Lang et al. (2006) cautioned, it is potentially risky performing DBS with PD patients who have a disease duration of less than five years due to the risk of performing the surgery on a patient with atypical PD. Thus, if these preliminary findings
are taken into account during pre-surgical assessment of PD patients, they need to be weighed against the risk of a misdiagnosis of idiopathic PD.

A significant relationship was found between Disease Duration and Social Support. As Disease Duration increased, QOL related to social relationships seemed to worsen. Preliminary evidence from empirical growth plots suggested no clinically significant differences between shorter and longer Disease Duration individual growth plots nor between pre-surgical and seven year follow-up Social Support PDQ-39 subscale scores (Peto et al. 2001). Thus, regardless of Disease Duration, Social Support seemed to be maintained for two years with gradual worsening. However, this worsening did not connote clinical significance.

Limitations- Research Design and Analysis

Some of the limitations of this study relate to research design. This was a prospective, longitudinal, cohort study of a group of PD patients who received DBS at Columbia University Medical Center. There was no control group, patients were not randomized to treatment, and evaluators were not blinded to their status. This type of design was typical of earlier DBS studies following cohorts of recipients in geographic regions throughout the world. This calls into question some of the empirical robustness of the preliminary evidence found in this study. A double-blind, placebo-controlled study is considered the gold standard for examining the results of interventions (Olanow, 2005). There appear to be controversial ethical issues related to performing controlled surgical studies such as providing sham surgery (Kim et al., 2005; Olanow). However, recent studies have compared DBS recipients with patients receiving best medical treatment with levodopa medications. There are many ways to compare these preliminary findings,
such as with other studies that followed cohorts of DBS recipients (Drapier et al., 2005; Lezcano et al., 2004; Martinez-Martin et al., 2002). Unfortunately there is no comparison group, which is a major limitation in that there is no control group with which to compare the findings.

Participants in this study received their surgeries as early as 1999; thus, the study’s research design is similar to other studies of that era. Cohorts of DBS recipients in various studies were followed from different geographical areas where surgical centers are located. The sample sizes were often small, ranging from 15 to 50 participants and suffered from problems with low statistical power. Woods et al. (2006) described the difficulty of low statistical power among studies examining the neuropsychological sequelae of DBS surgery in PD patients. The present study was no different.

Data collection problems occurred throughout the study, leading to lost data and a high percentage of missing data. In particular, there were concerning numbers of missing data among the independent variables of interest; over 45% in Disease Duration and around 8% in Age. There were several factors related to missing data. At previous waves of assessment, surveys were lost in the mail reducing the actual number of observations. Additionally, missing data for Age and Disease Duration could have been retrieved from the Center for Movement Disorders Surgery at Columbia Presbyterian Medical Center but due to logistical constraints, this was not done. In addition, it appears that the pattern of missingness is MNAR (Missing Not At Random). Thus, the pattern cannot be ignored and is likely related to the dependent variable, QOL, specifically the PDQ-39 Mobility subscale and Disease Duration. As a result, there is an increased risk of reaching incorrect conclusions (Collins et al., 2001). Therefore, all of these preliminary significant findings
could be called into question. Particularly, the findings that suggest relationships between variables such as Disease Duration and Emotional Well-Being, that have not been seen in the extant literature before could be erroneous and not different than zero. Missing data also impacted the data analysis. Graham et al. (2003) described a process where the numbers of cases for analyses were reduced to the point that non-significant results are found. Then, the researcher wades through highly technical journal articles discussing how to handle missing data. In this case, multiple imputation was chosen as a method only to discover that the software was not available to run the imputed data set. It is likely that significance levels should have been raised due to multiple testing in an effort to make sense of the data. Just and Ostergaard (2002) raised their significance level to compensate for running multiple analyses. Overall, there is some preliminary evidence for trajectories of changes in QOL after DBS intervention but admittedly, it stands on shaky ground.

Finally, there was not a full understanding of the data methods prior to proposing the study. Difficulties occurred in practical application of the methods. With nine potential occasions of measurement, an assumption was made that there would be sufficient data to conduct HLM individual growth analysis of change over time. Instead, there were only three participants measured for more than three waves of data resulting in insufficient power by which to conduct the analysis. Additionally, it was thought that complete data was not entirely necessary for a growth curve analysis because each participant would contribute at whatever time point they were measured (Singer & Willett, 2003). It was hoped that the data analysis method might compensate for the lack of complete data. However, in all likelihood, the HLM analysis may have taken the
analysis further than other methods requiring more complete data with equally spaced intervals of measurement, such as repeated measures ANOVA. A preliminary data analysis examining the sample size of participants who were measured for more than three occasions would have avoided this problem, allowing selection of a different analysis method. Much time, energy, and effort was spent attempting to complete an analysis that was doomed from the outset because there was insufficient data at critical points across time.

*PDQ-39*

One assumption of the study is that QOL is multi-factorial. The PDQ-39 is a disease-specific QOL measure which is different from more global and generic QOL measures such as the SF-36. However, it is not an all-encompassing measure of QOL for PD patients. In comparing the PDQ-39 with PD health-related QOL measures, Damiano, Snyder, Strausser & Willian (1999) found that the measure lacked items related to self-image and sexual functioning. Given that hypersexuality can be a chronic and sustained side-effect of DBS (Temel et al., 2006), it seems important that a measure examining QOL after DBS would need to assess this. Additionally, there is qualitative evidence from Schupbach, Gargiulo, et al. (2006) that suggests body image can potentially change after DBS finding that some of their patients had trouble accepting the presence of a stimulator in their body and electrodes in their brains. The PDQ-39 does not cover these areas of health-related QOL. Thus, it is possible that it does not produce a comprehensive assessment of QOL after DBS.

Another limitation of this study was the sole use of self-report measures; i.e., the PDQ-39. Other measures that are typically completed by clinicians, such as the Hoehn
and Yahr, were filled out by participants. Some researchers, such as Lezcano et al. (2004) and Martinez-Martin et al. (2002), have observed patient self-report as an important step in measuring the outcome of surgical intervention when used in conjunction with physicians’ reports. Others like Drapier et al. (2005) have noted discrepancies between physicians’ assessments and patient’s perceptions. Some researchers such as Gronchi-Perrin (2006) have questioned whether there are cognitive changes that occur as a result of DBS intervention that may influence the ability of patients to provide accurate self-report. The use of self-report alone potentially biases the findings of this study. However, the point of the study was to determine trajectories of change over time from the patients’ point of view, and that was accomplished as fully as possible given the limits of the data set.

Finally, one of the criticisms of working with the PDQ-39 is determining what a change in the scale actually means. Peto et al. (2001) provided scores to determine minimally important differences among PD patients in the general population. However, use of these scores to determine changes in QOL after DBS could be problematic in that DBS recipients may face different changes (Temel et al. 2005) not typically experienced by the general PD patient population.

**PD Clinical Issues**

One of the major difficulties in interpreting results of this study was differentiating between effects of DBS intervention and continuation of the Parkinson’s disease process. All treatments available to PD patients, including DBS, do not have the ability to arrest, slow, or reverse the disease process (Olanow et al., 2005). DBS potentially provides improvement in motor symptoms and the reduction of motor
fluctuations and dyskinesia (Benabid et al., 2006). However as the Parkinson’s disease process continues, it typically leads to varying degrees of dementia and disability; both of which could have impacted QOL measurement among participants in this study, especially given the relatively long, seven and a half year, average duration of follow-up.

In other studies examining the long term effects of DBS (Krack et al., 2003; Schupbach et al. 2005), patients are often evaluated on or off neurostimulation and medication in an effort to gauge state or effectiveness of treatment. This study did not address these factors, potentially providing a confounding variable in that there can be great differences in motor functioning and QOL depending on whether or not the stimulator is on or off and whether the patient is properly medicated (Krack et al.; Schupbach et al. 2005).

There continues to be a discrepancy between assessment of QOL outcomes assessed by patients and physicians. Agid, Schupbach, Gargiulo, Mallet, Houeto, Behar, et al. (2006) raised the issue of a contrast between motor functioning improvements and difficulties of patients to reintegrate into a normal life. Some studies appear to put blame on the patient stating that they may have unrealistic expectations despite efforts and information provided for informed decision-making provided by physicians (Montel & Bungener, in press). It is likely that resolving this discrepancy may involve perspectives from both physicians and patients. The findings of this study were based upon patient report without much input from the physicians.

Among those participants who reported having a poor outcome, there is some evidence to suggest that poor outcome may be a result of misplaced electrode leads (Ellis,
Foote, Fernandez, Sudhyahom, Rodriguez, Zeilman, et al. (2008). This area was not assessed and may have had an impact upon QOL measured among these participants.

Finally, there were two participants in this study who also received fetal cell transplant surgery. For further details of the study see McRae et al. (2004). Although measurements of these patients were used in the analysis involving the overall sample, they were not used in individual growth plot comparisons in an effort to avoid examining participants with potential interaction effects from surgical implantation of dopamine neurons. It is possible that these two participants may have biased the overall sample. Between the two participants, there were a total of four occasions of measurement for them; one measurement occurring at this seven and a half year follow-up.

Future Directions

As a result of DBS, we have learned much about the functioning of the subthalamic nucleus (Temel et al., 2005) and have an additional tool in managing patients with PD, providing significant gains in motor functioning once medical therapy cannot improve symptoms (Deep Brain Stimulation for Parkinson’s Study Group, 2001). However, in order to fully understand how this intervention impacts QOL in PD patients, a broader approach to QOL assessment needs to occur.

Harrison et al. (2000) suggested that there is no absolute relationship between the efficacy and the effectiveness of treatments. Efficacy involves the treatment’s ability to change what it says it will change. Effectiveness involves the treatment’s rippling effect once the alteration has occurred. Harrsion et al. gave the example of an intervention being able to significantly improve postural instability. This, in turn, may have an impact on the ability to perform activities of daily living which might lead to changes in quality of life.
However, a statistically significant positive change in one aspect of PD is not guaranteed to have a positive change in others. DBS appears to provide PD patients with a constellation of changes that may not change the disease progression but may alter the clinical manifestation of the disease for recipients, ultimately impacting quality of life. This study provided some evidence to suggest that a constellation of changes transpires after DBS. If the typical benefits of DBS surgery, such as improved motor functioning, reduction of motor fluctuations and dyskinesia, arose among this cohort of DBS recipients, then the constellation of changes appear to have involved Cognitions, Stigma, Emotional Well-Being, and Social Support subscales of the PDQ-39. It is possible that those with positive outcomes have a variety of factors that move in an adaptive and positive direction. For example, participants with increased motor functioning may utilize these improvements for activity related to maintaining social support related QOL such as contacting friends on a regular basis or attending social events. Those with negative outcomes suffer from or respond to a constellation of factors that result in difficulty and reduced QOL for the DBS recipient. For example, if a participant benefits from increased motor functioning but suffers from cognitive side effects, the individual may have difficulty adapting to these changes.

Within this constellation of changes, there appear to be constants and variability based upon age, disease duration, and time. One consistent constant appears to be improvements in motor changes and activities of daily living that are maintained for up to five years (Krack et al., 2003; Schupbach et al., 2005). Variability seems to occur in decline over time after the surgery. Krack et al. found that STN DBS recipients who were on-stimulation and off-medication showed improvements in speech one year after surgery.
which progressively worsened, returning to pre-surgical levels at five year follow-up. In contrast, Schupbach et al. (2005) did not report an improvement in speech but instead found worsening dysarthria in their cohort of DBS recipients.

DBS appears to alter a PD patient’s relationship with Parkinson’s disease (Schupbach et al., 2006) Conducting open, unstructured interviews in addition to using validated, commonly used PD measures, Schupbach et al. (2006) described one patient who had found meaning in combating the disease and in her work. After a 75% improvement in motor disability after the surgery, however, the patient had lost her pleasure in work and experienced a loss of inspiration for life. Based on this information, Schupbach et al. (2007) surmised that DBS may have an impact upon patients’ self-perception and understanding of their bodies.

It is possible that constellations of change begin to occur with patients’ expectations toward surgical outcome. The influence of pre-surgical expectations upon surgical outcome and QOL appears to be gaining more attention (Agid et al., 2006; Montel & Bungener, in press). Montel and Bungener thought that some PD patients treated with DBS had unrealistic expectations that lead to disappointment at follow-up. Given that quality of life is a multi-factorial construct, it will certainly be worthwhile to further explore expectations of surgery as a potential predictor for quality of life. This could assist potential DBS candidates in making informed consent decisions about whether to have the surgery or not.

Research should continue to identify factors that most influence a positive outcome. Hopefully, as this list of factors begins to grow, assessment of QOL could become more broad, comprehensive and thorough. For example, QOL assessment could
adopt a neuropsychological “flexible battery” approach in which there are many assessments available but some of which are used only when indicated to assess problem areas. For example, the PDQ-39 could be better utilized as a screening tool for QOL with follow-up to further evaluate areas of change by an experienced clinician or psychometrician to administer assessments. In essence, a somewhat individualized approach will begin to provide flexible tools so we can measure QOL adequately and also paint a clearer picture of how DBS ultimately affects patients.

Future studies interested in examining the long-term trajectory of QOL would need to measure their participants on at least five occasions of measurement with a higher frequency around the hypothesized change in QOL, which could be around six months (Schupbach et al., 2005) for some factors, or at one year (Krack et al.) over a period of at least five years. Additionally, future trajectory of change investigations should adopt a multi-center collection approach so that an adequate sample size can be collected allowing for potentially high-rates of attrition. Studies by Weaver et al. (2009) and Deuschl et al. (2006) provide examples of data collected from multiple DBS treatment centers.

Overall, the importance of providing surgical candidates with information to make informed decisions should be one of the major applications of ongoing QOL research related to DBS surgery. This could lead to satisfied DBS recipients who after receiving quality surgical intervention utilize the health system less, reducing the overall cost of health care. New treatments for PD patients are on the horizon. Potentially less invasive techniques such as Spinal Stimulation have been found to normalize movements in mice and rats with Parkinson-like symptoms (Kuehn, 2009). In addition, broader
applications for DBS are being investigated for use in psychiatric disorders such as Major Depressive Disorder, Obsessive Compulsive Disorder, and Tourette’s Syndrome (Goodman & Insel, 2009). Thus, findings from QOL DBS studies on PD patients, such as this one, may be applicable to upcoming PD treatments or new applications of the DBS intervention.

Summary

In this study, time at seven and a half year follow-up was suggestive of a decline in QOL related to cognitions. Time was non-significant in determining overall QOL. However, this finding was likely related to power limitations of the data set. Age appeared to have a significant relationship with Stigma-related QOL, with younger age at DBS intervention resulting in a longer period of maintained gains. Disease Duration significantly correlated with three subscales of the PDQ-39: (a) Emotional Well-Being, (b) Stigma, and (c) Social Support. Emotional Well-Being seemed to improve as Disease Duration increased after DBS. Shorter Disease Duration at time of intervention resulted in less clinically significant differences in the Stigma subscale at seven and a half year follow-up. Ultimately, these preliminary findings suggested a constellation of changes that developed after DBS neurostimulation. It is important for future research to explore the domains and dimensions of this “constellation” and to explore ways to measure it that are most helpful to the health care community and most faithful to the depth and breadth of the meaning of QOL.
References


