8-1-2010

Neuropsychological Aspects of Fetal Transplant Surgery for the Treatment of Parkinson's Disease: A Longitudinal Study

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Neuropsychological Aspects of Fetal Transplant Surgery for the
Treatment of Parkinson's Disease:
A Longitudinal Study

A Dissertation
Presented to
the Morgridge College of Education
University of Denver

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

by
Gina M. Signoracci
August 2010
Advisor: Dr. Cyndy McRae
Abstract

Parkinson’s disease (PD) is a neurodegenerative disease often characterized at the time of diagnosis by resting tremor, rigidity, and/or bradykinesia. Over the course of the disease, motor functioning, cognitive functioning, and quality of life typically decline as the effectiveness of drug therapies diminishes. This study utilized medical, neuropsychological and quality of life data that were collected as part of a double-blind placebo surgery trial in which 40 patients were randomly assigned to receive bilateral transplantation of embryonic mesencephalic dopamine cells into the putamen or sham surgery. Nineteen women and 21 men participated in the study. Analyses focused on relationships between neuropsychological, motor, and quality of life data at baseline, 12, and 24 months post-surgery. Other analyses investigated differences between older (61+) and younger (≤ 60) patients in regard to neuropsychological functioning, as well as neuropsychological differences between those who thought they received the transplant and those who thought they received sham surgery at 12 months.

Results of this study indicated that a measure of verbal fluency and two measures of visual memory correlated most consistently with measures of motor functioning and quality of life. Depression was related to lower scores on neuropsychological assessments at 12 months and perceived support was related to higher neuropsychological scores at 24 months. Other results indicated that younger participants obtained higher scores on measures of verbal fluency and verbal memory than older participants. Finally, there
were no differences between those who thought they received the transplant and those who thought they received the sham surgery before the double-blind was lifted at 12 months in regard to neuropsychological performance. Thus, the placebo effect, which was apparent in previous medical and quality of life analyses using these data, did not extend to neuropsychological test performance.
Acknowledgements

To complete a task of this magnitude, I was supported and encouraged by many. A special thanks to Dr. Cyndy McRae, who led me through this experience. I will always remember you for your generosity and encouragement. A special thanks to Dr. Yakkov Stern for allowing me to collaborate on this special project. Thank you to Dr. Dan Russell for being available for consultation along the way. I thank Dr. Barbara Vollmer, Dr. Kathy Green, and Dr. Matin for being thoughtful and supportive committee members. I am grateful for your investment of time and energy to my experience.

To my mother, thank you for supporting me through every step of the doctoral process including this dissertation. I have been successful because of your example, friendship, encouragement, and love. Life has challenged us many times and in many ways and it is because of how we have handled these tests that we have such wonderful testimonies. It is also because of these tests that we have learned to celebrate the things that matter most. Thank you for being available to ground me and offer perspective in the most trying of times. Our relationship is all the proof necessary of something bigger than us, something unexplainable that guides us to all of our experiences. While I am proud of the things I have accomplished and eagerly await future blessings, I will always be most proud that I am your daughter. Thank you for being you and for helping me to become what I am meant to be.
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Chapter I

Introduction

*Description of Parkinson’s disease*

Parkinson’s disease (PD) is a neurodegenerative disease characterized by resting
tremor, rigidity, and bradykinesia, among other motor deficits. This progressive
neurological disease results in loss of nerve cells in the substantia nigra and dopamine
depletion in the striatum (Gilbert et al., 2005).

PD was first described by James Parkinson in 1817 when he wrote “An essay on
shaking palsy” in which he presented the onset and progression of motor symptoms.
Since this essay, medical advances have been made with respect to understanding the
nature of the disease and subsequent treatment. While several treatments, including
medication management, have been utilized to slow degeneration of the disease, little
advancement has been made in the way of a cure.

While PD causes motor dysfunction, persons with PD often experience
neuropsychological deterioration resulting in difficulties in activities of daily living
(ADL) and quality of life. Areas of neuropsychological dysfunction include verbal
fluency, verbal memory, immediate memory, learning, visuospatial skills, and executive
functioning. While neuropsychological abilities decrease as the disease progresses,
decline in neuropsychological ability can be detected even in early stages of the disease
(Dubois & Pillon, 1997; Taylor & Saint-Cyr, 1995). To date, neurological assessment and
positron emission tomography (PET) scans are the most commonly used tools to assess neuropsychological and neurological functioning in PD.

Activities of daily living (ADL) are activities related to daily functioning. ADLs include activities related to hygiene, mobility, communication, basic bodily functions, sleep, work and leisure, and use of personal devices such as glasses, and hearing aids. Due to neuropsychological and motor decline in PD, many activities of daily living become difficult to perform, sometimes requiring assistance from, if not complete dependence upon others for help to complete these tasks. While not every person with PD is rendered completely dependent on others, most will experience deficits in several areas of ADLs over time.

Quality of life (QOL) refers to one’s ability to engage satisfactorily in ADLs and to experience global satisfaction with life. Quality of life in persons with PD is an important measure of the effectiveness of treatment. While the medical field is constantly on a search for a cure of PD, current treatment is focused on slowing the effects of the disease and preserving quality of life as long as possible.

Medications for Parkinson’s disease

Treatment of PD begins with medication management. A variety of medications are used to treat the disease, which are categorized as dopaminergic and non-dopaminergic drugs (Schapira & Olanow, 2004). Antiparkinsonian medications are prescribed to reduce symptoms of the disease; however, close monitoring of these drugs is required as use of the medication can lead to dopaminergic hallucinations and psychoses (Siderowf, 2001).
Levodopa (L-dopa) continues to be the most effective and most often prescribed dopaminergic agent (Ahlskog, 2001; Lang & Lozano, 1998b). PD patients using L-dopa often experience some improvement in rigidity and bradykinesia. While L-dopa has been shown to be beneficial, a ceiling effect can be experienced, rendering need for additional or alternate medications.

Metabolic inhibitors are sometimes used in conjunction with L-dopa in order to prolong plasma levels of the medication (Lang & Lozano, 1998b). Decarboxylase (Carbidopa) and Catechol-O-Methyltransferase inhibitors (Entacapone) are the two most common types of inhibitors prescribed. Bromocriptine, Pergolide, and Apomorphine are dopamine agonists that can be helpful in treating early stage PD and can delay the need for use of L-dopa (Lang & Lozano, 1998b; McPhee & Stewart, 2001). In addition, these medications are used to treat tremor, dystonia, depression, and drug-induced psychosis, enhance drug absorption, and reduce oxidative processes in the brain (Ahlskog, 2001).

*Surgical Treatment for Parkinson’s disease*

When tolerance to medication develops (e.g. the medications become less effective), the next step in treatment may be neurosurgery (Honey, Gross, & Lozano, 1999). Ablation, deep brain stimulation, and fetal cell transplantation are the three most common types of surgery used to treat PD (Honey, et al., 1999). While all procedures hold promise, fetal cell transplantation is the focus of this study.

During the 1980s, four patients with PD received transplantation of adrenal medulla tissue into part of the brain (Lindvall, 1989). Results from the initial studies seemed to hold promise, with subsequent studies supporting these findings and demonstrating moderate improvement in approximately 30 percent of the sample (Honey,
Gross, & Lozano, 1999). In the late 80s, intrastriatal grafts of fetal dopaminergic neurons were performed with modest results (Honey, Gross, & Lozano, 1999; Lindvall, 1989). Following these advancements, progress was made with respect to tissue preparation and transplant processes (Brundin et al., 2000; Clarkson et al., 1998; Kordower et al., 1995). Positive outcomes from these procedures included increased fluorodopa intake, exhibition of long-term grafted tissue survival, and some clinical improvement (Brundin et al., 2000; Freed et al., 2001; Kordower, Freeman et al., 1995).

Early transplant studies were largely focused on improvements in motor and quality of life. Freed et al., (2001) conducted a study of patients participating in the double-blind placebo surgery trial for the treatment of PD. In the double-blind placebo surgery trial, patients received bilateral transplantation of embryonic mesencephalic dopamine cells into the putamen or sham surgery. Stern and colleagues, part of the research group at Columbia University, reported on the neuropsychological aspects of the original fetal cell transplant study (Trott et al., 2003). They investigated possible changes in cognition from baseline to 12 months following the procedure in the transplant and sham groups.

Statement of Problem

Because the neuropsychological data were only analyzed from baseline to 12 months and considered differences only between the real and sham surgery groups, there is much still to be learned from these data. One of the most important questions in the original study was whether neuropsychological functioning changed over time. As described elsewhere in regard to this study (McRae et al., 2004), 12 months was not a long enough time to realize all of the changes resulting from the transplant. Thus, it is
very important to analyze the neuropsychological data as thoroughly as possible and to consider analyses extending out to 24 months in each group; those who originally received the transplant and those who first received the sham surgery and then received the transplant.

The current study will continue the analyses of neuropsychological data to assess changes in cognition from baseline to 24 months in the group who received the transplant surgery and also to examine changes in the group who received the sham surgery first and then received the transplant surgery. Instruments were chosen to gather a comprehensive picture of neuropsychological functioning in patients receiving bilateral transplantation of embryonic mesencephalic dopamine cells into the putamen and those receiving sham surgery (Freed et al., 2001). Together, these assessment instruments aimed to capture ability for verbal fluency, verbal learning and memory, executive functioning, and visual memory.

Verbal fluency is the ease with which a person uses language, the speed with which an individual can make word associations, and the ability to organize verbal output (Ostrosky-Solis et al., 2007; Scholtissen et al., 2006). Verbal learning and memory allows individuals to store new information that is said to them or that they are able to hear. Executive functioning is comprised of capacities that allow an individual to successfully engage in independent, purposive, and self-serving behavior and includes mental flexibility, ability to assess self and others, and to plan, initiate, and follow through among others. Visual memory is the ability to learn and store new information that is shown to them or that they are able to see (Lezak, Howieson, & Loring, 2004).
The present study will focus on several tests that represent the broad domains assessed in the original study. The tests include: the Controlled Oral Word Association Test (COWAT; Coelho, 1984; desRosiers & Kavanagh, 1987; Spreen & Strauss, 1991), Boston Diagnostic Aphasia Evaluation (BDAE; Goodglass & Kaplan, 1972; Goodglass & Kaplan 1983b; Spreen & Strauss, 1991), Digit Span Forward and Digit Span Backward subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Kaufman & Lichtenberger, 1999; Strauss, Sherman, & Spreen, 2006; Wechsler, 1981), the California Verbal Learning Test (CVLT; Delis et al., 1987; Strauss, Sherman, & Spreen, 2006), the Benton Visual Retention Test (BVRT; Benton, 1981; Swan et al., 1990; Whaler, 1956; Spreen & Strauss, 1991), and the Wisconsin Card Sorting Test (WCST; Berg, 1948; Grant & Berg, 1948; Heaton et al., 1981).

In addition to the focus on neuropsychological functioning, this study will also incorporate and examine relationships between neuropsychological functioning, motor functioning, and quality of life at baseline, 12, and 24 months post-surgery in both the real and initial sham surgery groups. Motor functioning and severity of symptoms were assessed primarily using the Unified Parkinson’s Disease Rating Scale (UPDRS); (Fahn & Elton, 1987). Assessment was completed when patients were deemed at their best (“on”) and at their worst (“off”). “On” and “off” refer to patients being on and off optimal levels of medication, which then affects their physical functioning. Scores on the UPDRS were averaged across several administrations at baseline and follow-up. Ultimately only the data during the practically defined “off” periods were used. When patients were “off” PD medications, they had not taken these particular medications for approximately 24 hours. Although data were collected for both “on” and “off” periods,
only data from “off” periods were analyzed in this study as UPDRS results during “off” times were unaffected by medication changes (Freed et al., 2001). The Hoehn and Yahr Stage of Disease Scale (Hoehn & Yahr, 1967), Schwab and England Activities of Daily Living Scale (Schwab & England, 1969), and Global Rating of Motor Functioning (Freed et al., 2001) were administered during the same times as the UPDRS and were used to capture stage of disease and ability to perform ADLs.

Quality of life was originally examined in terms of three primary domains: Physical Functioning, Emotional Functioning, and Social Functioning (McRae, 2004). For purposes of this investigation, only a few scales from the composite variables comparing these domains were used. These include the Center for Epidemiologic Studies Depression Scale (CES-D); (Hahn et al., 1999; Radloff, 1977), Social Provisions Scale (SPS); (Cutrona & Russell, 1987), one item from the Short-Form Health Survey (SF-36); (Ware & Sherbourne, 1992), and the “Free or Restricted” item from the original QOL questionnaire (McRae et al., 2004). These measures were sent through the mail approximately one week after the neurological and neuropsychological assessments.

Use of Placebo

Stewart-Williams (2004, p.198) defined the placebo effect as “any genuine psychological or physiological response to an inert or irrelevant substance or procedure.” Recent biochemical evidence has indicated that the placebo effect in PD patients is related to dopamine release in the striatum, which is believed to be triggered by the expectation of clinical benefit (de la Fuente-Fernandez, 2004).

Results of the original study, of which this is a part, showed a strong placebo effect in terms of perceived treatment, or the type of surgery patients thought they
received. Thus, an additional focus of this study was to analyze the data in terms of perceived treatment at 12 months. These analyses were done to examine the influence of the placebo effect on neuropsychological functioning. Previous studies have shown that the placebo effect can positively influence patients’ quality of life. Therefore, this study examined this phenomenon more comprehensively by considering its possible effect on neuropsychological data.

Data Collection and Research Questions

The original data for this study were collected by Yakkov Stern and colleagues at the Taub Institute at Columbia University (Trott et al., 2003). This study served as a collaborative investigation between the group at Columbia and this author.

Research questions relevant to this study are as follows:

1) What are the relationships between neuropsychological functioning and QOL for real and sham surgery groups at baseline, 12, and 24 months post-surgery?

2) What are the relationships between neuropsychological functioning and motor functioning for real and sham surgery groups at baseline, 12, and 24 months post-surgery?

3) Are there any differences at baseline, 12, and 24 months between older (61+) and younger patients (≤60) in the domain of neuropsychological functioning?

4) Are there any differences at 12 months between those who thought they received the fetal cell transplant and those who thought they received the sham surgery in terms of neuropsychological functioning?
Because this study deals with neurological and neuropsychological terms and information that are not commonly known, definitions of terms used throughout this dissertation are presented below.

**Activities of daily living (ADL):** activities related to daily functioning. ADLs include activities related to hygiene, mobility, communication, basic bodily functions, sleep, work and leisure, and use of personal devices such as glasses, and hearing aids (Wiener, J.M., Hanley, R.J., Clark, R., & Van Nostrand, J.F., 1990).

**Bradykinesia:** general slowness of movement (Paulson & Stern, 2004).

**Dopamine:** “a neurotransmitter associated with involuntary movement disorders and several neuropsychiatric syndromes” (Loring, 1999).

**Putamen:** “the part of the midbrain involved most prominently in the motor functions of the basal ganglia. The putamen is receives afferents from cerebral cortex (primarily motor and somatosensory areas), and from the substantia nigra (compact part) and the centromedian nucleus of the thalamus” (Nolte, 2002).

**Quality of life (QOL):** “the characterization of health concern or disease effects on patient lifestyle on daily functioning” (Loring, 1999).

**Substantia nigra:** “large midbrain nucleus that is often considered part of the basal ganglia and is associated with motor functioning. Many cells in the substantia nigra contain dopamine and melanin, a byproduct of dopamine metabolism” (Loring, 1999).

**Verbal fluency** is the ease with which a person uses language, the speed with which an individual can make word associations, and the ability to organize verbal output (Ostrosky-Solis et al., 2007; Scholtissen et al., 2006).

**Verbal learning and memory** “acquisition and retention of stimuli that are verbal or linguistic in nature” (Loring, 1999).

**Executive functioning** “cognitive abilities necessary for complex goal-directed behavior and adaptation to a range of environmental changes and demands” (Loring, 1999).

**Visual memory** is the ability to learn and store new information that is shown to them or that they are able to see (Lezak, Howieson, & Loring, 2004).
In summary, this chapter reviewed the nature of Parkinson’s disease, treatment, domains commonly affected by the disease, and previous research that has been conducted and that inspired the current study. Trott et al., 2003 examined data from baseline to 12 months post-surgery and this author was interested in examining additional changes over time. This study is an important contribution to the literature on treatment of Parkinson’s disease. Studies such as this offer direction related to appropriate medical intervention and its influence on overall functioning and quality of life in persons with PD.

Chapter II will discuss literature related to PD, including neuropsychological functioning, motor functioning, and quality of life.
Overview of Parkinson’s disease

Parkinson’s disease (PD) is a progressive neurodegenerative disease resulting in declines in neuropsychological and physical functioning as well as quality of life. The neurodegenerative aspect of PD includes dopaminergic cell loss in the substantia nigra and the presence of Lewey bodies, which project to the striatum (Hague, Klaffke, & Bandmann, 2007; Kish, et al., 1988; Rongve, & Aarsland, 2006). This dopaminergic cell loss results in motor symptoms, which have become characteristic of the disease and include resting tremor, cogwheel rigidity, bradykinesia, postural instability, and problems with gait (Geng, Li, & Zee, 2006). The motor symptoms develop over time and often increase in intensity. Changes in motor symptoms and functioning pose challenges to the individual and can affect overall quality of life.

Results of studies using neuropsychological testing have found neuropsychological deficits in individuals with PD even in early stages of the disease (Dubois & Pillon, 1997; Taylor & Saint-Cyr, 1995). Due to neurological degeneration, overall neuropsychological impairment occurs in individuals with PD and greatly increases the likelihood of dementia. Psychotic symptoms may also be present and are often regarded as concerning features of dementia and include delusions and hallucinations (Rongve & Aarsland, 2006).
Both cortical and subcortical deficits are seen in individuals with Parkinson’s disease. These deficits are evidenced by reduced speed and attention, impaired working memory, poor performance on executive and visuospatial tasks, memory and language problems. While stages of disease tend to progress in a sequential manner, neuropsychological profiles of individuals with PD vary throughout the stages (Rongve & Aasrsland, 2006; Hoehn & Yahr, 1967). Although the cause of PD is unknown, many treatments have been developed to address the symptoms of the disease.

**History of Parkinson’s disease**

Dr. James Parkinson first brought attention to what is now known as Parkinson’s disease in 1817 with his essay entitled “An essay on the shaking palsy.” Dr. Parkinson wrote about his observations related to onset, slow progression of, and the asymmetrical presentation of symptoms, which he noted most often began in the hand or arm. Dr. Parkinson commented on the fact that individuals with the disease often did not seek medical attention until later stages of the disease. Throughout Dr. Parkinson’s essay, he explained and described symptoms such as insidious onset, resting tremor, asymmetric weakness and tremor (often in the hand or arm), postural instability, akinesia, gait difficulty, sleep disturbance, loss of fine motor skills, decrease in ability to perform activities of daily living, stooped posture, drooling, and constipation (Parkinson, 1817). Even in this early report on the disease, Parkinson noted that the disease most often occurred in individuals fifty years of age or older.

Throughout the essay, Parkinson described symptoms of the disease that were similar to the symptoms of other known diseases at the time while noting differences unique to PD. He also briefly reviewed several cases from which he then concluded that
the disease stemmed from “a diseased state of the medulla spinalis”, which has greatly influenced today’s research of the disease. He concluded this now famous essay with his hopes to find effective treatments and/or a cure for the disease. It seemed that even then he understood the challenges that were ahead.

James Parkinson’s work inspired further research and led to Charcot’s more exacting exploration into the symptoms of “shaking palsy.” In 1888 Charcot named this well-described complex group of symptoms, Parkinson’s disease (Goetz, et al., 2000). While research and technology have progressed with regard to understanding and treating PD, a cure continues to elude the medical field and those living with the disease.

Clinical Characteristics and Diagnosis

James Parkinson (1817) identified and described most of the characteristics still used today to diagnose the disease. Of the many motor symptoms, resting tremor, rigidity, and bradykinesia are regarded as the hallmarks of PD. Additional motor symptoms include akinesia, postural instability, loss of fine motor skills, oculomotor abnormalities, blink rate, facial mask, freezing, and speech abnormalities (Gelb, Oliver, & Gilman, 1999). These symptoms can cause discomfort and disability.

Up to 90 percent of patients with PD experience resting tremor (Gelb et al., 1999; Lang & Lozano, 1998a). Resting tremor is most obvious when the patient is in nonstanding positions such as sitting or reclining and is agitated by stressful conditions. Temporary breaks in resting tremor can be experienced and typically are due to voluntary movement. Tremors are not present during sleep (Bunting-Perry, 2006).
Rigidity is defined as resistance to passive movement while extending and flexing through entire range of movement and is experienced by up to 99% of PD patients (Bunting-Perry 2006; Gelb, et al., 1999).

Bradykinesia is slowness of movement or the inability to move quickly. With progression of the disease, akinesia becomes more common and describes the inability to initiate and/or maintain movement (Siderowf, 2001).

PD is often described using stage criteria as defined by Hoehn and Yahr (1967). Hoehn and Yahr used the symptoms identified by Parkinson (1817), along with further clinical research to define the stages of disease that are used widely today. The Unified Parkinson’s Disease Rating Scale (UPDRS) is a commonly used measure, which assess severity of typical symptoms of the disease.

Parkinson (1817) noted that onset of symptoms can often be asymmetrical and begin in one hand or foot in the form of a tremor. The tremor then often affects other body parts on the same side of onset (ipsilaterally) and will then move to the opposite side of the body (contralaterally) (Siderowf, 2001). Siderowf reported that up to 40 percent of PD patients also experience numbness, tingling, aching, and muscle soreness.

In addition to motor symptoms and discomfort, between 74% to 98% of patients experience sleep disturbance. This disturbance can present as excessive daytime sleepiness, insomnia, rapid eye movement (REM) sleep disturbance, and restless legs syndrome (RLS); (Siderowf, 2001).

Neuropsychological Impairment

The neurodegenerative nature of PD often leads to neuropsychological impairment and psychiatric symptoms. With progression of the disease and age of
patient, the risk of neuropsychological impairment and dementia increases. Overall neuropsychological impairment can be found even in patients newly diagnosed with PD. Muslimović, Post, Speelman, and Schmand (2005) conducted a study to determine the profile of neuropsychological dysfunction in newly diagnosed PD patients as compared to healthy controls. Of 129 potential participants, several were excluded due to refusal, stroke, difficulties with comprehension, and global neuropsychological deterioration, leaving 115 participants to participate and compare with 70 healthy controls. The Unified Parkinson’s Disease Rating Scale was utilized to rate motor symptoms, the Hoehn and Yahr Stage of Disease Scale was utilized to determine stage of disease, and the Schwab and England Activities of Daily Living Scale was utilized to capture aspects of daily functioning. Many neuropsychological assessments were administered to the participants including the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Test, Trail Making Test Part A, Stroop Colour Word Test Part A and B, an adapted version of the WAIS-R Forward and Backward Digit Span, Boston Naming Test (BNT), Visual Association Test (VAT), Modified Wisconsin Card Sorting Test (MWCST), Controlled Oral Word Association Test (COWAT), and the Judgment of Line Orientation test (JOLO). Additionally, the Hospital Anxiety and Depression Scale (HADS) was used to capture affective disturbances.

Results of the study indicated the presence of neuropsychological dysfunction in PD patients particularly in the areas of memory, attention, and executive function. In general, PD patients performed lower on the neuropsychological assessments than controls, with the Digit Symbol Test differentiating PD patients from controls most effectively. Authors also found that the degree of neuropsychological dysfunction was
not associated with severity of any of the cardinal motor symptoms of the disease (bradykinesia, tremor, and rigidity). This was evidenced by the fact that patients exhibited neuropsychological decline without worsening of physical symptoms. The authors reported that this finding suggests that neuropsychological neuropathological changes are different from those responsible for motor functioning. This finding facilitated greater understanding of neuropsychological decline in PD patients as well as delineation of neuropsychological and motor processes.

The importance of assessing verbal fluency in PD patients was explained by Abernathy, Donovan, Mcdowall, and Siegert (1999). The authors reported that there are four neuropsychological processes that are involved in such tasks. These four processes, as described by Auriacombe, Grossman, et al. (1993), are attention and vigilance, a lexical or semantic store, a retrieval mechanism, and working memory. The authors further reported that it can be difficult to isolate the particular processes at work during verbal fluency tasks because they are not directly observable or quantifiable. Therefore, the study by Abernathy, Donovan, Mcdowall, and Siegert was designed to focus on clustering and switching to better differentiate processes. This decision had been preceded by the work of Troyer et al. (1997) who suggested that clustering involves accessing a word store while switching involves search processes. Therefore, the four identified processes of attention and vigilance, a lexical or semantic store, a retrieval mechanism, and working memory can be assessed through focus on clustering and switching. The authors defined clustering as generation of words that share a semantic or phonemic similarity while switching was defined as the ability to shift between the clusters.
Thirteen PD patients were compared with eleven healthy controls on a semantic and a phonemic verbal fluency task to assess verbal fluency abilities of clustering and switching in PD patients. Comprising the PD subject pool were nine male and four female participants between the ages of 45 and 85. The control group consisted of four male and seven female participants and ranged in age from 46 to 81. All thirteen participants in the experimental group were in early or middle stages of disease as described by Hoehn and Yahr (1967). Duration of illness for the experimental patients ranged from just under one year to eighteen years with most patients exhibiting motor symptoms of bradykinesia and tremor.

Prior to verbal fluency tasks, each participant was given the Mini-Mental Status Exam (MMSE) and the Wechsler Adult Intelligence Scale-Revised (WAIS-R). Each participant was then administered the Controlled Oral Word Fluency Test (COWAT) from the Multilingual Aphasia Examination (Benton & Hamsher, 1976). This phonemic fluency test required patients to list words beginning with the letters F, A, and S. Patients were instructed not to use proper nouns or root words with different suffixes. Sixty seconds were given for each list to be completed. Patients were also given the semantic naming task, known as the Animal Naming subtest, from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1972). This test required patients to name animals. While this test typically allows 90 seconds to complete, the authors shortened the length of time to 60 seconds to make it compatible with the COWAT. Before the Animal Naming test was given, patients were given a trial test, which required patients to name vegetables. The presentation of phonemic and semantic tasks was randomized across participants.
Results of this study concluded that PD patients exhibited impairment on both phonemic and semantic tasks as compared to healthy controls. The exhibited deficits on switching tasks are indicative of PD patients having challenges with retrieval, which is a result of dysfunction in the prefrontal cortex. Further, retrieval involves other processes such as the ability to monitor words produced, ability to quickly access words when a specific category or letter is exhausted, and to disengage from one category and switch to a different one. Little difference was seen between the two groups on clustering tasks, which depend on intact temporal-lobe functioning. Authors added that the difference that was seen may reflect the difficulty for the PD patient in switching and set shifting, but that nothing conclusive could be noted. Overall, this study by Abernathy, Donovan, Mcdowall, and Siegert (1999) contributed to previous findings supporting deficits in frontal and temporal lobe functioning in PD patients as compared to healthy controls and brings to light deficits in neuropsychological processes that warrant further examination.

Further examination of neuropsychological impairment in PD was done by Bouquet, Bonnaud, and Gil (2003) who designed a study to focus on attention and verbal fluency. The authors investigated attention and verbal fluency as these tasks are correlated with executive functioning in the PD patient, or the ability to organize behavioral tasks. They hypothesized that performance on attention and verbal fluency tasks may explain neuropsychological resources that relate to executive processes in this population.

The authors conducted a study, in France, involving 20 patients, 12 men and 8 women, diagnosed with PD. Severity ranged between stages 1 and 3 as described by the Hoehn and Yahr Stage of Disease Scale. These 20 PD patients were compared with 20
healthy controls. All participants were administered an adapted version of the Hayling Test for French Speakers as described by Burgess and Shallice (1996) to evaluate the ability to inhibit a prominent response. The Hayling Test consisted of 28 sentences for which the final word was omitted. Sentences were selected with guidance from Robichon, Besson, and Faita (1996), who had previously established norms for French speakers. In section A of the test, sentences were read to the patient with the expectation that the patient would provide an appropriate word to complete the sentence. In section B of the test, sentences were read to the patient with the expectation that the patient would provide a nonsense word to complete the sentence. In section B, if the patient provided a word that related to the sentence, the patient was told that the word was related to the sentence, instructions were repeated, and errors documented.

Three verbal fluency tasks were completed by each subject and included a Phonemic Word Fluency task, a Semantic Word Fluency Task, and an Alternating Word Fluency task. The Phonemic Word Fluency (PWF) task required patients to generate words with the initial letter M, with further instruction that proper nouns and simple variations of words could not be used. The Semantic Word Fluency (SWF) task required patients to list animals, and the Alternating Word Fluency (AWF) task required patients to generate words from the categories of boys’ names and fruits, with the expectation that the patient alternately generate exemplars from each category. Each task was given a time limit of 60 seconds. Finally, the Trail Making Test (TMT) was administered as described by Lezak (1995), with both Parts A and B given respectively. Part A of the TMT required patients to connect numbers in consecutive order while Part B required patients to alternately connect numbers and letters in consecutive order; ie., 1, A, 2, B, etc.
Results of the analyses indicated that PD patients exhibited greater latencies on both sections of the Hayling Test compared to controls. Notably, both patients and controls exhibited the same number of errors on section B, which required completion of sentences with a nonsense word. Additionally, PD patients performed poorer on all three verbal fluency tasks compared to controls, which may be evidence of impairment in some executive processes such as inhibition.

Additional exploration of verbal capabilities was conducted by Gilbert, Bherer, Belleville, and Chouinard (2005), with a specific investigation of verbal working memory in PD patients. The authors assessed 14 non-demented PD patients with 14 matched controls to test three areas related to working memory. Most of the experimental participants were receiving L-dopa treatment or some related combination of medication. Two patients were taking anticholinergic medications only, and one participant was unmedicated. The PD participants varied between stages one and three of the disease with a mean duration of illness of 7.29 years. The authors were interested in investigating decrements in working memory specific to storage deficits and executive impairment, relation of reduction in psychomotor speed to working memory deficits, and measurement of executive components.

All patients were administered the following assessments: an adapted version of the Forward Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) to assess storage, alphabetical recall test and updating memory (direct) task to assess executive function, the Purdue Pegboard test, Digit Symbol Substitution Test (DSST), and a reaction time (RT) task to assess motor and psychomotor abilities. Within the alphabetical recall test there were two conditions: alphabetical and direct. Participants
were read a list of words and then asked to recall them. In the direct condition participants were asked to recall the words in the same order as they were given. In the alphabetical condition participants were again asked to recall the list of words, this time with the added requirement to rearrange them in alphabetical order.

Although not statistically significant, results of the Alphabetical Recall test showed that PD participants exhibited lower alphabetical recall than direct recall. Both groups performed similarly on the Updating Task. Results of the motor and psychomotor speed measures revealed the greatest differences between PD participants and controls. On the Purdue Pegboard Test, PD participants exhibited significant motor slowing compared to controls. Slower performance was also seen in the PD groups on the DSST and RT tasks although no statistical differences were found. Overall, authors reported that this study indicated that verbal short-term storage in the PD participants was intact as evidenced by performance on a digit span task. Performance on a test for updating memory was also concluded to be normal. Alternatively, data supported a deficit in executive functioning, which was specifically evidenced on a task requiring manipulation processes. Finally, motor and psychomotor speed was decreased in experimental participants versus controls.

Another group of authors investigating verbal working memory deficits were Graceffà, Carlesmino, Peppe, and Caltagirone (1999). Specifically, functionality of the Articulatory Loop and of the Central Executive during verbal tasks was assessed. Lezak et al., (2004) explained that many processes, including decision making, contribute to working memory. Therefore, assessing performance on verbal tasks captures an important aspect of working memory function in the individual with PD.
The authors explained that the Central Executive is comprised of the Articulatory loop and the Visuospatial Sketchpad and that these two components are known as slave systems. The Central Executive is devoted to reasoning, planning, and to the retention of activity of slave systems. The Articulatory Loop also has two components and is a system specialized for storage of verbal material. Its subcomponents include the phonological store and articulatory rehearsal. The phonological store maintains material in a phonological code while the articulatory rehearsal refreshes temporary traces preventing decay of stored material. The Visuospatial Sketchpad is a system that is devoted to the handling of mental images and to temporarily store visuospatial information. Baddley and Hitch (1974) and Norman and Shallice (1986), as cited in Lezak et al., (2004), added that in addition to the Central Executive, a supervisory attentional system is also involved. Measures of attention are often embedded within assessments of working memory to capture performance on the multiple constructs that contribute to working memory.

The authors assessed 12 patients presenting with a bilateral form of rigid-akinetic, non-demented PD. All patients were on medication and were exhibiting a stable response to it. A modified version of a word span test developed by Brizzolara et al. (1993) and the Brown-Peterson Paradigm developed by Brown (1958) and Peterson (1959) were utilized in this study. The word span test was composed of five word lists composed of sequences of strings of two to eight words in length. The first three lists of the test were composed of two-syllable words differing for use frequency and phonological similarity. Lists four and five were composed of four-syllable, phonologically dissimilar, high and low frequency words respectively. During the Brown-Peterson Paradigm participants were
asked to recall three consonant strings following 5, 10, and 20 second retention times. Retention times were filled by either no concurrent task or by a serial subtraction task. PD patients in this study displayed normal word span performance with no reduction due to word length, performing similarly to controls. PD patients also exhibited normal phonological similarity and word frequency effects in word span. The authors reported that these results demonstrated preserved retention capacity of the phonological store and a normal contribution of lexical-semantic knowledge to short-term memory tasks, thus supporting normal functioning of the Articulatory Loop in this PD sample. PD patients showed normal letter recall on the Brown-Peterson procedure when there was no concurrent task during retention time. However, in the presence of the serial subtraction concurrent task, PD patients displayed noticeable and premature performance decay when compared to controls. Ultimately, results of this study did not support previous research suggesting that PD patients experience Central Executive and Articulatory Loop deficits.

Further examination of verbal memory was done by Ivory, Knight, Longmore, and Caradoc-Davies (1999). The authors based their research on previous work using the Wechsler Memory Scale (WMS) to identify global patterns of deficits in PD patients. For this study, the authors’ objective was to document deficits within a single, well-defined sample of non-demented PD patients. Of particular interest to the authors were the areas of direct and indirect memory, verbal memory, remote memory, metamemory, and awareness of mnestic deficits. 20 non-demented PD patients were compared to 20 medical control group patients with similar physical disabilities, such as motor slowing
and gait. The PD group had a mean age of 70.80 and an average duration of disease of 5.15 years. The PD patients received standard forms of medical management.

Four subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R, Digit Span, Picture Completion, Similarities, and Arithmetic) were administered to participants along with the Controlled Oral Word Association Test (COWAT) to assess for global deficits. Additional tests were given to assess for specific types of memory. Indirect and direct memory were assessed by focusing on free recall and word completion priming and with use of word lists built from the work of Burke et al., (1994). In these tasks, participants were asked to complete word stems from two different word lists and to recall as many of the ten stimulus words as possible. Verbal memory was explored using the Rey Auditory Verbal Learning Test (RVLT) as described by Lezak (1995). In this task an original word list was presented with opportunity to recall the words. An interference list was then presented with the same opportunity for recall. Finally, participants were asked to recall as many words as possible from the original list of words. Remote memory was tested with focus on memory for public information using The Otago Test of Remote Memory (OTRM). In this task patients were presented with a list of 70 famous people spanning many decades. Participants were asked to describe the people listed. Metamemory was examined through asking 23 general knowledge questions. These 23 questions were extracted from an original pool of 300 designed by Nelson and Narens (1980). In this task, participants were asked to answer the general knowledge questions and then rate their level of confidence with each answer. Awareness of mnestic deficits was assessed following the format of Squire and Zousounis (1988)
using 16 questionnaire items asking participants to rate their own ability to recall and to maintain attention.

Results of this study indicated that on measures of global deficits, only performance on Digit Span differentiated PD participants from controls. On average, PD participants performed two points below controls, but no clinical significance was obtained. PD patients recalled fewer words in the direct memory, free recall tasks. However, there were no significant differences between PD participants and controls on the indirect memory, word completion task. Upon further exploration of particular trials of the RVLT, PD patients exhibited significant impairment on the direct memory, free recall task in the incidental learning context. Results of remote memory testing revealed no significant difference between groups. However, PD participants exhibited inferior performance on items from earlier decades versus later. Upon examination of results from the general knowledge, metamemory task, PD and control participants performed similarly. Finally, evaluation of confidence ratings on each question to assess awareness of mnestic abilities concluded that both groups rated items in a similar manner.

In conclusion, this study found that PD participants performed relatively similarly to control participants. Only the areas of incidental learning specific to verbal recall and remote memory differentiated the PD group. Although statistical significance was not obtained, results suggested that mild impairment was present in this particular group of PD patients.

A nonverbal aspect of working memory is visuospatial memory. Postle et al., (1997) created a study designed to better understand spatial visual working memory in early stage PD patients. Authors used a modified version of a visual delayed response test
developed by Smith et al. (1995) during which participants were presented with two stimuli and then, after a delay period, were asked to match a probe stimulus to one of the two originally presented. Participants were required to match probes to original stimuli by proximity (spatial condition) or by similarity (object condition). The stimuli were irregular polygons as designed by Attneave and Arnoult (1956) and Vanderplas and Garvin (1959). Fifteen PD patients who were determined to be in early stages of their disease and fifteen control participants were assessed. One purpose of the study was to examine the correlation between side of onset of the disease and performance on the research tasks. Eleven of the PD participants had left-side onset leaving only four with right-side onset. In the spatial condition, participants responded to probes matching, being near to, or far from the original stimuli. In the object condition, participants responded to probes matching, being similar to, or dissimilar to original stimuli. All trials were conducted through use of a computer allowing for timed presentation of stimuli as well as recording of reaction time (RT). In both conditions, spatial and object, perceptual and memory tests were embedded within the trials. The Perceptual Test consisted of varying exposure of targets on each 20-block trial until the participant was able to achieve criterion level performance of 80%-90% correct on two consecutive blocks. When this was achieved, the Memory Test was engaged, keeping the exposure time determined during the perceptual test and then increasing the delay by 3 seconds. The Memory Test consisted of four, 40-trial blocks in each condition. Complete testing took place in two sessions, one for object and one for spatial tasks, with several hours between the sessions. The order of the sessions was counterbalanced within each group.
Results of the Perceptual Test indicated that both groups required longer target exposure time to achieve the desired percentage correct in the Object Test versus the Spatial Test and that PD participants required longer exposure times than controls in both conditions. When evaluating Memory Test results, PD participants and controls differed in performance on the Spatial Test but not on the Object Test. Further, control participants made significantly fewer errors on the Spatial Test than did PD participants. Both groups exhibited faster reaction times for Spatial Memory than for Object Memory without significant differentiation between the groups. Finally, the authors examined the relationship between side of onset and age with Memory Test performance. Results indicated that performance of PD participants on the Memory Test was not affected by severity of disease, nor was it correlated with degree of basic motor deficits. However, when evaluating complex Motor Functioning, Memory Test performance appeared to vary. Understanding that the PD subject pool was unequal with respect to side of onset, it did not appear that side of onset affected performance on the Memory Test.

To conclude, results from this study indicated that individuals with PD exhibited spatial memory deficits when compared to controls. Results also suggested that spatial delayed response of PD patients on this type of memory test cannot be attributed to basic motor deficit or severity of disease. Analyses of the data supported the idea that visual working memory is comprised of two material-specific systems. One system is responsible for storing and manipulating memory for locations in space while the other is responsible for storing and manipulating memory for the features of objects.

Kemps, Szmalec, Vandierendonk, and Crevits (2004) examined visuospatial processing in PD with particular interest in locus of such deficits. The authors were
interested in assessing visuospatial deficits while working to determine if the deficit is most related to the Central Executive or the Visuospatial Sketch Pad. As previously described, the Central Executive is a system responsible for selecting and updating information, inhibiting stereotyped responses, and the coordination of simultaneously performed tasks (Kemps et al., 2004). The Visuospatial Sketch Pad is a slave system to the Central Executive and is involved in temporary storage and processing of verbal and visuospatial information. Authors utilized three tasks in this study: the Corsi blocks task, a concurrent Visuospatial Sketch Pad task, and a concurrent Central Executive task to assess these systems in persons with PD.

The Corsi blocks task (Milner, 1971) requires participants to recall increasingly longer sequences of spatial locations of blocks. The experimenter touches a sequence of blocks and requests that the person reproduce the sequence by touching the blocks themselves. The concurrent visuospatial task requests that participants repeatedly tap four keyboard keys with their dominant hand while looking at the Corsi block display. The concurrent Central Executive task requests participants to press a space bar in response to hearing random beeps. All participants completed the Corsi block task first, followed by the spatial tapping and random interval tasks, which were counterbalanced across participants.

Fifteen PD participants were compared with 15 healthy controls across assessments. Both groups ranged in age from 60-75. Those with PD had an average duration of illness of 11.93 years and ranged between stages one and three of illness. Results indicated no significant differences between experimental and control groups in performance of the concurrent spatial tapping and random interval repetition tasks. Upon
examination of data from the Corsi block task, PD participants recalled fewer trials correctly. Data analysis of recall scores for PD patients revealed significant stage by concurrent task interaction. Specifically, stage 1 patients’ recall performance was most adversely affected by the random interval repetition task while the recall performance of participants in stages 2 and 3 was most adversely affected by spatial tapping. Authors also evaluated the effect of age on tasks, finding that within the PD group, age significantly correlated with performance on the Corsi Block task, which was not the case in the control group.

Ultimately, this study of working memory deficit specific to Visuospatial Sketch Pad and the Central Executive found that PD patients performed worse than controls on the Corsi Block task. Also, PD patients showed deficits on recall tasks with data analysis showing that age significantly and adversely affected performance compared to healthy controls. These results suggest that impaired visuospatial processing in PD results from dysfunction in both the Visuospatial Sketch Pad and the Central Executive. These deficits are related to dysfunction in the prefrontal-basal ganglia circuit. Results also showed that for PD patients, performance on the Corsi Block task was impacted by stage of disease. Taken together, these results suggest that Central Executive deficit is more prominent at disease onset while Visuospatial Sketch Pad deficits emerge in moderate stages of the illness. Also, because of the significant impact of age in the PD group, it can be inferred that PD patients are more susceptible to neuropsychological aging than healthy controls.

Cronin-Golomb and Braun (1997) designed a two part study to investigate visuospatial dysfunction and problem solving in PD. In this study, 50 PD participants, all engaged in varied medication management, were compared with 39 controls. Many
assessments were utilized in this study, including tests of problem-solving, visuospatial
performance, executive function, and verbal memory.

The Raven’s (Coloured) Progressive Matrices (RCPM) task was utilized to assess
problem solving. The assessment was designed by Raven (1965) and is comprised of
three subtests. Subtest A consists of items that are solvable through visual closure and is
described as having problems in the continuous pattern. Subtests Ab and B move from
closure problems to those in which symbols are used in an analogies test. Several
additional visuospatial tests were used in the study to assess spatial cognition and
visuoconstructive function (figure copying). Luria’s Mental Rotation Test required
participants to select one square from a four choice array that matched a rotated sample.
The Standardized Road-Map Test of Direction Sense required participants to trace a
dotted pathway on a map and indicate the direction at each turn. The Geometric Figures
Test was developed by the researchers and required participants to copy one simple and
one complex geometric figure. A recall condition took place ten minutes after the original
presentation and required participants to redraw the original two shapes.

Executive function was measured with a number of assessments. Symbolic
fluency was assessed by requiring participants to name as many words as possible that
began with the letters S and F with each trial limited to 60 seconds. Semantic fluency was
assessed by requiring participants to list as many members as possible in 60 seconds
within the categories of vegetables and four-footed animals. The Stroop Color-Word Test
was utilized to assess set-shifting ability. A mixed condition was included which
required participants to look at a stimulus with which incongruent color names were
written and name as many ink color as possible based on the stimulus. The Picture
Arrangement Test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) was used to assess concept formation.

Verbal memory was assessed with the paragraph (story) subtest of Randt, Brown, and Osborne’s Memory Test. Participants read a short story and after ten minutes were asked to report verbatim as much story content as possible. They were then required to answer questions about the story by choosing correct statements from a four choice array. Additional assessments utilized were the Benton Visual Recognition Test (BVRT) to assess visuospatial memory and the Boston Naming Test. The subtest of the BVRT that was used consists of presenting participants with a complex design for 10 seconds after which they are required to choose the target from a four-choice array. The Boston Naming Test examines participants’ ability to name objects and animals represented by line drawings.

In the first part of the study, authors examined performance on the RCPM alone. Results indicated that PD participants performed significantly worse on Subtest B than on Subtests A and Ab with undifferentiated results on these two tests. This outcome indicated that PD participants had left hemisphere (analogic reasoning) dysfunction.

Part two of the study examined the relation of performance on the RCPM with the other neurological tests. Overall, PD participants performed more poorly than controls. Authors utilized composite scores using multiple regression analysis to predict performance on the RCPM. The executive function composite score predicted performance on subtests Ab and B of the RCPM and the verbal memory composite score predicted performance on subtest B of the RCPM for PD participants. After running the same analyses for control participants, no composite scores were successful in
significantly predicting performance. The analyses required that the best three predictors of performance on Subtest A of the RCPM were the BVRT, Picture Arrangement and Road Map Tests. The Boston Naming Test, animal naming, and Picture Arrangement were significant predictors for performance on Subtests Ab and B. Authors then took a final step of reducing the analysis to only those significant predictors to conclude final, and most powerful, predictors of performance on the RCPM. The Road Map Test emerged as the only significant predictor of performance on Subtest A for PD participants. The Boston Naming Test, fluency-animals, and Picture Arrangement remained significant predictors of performance on Subtest Ab. The Boston Naming Test and Picture Arrangement were the only significant predictors of performance on Subtest B. Authors reported no evidence of multicolinearity. Results indicated that for PD participants, the visuospatial composite score was predictive of performance on Subtest A while the executive function composite score was predictive of performance on Subtests Ab and B.

In summary, when examining problem solving in persons with PD, impairment was exhibited and explained at least in part, by visuospatial deficit. Authors aimed to understand the relationship of the RCPM with other neurological tests and concluded that other tests were predictive of performance in the RCPM.

Learning is another important area of neuropsychological functioning in PD. To investigate the role of implicit learning and the degree to which it is either impaired or preserved in persons with PD, Siegert, Taylor, Weatherall, and Abernathy (2006) conducted a meta-analysis. The authors reported that implicit learning is inferred when an individual’s performance on a particular task greatly exceeds their ability to provide a
verbal account of the skill. Examples of skills with which implicit learning is present are juggling, driving, and riding a bicycle. Implicit or procedural learning is of interest because of the role the basal ganglia plays in the process and because of the neuro-degeneration that takes place in the basal ganglia in PD patients. Authors were particularly interested in studies examining implicit learning assessed with serial reaction time (SRT) tasks. The authors reported that SRT tasks are the most frequently used experimental task to examine implicit learning in PD. During SRT tasks designed by Nissen and Bullemer (1987) along with Stadler and Frensch (1998), participants are required to press one of four keyboard keys, each key corresponding to a stimulus appearing on a computer monitor. Stimuli are presented in any one of four locations on a computer screen with varying lengths of speed of presentation. The participants must then press the key corresponding with the location of the stimulus. Research on implicit learning measured by SRT have yielded inconsistent results, which led the authors to conduct the meta-analysis.

After searching several electronic databases for studies that included use of control groups, along with other inclusion criteria, Siegert, Taylor, Weatherall, and Abernathy analyzed the data from six studies published between 1999 and 2004. While many more studies have been published on this particular topic, a wide variety of experimental methods were utilized making them unsuitable for inclusion. Taken in total, data for 67 PD patients and 87 healthy controls were analyzed. The mean age of PD patients was 60 years of age and the mean age for the healthy control group was 61 years of age. Results of the meta-analysis showed that implicit learning was impaired in PD
patients as compared to healthy controls. This impairment supports the idea that the basal ganglia plays an important role in implicit learning and suggests that the neurodegeneration experienced by PD patients is linked with deficits in this area.

Price (2006) investigated explicit category learning in PD patients. Explicit category learning is one process by which individuals organize encountered events and objects. Previous research has shown that PD patients exhibit impaired explicit category learning performance. The authors reported that one of the most frequently utilized assessments in this area is the weather prediction task, (Gluck & Browser, 1988), which was utilized in this study along with several other neurological assessment tools. Also included was the COWAT, which assessed verbal fluency. The WCST was utilized to assess set shifting ability, which was determined by perseverative errors. The WCST was also used to assess the consistency with which individuals apply a particular rule, which is determined by nonperseverative errors. The Computation Span (CSpan) task was used to assess working memory capacity. Finally, a categorization task was also used which required participants to assign a math or verbal label to a cue combination which was followed by feedback indicating accuracy of the label. Included in the task were blank trials in which no feedback indicating accuracy is given. Sixteen PD patients with an average disease duration of 8.2 years who were medically well managed were compared to 17 matched controls.

Results indicated that while explicit learning deficits were present, it did not appear that these deficits were related to working memory capacity. When analyzing errors made throughout the tasks, results indicated that PD patients could maintain information in the working memory, but that they had difficulty monitoring this
information when feedback was given. PD participants did not evidence difficulty with set shifting.

Overall, results showed deficits in PD patients on explicit learning tasks specific to category learning, problem-solving, and monitoring information. Further, authors concluded that performance impairments evidenced by the PD group suggested dysfunction in the anterior cingulate which is congruent with previous research indicating that dopamine projections from the ventral tegmental area to the anterior cingulated are damaged in PD patients (Bruck, Aalto, Nurmi, & Rhine, 2005; Grossman, Crino, Reivich, & Stern, 1992).

Taken together, it appears that PD patients experience more deficits in neuropsychological functioning than appropriate control groups across a variety of neuropsychological domains. Several treatments are available to persons with PD including medication and fetal cell transplant. These treatments are intended to slow disease processes, maintain functioning, and quality of life.

Treatment

Current treatment for PD is based on palliative care and includes physical therapy, mental health therapy, medications, and neurosurgery (Fahn, 1998). Reuter, Engelhardt, and Stecher (1999) reported that physical therapy and sports-related activity utilized at all stages of the disease helps to maintain physical functioning. Mental health therapy can be beneficial to assist patients and families cope with and adjust to the disease and its changes over time.
Medication

Medications are utilized frequently for treatment of PD. There are many medications used to treat the disease, which exist within the categories of dopaminergic and non-dopaminergic drugs (Schapira & Olanow, 2004). While antiparkinsonian medications are often prescribed to reduce symptoms of the disease, use of the medication can lead to dopaminergic hallucinations and psychoses (Siderowf, 2001).

Levodopa continues to be the most effective and most often prescribed dopaminergic agent (Ahlskog, 2001; Lang & Lozano, 1998b). Through use of Levodopa (L-dopa), as many as 80% of patients show substantial improvement with respect to rigidity and bradykinesia. Tremor has also been shown to improve, but with less predictability. While L-dopa is quite helpful in decreasing these motor symptoms, it is believed that its window of effectiveness spans five to seven years before patients will experience a ceiling effect. Also noted is that dyskinesia is the most common long-term complication associated with L-dopa (Lang & Lozano, 1998b).

Due to the complication of therapeutic effectiveness, metabolic inhibitors are prescribed to be used in conjunction with L-dopa in order to prolong plasma levels of the medication (Lang & Lozano, 1998b). The benefit of metabolic inhibitors is that they reduce the rate at which L-dopa is metabolized, which in turn, increases the length of time of therapeutic effectiveness. Decarboxylase (Carbidopa) and Catechol-O-Methyltransferase inhibitors (Entacapone) are the two most common types of inhibitors prescribed. Bromocriptine, Pergolide, and Apomorphine are dopamine agonists that can be helpful in treating early stage PD and can delay the need for use of L-dopa (Lang & Lozano, 1998b, McPhee & Stewart, 2001). Non-dopaminergic agents are used to treat a
wide-variety of PD symptoms, which include tremor, depression, drug-induced psychosis, enhance drug absorption, dystonia, and reduce oxidative processes in the brain (Ahlskog, 2001).

Due to the progressive nature of PD, patients may build tolerance to medications over time rendering them less effective. When this occurs, the next step in treatment may be neurosurgery (Honey, Gross, & Lozano, 1999). Ablation, deep brain stimulation, and fetal cell transplantation are the three most common types of surgery used to treat PD (Honey, et al., 1999). While all procedures hold promise, fetal cell transplantation has gained recent attention and is the focus of this study.

Fetal Cell Transplant

During the 1980s, the first four patients with PD received transplantation of adrenal medulla tissue into part of the brain (Lindvall, 1989). Results from the initial studies seemed to hold promise with subsequent studies supporting these findings and demonstrating moderate improvement in approximately 30 percent of the sample (Honey, Gross, & Lozano, 1999). While moderate gains were promising, complications from the procedure appeared to outweigh the benefits causing the adrenal medulla grafting to be largely abandoned in the late 1980s (Lindvall, 1989).

In 1987, intrastriatal grafts of fetal dopaminergic neurons were performed with modest results (Honey, Gross, & Lozano, 1999; Lindvall, 1989). Following this advancement, progress was made with respect to tissue preparation and transplant processes (Brundin et al., 2000; Clarkson et al., 1998; Kordower et al., 1995). Positive outcomes from these procedures included increased fluorodopa intake, exhibition of
long-term grafted tissue survival, and some clinical improvement (Brundin et al., 2000; Freed et al., 2001; Kordower et al., 1995).

Hagell and associates (1999) examined the effects of a second graft of human embryonic mesencephalic tissue. Five patients had initially received unilateral implantation in the striatum 10-56 months previous to the second graft. The second graft then took place and human embryonic mesencephalic tissue was implanted on the contralateral side of the brain in the putamen or the putamen plus caudate (received by one patient). The Unified Parkinson’s Disease Rating Scale (UPDRS) and Hoehn and Yahr Stage of Disease Scale were utilized in the study to assess current functioning along with other assessments. Results of the study indicated that all participants benefited from the procedure, showing increased flouradopa in the grafted putamen. Additionally, the authors concluded that the second grafting in no way interfered with or disrupted the original transplantation and that the successful initial transplantation did not disrupt or interfere with the second grafting. Four of the five patients receiving the second graft (complete bilateral transplantation) showed marked improvement in symptoms of gait, speech, and balance. Additionally, two patients were able to withdraw from L-dopa medication completely. These findings were notable and supported further research in this area.

With interest in evaluating the long-term effects of fetal cell transplant, Hauser et al., (1999) followed 6 patients with advanced PD up to 24 months after bilateral fetal cell transplantation. Utilizing the UPDRS and Schwab and England Activities of Daily Living Scale to assess for overall functioning, authors found that patients benefited from the surgery, showing a mean of 32% improvement in UPDRS scores. Additionally, patients
exhibited a decrease in waking day dyskinesia and an overall increase in fluorodopa intake.

As mentioned previously, Freed et al., (2001) conducted a placebo-controlled clinical trial to further understand the effectiveness of fetal cell transplant. The study utilized a double-blind design and patients in the study received either fetal cell transplant or a sham (placebo) surgery. Forty patients with PD were recruited for the study. The participants ranged in age from 34-75 and were considered to have severe PD, having at least two of three main signs including bradykinesia, rigidity, and tremor at rest. All patients were determined to have responded to L-dopa and had positron-emission tomographic (PET) scans compatible with the presence of PD. Assessments used in the study included the Unified Parkinson’s Disease Rating Scale (UPDRS), Schwab and England scale, Hoehn and Yahr, and PET scans.

The UPDRS is a comprehensive inventory of PD symptoms and captures information related to mental activity, mood, activities of daily living, motor performance, muscle rigidity, speech, and gait. The Schwab and England Activities of Daily Living Scale measures performance in activities of daily living with a range of normal (100%) to completely disabled (0%). PET scans were utilized to determine the survival of fetal cells as evidenced by an increase in fluorodopa uptake.

Twenty participants were assigned to each group (real and sham) and underwent their respective procedures. One patient died in an automobile accident seven months after surgery. All participants were examined with PET scans to measure changes in neurological functioning.
At approximately thirteen months following the surgery, participants were told which procedure they had received. Those who had received the sham surgery were then offered the option of undergoing the actual fetal cell transplant. Examples of the PET scans can be found in Appendix A.

Results of the study indicated that younger participants were found to benefit the most from surgery and that the placebo was relatively strong. Transplant group participants showed significant improvement from baseline to 12 months in scores on the Schwab and England scale, with the younger patients in the transplant group improving significantly more than those in the sham surgery group. Transplant group participants also showed improvement on the UPDRS with men scoring significantly better than women. PET scans in 17 of the 20 transplant recipients showed survival of transplanted cells regardless of age. This finding demonstrates that the cellular and chemical signals necessary to support the development of embryonic dopamine neurons were present in patients with PD.

Neuropsychological aspects of the fetal cell double-blind trial were investigated by Yakov Stern and others at Columbia University and North Shore University Hospital. These researchers focused on neuropsychological performance of the 40 participants in the double-blind study. Participants, ranging in age from 34-75 years of age at the time of enrollment, exhibited motor symptoms of bradykinesia, rigidity, and/or resting tremor. A variety of neuropsychological measures were utilized to analyze neuropsychological ability before and one year following surgery. A partial list of the measures included: 10 designs from Form C of the BVRT, Digits Forward and Backward from the WAIS-R, CVLT, COWAT, BDAE, and the WCST. PET scans were utilized to assess cell growth
and fluorodopa uptake. The scans were utilized in some analyses, but were not a focus of outcomes. Additional measures of functioning related to PD included the Unified Parkinson’s Disease Rating Scale (UPDRS), Hoehn and Yahr Stage of Disease Scale and the Schwab and England Activities of Daily Living Scale.

Results indicated that neuropsychological performance did not differ significantly between the two groups one-year post-surgical procedure (Trott et al., 2003). Neither group showed significant change on most measures from baseline to one-year follow-up. When changes were seen, they were more likely to be seen in both groups and could be expected due to the neurodegenerative nature of the disease.

**Placebo Effect**

Stewart-Williams (2004, p.198) defined the placebo effect as “any genuine psychological or physiological response to an inert or irrelevant substance or procedure.” Recent biochemical evidence has indicated that the placebo effect in PD patients is related to dopamine release in the striatum, which is believed to be triggered by the expectation of clinical benefit (de la Fuente-Fernandez, 2004). Supporting this notion was a study by Pollo et al. (2002) who examined seven PD patients who had received subthalamic (STN) deep-brain stimulation (DBS). Results of this study indicated that Motor Functioning was better in the patients with expectation for improvement than in those expecting deterioration.

A study exploring expectation and dopamine release in PD was conducted by de la Fuente-Fernandez et al. (2002). In this study the authors utilized PET to estimate dopamine release induced by pharmacology or placebo. Specifically, the authors examined \(^{11}\)Craclopride (RAC) binding to D\(_2\) and D\(_3\) receptors and endogenous
dopamine. The authors explained that with decreased RAC binding there is increased release of endogenous dopamine in the striatum. Six patients with PD were examined for striatal RAC binding potential in two conditions. The first condition was a blinded, placebo controlled study. The second condition was an open study with the same patients, but without placebo. The drug utilized in the study was Apomorphine, a dopamine receptor agonist, and the placebo was saline. Results of this study were indicative of decrease in RAC binding potential when patients received the placebo treatment. The decrease in RAC binding potential was seen in all patients and all within the striatal subregion, with the greatest effect seen in the posterolateral portion of the putamen. The authors reported that the magnitude of the placebo response was comparable to therapeutic doses of L-dopa or Apomorphine. Additionally, the release of dopamine was greater in patients in the placebo condition than those who were not. It appears that the placebo effect was mediated by an increase in dopamine release in the striatum and that PD patients engaged in drug therapy in the context of a placebo control benefited from the drug as well as the placebo effect.

In 2004 de la Fuenta-Fernandez and Stoessl published another study related to placebo effect in PD using PET scans. In the article studies of double-blind trials of Pergolide as treatment for PD were cited. Pergolide is a medication used to treat stiffness, tremor, and poor motor control. de la Fuente-Fernandez and Stoessl reported that Diamond et al. (1985) compared patients treated with Pergolide with those treated with placebo, finding improvement in both groups. Further, the authors reported a study by Goetz et al. (2000) who examined patients enrolled in a randomized, placebo-controlled clinical trial of Ropinirole monotherapy. Ropinirole is a drug used for restless leg
syndrome. de la Fuente-Fernandez reported that Goetz et al. (2000) concluded that patients in the placebo condition obtained 50% improvement in all domains of parkinsonian disability, noting that bradykinesia and rigidity were more susceptible to the placebo effect than tremor, gait, or balance. Like de la Fuenta-Fernandez’s previous study, the authors utilized previous results adding the analysis of expectation of reward and actual clinical benefit. PET scan information was utilized to objectively measure dopamine release in the striatum and the author used previous data showing a strong placebo effect. When patients were asked to rate clinical benefit of treatment, only half of placebo participants reported clinical benefit in motor functioning. Goetz et al. (2000) concluded that dopamine release was triggered by expectation of reward (expectation of clinical benefit) rather than the reward itself (perception of clinical benefit).

Quality of Life

Little research has been done with respect to quality of life (QOL) and fetal cell transplant. However, some research has been conducted on quality of life as it relates to PD in general. Martinez-Martin (1998) reported that a common definition of QOL has not been agreed upon; however, it is often considered complimentary to duration (quantity) of life. The World Health Organization views QOL as an interaction of several domains and reported “Health is a state of complete physical, mental, and social well-being and note merely the absence of disease or infirmity.” Therefore, while patients with PD obtain treatment to control motor and neuropsychological decline, QOL proves to be an elusive but important area of focus is certainly influenced by the disease and is often influenced by medical treatment.
Habermann (1996) surveyed 120 PD patients to assess the day to day demands of PD. Results of the study indicated that patients felt that practitioners were not concerned with personal issues related to PD and were only interested in prescribing medications. Additionally, Habermann concluded that perspectives of medical personnel and patients were often incongruent with respect to severity of patient symptoms. This inspired further study by Abudi et al. (1997), who found similar results. Studies such as these acknowledged discrepancies between patient and medical professional perspectives related to experience of symptoms and functioning, underscoring the need to address quality of life for PD patients.

Phillips (2006) designed a qualitative study during which she interviewed six men and five women with PD to gather information on emotional responses to being diagnosed with the disease and helpful coping strategies. Patients ranged in length of diagnosis from 6 months to 15 years, had a mean age of 69, and ranged in stage of disease between 1 and 4 according to the Hoehn and Yahr Stage of Disease Scale. The authors concluded that while the experience of being diagnosed with PD was different for each participant, a general theme of being confused and overwhelmed was shared among them. Further, the participants suggested that interacting with other PD patients and continued education on the disease were most helpful in adjusting to the disease in addition to medication to treat symptoms. Other helpful resources were identified as occupational therapy and structured daily activities. Studies like this are essential in understanding quality of life in patients with PD.

Hariz et al. (2003) examined gender differences in relation to disability and health related quality of life (HRQoL) pre- and post- Deep Brain Stimulation (DBS). Forty-one
PD patients shown to be responsive to L-dopa participated in the study. The participants were comprised of 15 females and 26 males. The mean age of the group was 65.7 years of age and mean duration of illness was 12 years.

A structured interview was completed with all participants to assess for patients’ expectations regarding the outcome of surgery and perceived side effects. The Mini-Mental Status Exam (MMSE) was completed to assess for dementia and aspects of cognition. The Unified Parkinson’s Disease Rating Scale (UPDRS), Hoehn and Yahr Stage of Disease Scale, and Schwab and England Activities of Daily Living Scale were used to capture stage of severity of illness, stage of disease, and activities of daily living (ADL). The ADL Taxonomy was also used. It is an occupational therapy rating of ADLs that assesses the patient’s ability to sequence activities as well as level of independence with specified activities. The Nottingham Health Profile (NHP) is a generic instrument based on self-assessment of perceived distress related to an individual’s health. The Visual Analogue Scale (VAS) was utilized to evaluate the impact of disease on life including social functioning. Finally, the Life Satisfaction Questionnaire was used to assess overall life satisfaction as well as satisfaction in several domains of life.

The authors noted that at the time of surgery, men and women did not differ in age, but women had lived with the disease an average of 5 years longer than men. MMSE scores were different between genders with scores for men being significantly lower than for women both before and after surgery. The scores remained unchanged at pre- and post-surgery assessments. Preoperatively, women showed lower (better) scores than men on UPDRS part II and part IV as well as on the Schwab and England Activities of Daily Living scale pre-surgically. However, these differences disappeared post-operatively.
Specific items showing marked improvement for both genders were writing, using knife and fork, and severity of tremor. Results on the ADL Taxonomy indicated improvement for women, but not for men with preoperative differences persisting postoperatively. NHP results indicated only one change postoperative and that was a decrease in emotional constraints for women. No differences were seen on the VAS between genders at either data point. Life satisfaction overall was different between genders with men being more satisfied than women; results did not change post-surgery. With all results taken together, both genders exhibited improved quality of life post-surgically with women showing the most improvement in the areas of ADL, emotional constraints, and social life.

To summarize, the authors found that PD patients improved on some measures of QOL following DBS.

Mood is an important component of quality of life and can directly impact performance on ADLs. Depression is a major symptom of PD and is related to the decrease in dopaminergic activity as well as a more general emotional response to having the disease and experiencing changes in function. While there continues to be some uncertainty about the etiology of depression in persons with PD, it is considered to be a consistent feature of the disease with estimates of its occurrence ranging from 40% to 60%. However, it has been reported to occur as much as 70% of the time (Askin-Edgar, White, & Cummings 2002; Bieliaukas & Glantz, 1989; Lieberman, 1998). Treatment with L-dopa can improve depression somewhat, but this improvement is largely transient and insignificant (Santamaria & Tolosa, 1992). Depression is important to consider when examining quality of life in persons with PD. The effects of depression influence all
aspects of life including motor functioning and motivation for physical activity, and negative thoughts and feelings about self and life. Depression also interferes with neuropsychological functioning (Leentjens & Verhey, 2002).

The hallmark of quality of life is one’s perception that they can participate in daily living as they wish. Depression often leads to loss of motivation to engage in physical activity and low endurance, which can decrease participation in ADLs. Living with depression causes the individual to view themselves, their situation, and life in general in a negative way. This, in turn, is linked to significant emotional discomfort and disturbance that can compromise many aspects of an individual’s life including relationships and motivation for treatment. Finally, depression interferes with attention, which is important in learning and memory. Depression also interferes with thinking and reasoning as it often skews the individual’s toward the negative, resulting in irrational thinking and an inability to reason effectively (Padesky & Greenberger, 1995).

McRae et al., (2004) participated in the study conducted by Freed et al., (2001) by investigating quality of life. The study by Freed et al., (2001) served as a parent study to McRae and colleagues. Thirty participants of the original 40 agreed to participate in the quality of life study. Of the 30 participants, 12 received the actual fetal cell transplant procedure and 18 received the sham (placebo) procedure. McRae et al. examined quality of life in three domains, which included Physical Functioning, Emotional Functioning, and Social Functioning. Overall, results indicated that participants in both surgery groups showed significant improvement in Physical Functioning at 12 months. No differences between treatment groups were seen at 12 months in the areas of Emotional and Social Functioning.
To conclude, quality of life is an important point of consideration when evaluating outcomes of medical treatment. While some research has been conducted related to PD and quality of life generally, evaluating quality of life outcomes specific to fetal cell transplant contributed to knowledge about the perceived benefits of this treatment based on patient perspectives.

Chapter II discussed neuropsychological assessment as an important indicator of cognitive functioning in persons receiving embryonic dopamine neuron implantation. Over the normal course of PD, diffuse neuropsychological deficits are often seen. There is not a typical or expected lock-step sequence of these deficits. Rather, it appears that persons with PD ultimately have difficulty with executive functions including the ability to shift sets, visual memory, visual perception, and visuo-constructional abilities, verbal learning and memory, working memory, and verbal fluency. Neurodegeneration due to PD and the aging process may confound results of these assessments. However, neuropsychological assessments are the best means of capturing the status and changes in neuropsychological functioning over time.

This chapter also discussed motor functioning and quality of life in persons with PD. With progression of the disease, there are expected declines in motor functioning and quality of life. Persons with PD experience increases in severity of symptoms including resting tremor, rigidity, bradykinesia, among other deficits. Further, PD patients are at risk for depression, inability to participate in activities of daily living, and social isolation.
Chapter III will outline methods of this study including purpose, participants, and assessments used to examine neuropsychological functioning, motor functioning, and quality of life.
Chapter III

Methods

Purpose of study

The aim of the current study is to examine longitudinal neuropsychological data of patients participating in the double-blind placebo surgery trial for the treatment of PD. Twenty patients received bilateral transplantation of embryonic mesencephalic dopamine cells into the putamen, and 20 received sham surgery. Patients who received the actual fetal cell transplant are referred to throughout the rest of this paper as the “real” surgery group. Patients who had the sham surgery are referred to as the “sham” group.

Stern and colleagues (Trott et al., 2003) focused on possible changes in cognition 12 months following the procedure. The current study will continue the analyses of neuropsychological data to assess changes in cognition from baseline to two years. In addition, this study will incorporate and examine data related to motor functioning and quality of life at baseline, 12, and 24 months post-surgery. This study will explore the relationships between these variables at each data point.

Participants

A total of 40 patients comprised of 19 women and 21 men participated in the original study (Table 1). The ages of the patients ranged from 34-75 at the time of enrollment. The majority of patients were Caucasian. Patients older than 61 years of age were deemed “older” while patients 60 years of age and younger were deemed
“younger.” All patients were determined to have idiopathic PD and exhibited at least two of the following symptoms: resting tremor, rigidity, and bradykinesia. The range of duration of illness was 7 to 21 years with an average duration of 14 years. All potential patients were screened with the Mini-Mental State Examination (MMSE) and excluded if a score of less than 24 out of 30 was obtained. Other reasons for exclusion included: hallucinations or delusions while on L-dopa, major depression, dementia, other severe medical disease, previous brain surgery, or evidence of other neurological disorder as determined by magnetic resonance imaging (MRI).
### Table 1

**Participant Demographics**

<table>
<thead>
<tr>
<th>Gender</th>
<th>Men</th>
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<td>Women</td>
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<tr>
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</table>

<table>
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<tbody>
<tr>
<td></td>
<td>Sham Surgery</td>
<td>11 younger ≤60, 9 older 61+</td>
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<table>
<thead>
<tr>
<th>Excluded Data</th>
<th>1 older, 1 younger (developed dementia prior to 1 year post-surgery)</th>
<th>Transplant surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 older (developed dementia prior to 1 year post-surgery)</td>
<td>Sham surgery</td>
</tr>
<tr>
<td></td>
<td>1 older (died in car accident at 7 months post-surgery)</td>
<td>Transplant surgery</td>
</tr>
</tbody>
</table>

The original study, as described previously, utilized a number of neuropsychological assessments to examine cognition across a broad range of functioning. Assessments were related to the commonly affected areas of functioning in
PD, including verbal fluency, verbal learning and memory, executive functioning, and visual memory.

Neuropsychological evaluation

The specific assessment instruments used in this study to assess neuropsychological functioning and reviewed below included: the Controlled Oral Word Association Test, Boston Diagnostic Aphasia Evaluation, Digit Forward and Digit Backward subtests of the Wechsler Adult Intelligence Scale-Revised, the California Verbal Learning Test, the Benton Visual Retention Test, and the Wisconsin Card Sorting Test.

*Controlled Oral Word Association Test (COWAT)*

The purpose of the COWAT is to assess the production of words under restricted search conditions; e.g., words that begin with particular letters within a specified amount of time, usually 1 minute (Spreen & Strauss, 1991). Test administration consists of three trials and takes about five minutes. The score is the sum of all admissible words for the letters given and/or the average score across trials. Inadmissible words include proper nouns, wrong words (wrong letter), variations of the same word, and repetitions. These words are not counted as correct and are not included in the total score.

Snow et al. (1988) reported both interscorer reliability and one-year retest reliability in older adults as .70. desRosiers and Kavanagh (1987) reported retest reliability after 19-42 days in adults as .88. Coelho (1984) reported that concurrent validity has been established in several studies.

In this study, the COWAT was used to assess verbal fluency and required patients to list as many words as possible beginning with particular letters within a one minute
time frame for each letter. English speakers were asked to generate lists beginning with the letters of C, F, and L and Spanish speakers were asked to generate lists beginning with the letters of P, S, and V.

*Boston Diagnostic Aphasia Evaluation (BDAE)-2*

The Boston Diagnostic Aphasia Evaluation is used to comprehensively assess language functioning (Spreen & Strauss, 1991). Goodglass and Kaplan published the first edition in 1972 and a second edition in 1983 (Goodglass & Kaplan, 1983b). The second edition was utilized in this study. The assessment is organized into five sections including: conversational and expository speech, auditory comprehension, oral expression, understanding written language, and writing (Spreen & Strauss, 1991). Estimates of reliability of the test is reported to range from greater than .95 for Sentence Repetition to less than .65 on measures of Auditory Comprehension.

In this study, only the animal naming subtest of The Boston Diagnostic Aphasia Evaluation was utilized. This subtest was employed in conjunction with the COWAT to assess verbal fluency. The test required patients to list as many animals as possible within a one minute time period.

*Wechsler Adult Intelligence Scale-Revised (WAIS-R)*

The WAIS was first published in 1939 as the Wechsler-Bellevue Intelligence Scale and has since gone through several revisions. The WAIS-R has been widely used to assess general intelligence, neuropsychological potential, and neurological dysfunction (Kaufman & Lichtenberger, 1999; Strauss, Sherman, & Spreen, 2006). The WAIS-R was used in the original study as assessments begin in 1995, before the publication of the
current version, WAIS-III. The following information pertains to the WAIS-R because of its use in the original study.

Scoring of the WAIS-R is reported in terms of the three main scales of Full Scale IQ (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ). Digit Span Forward and Backward are subtests that capture working memory performance. The WAIS-R manual reported reliability coefficients for all subtests, VIQ, PIQ, and FIQ across age ranges as well as overall reliability averages for each subtest. The average reliabilities for the subtests are as follows: Digit Span .83, VIQ .97, PIQ .93, and FIQ .97 (Wechsler, 1981).

Test-retest reliability was also averaged across age groups and reported for age groups 25 to 34 and 45 to 54. Test-retest reliability for the Digit Span subtest was reported to be .89 for age group 25 to 34 and .82 for age group 45 to 54. Wechsler (1981) did not report specific validity coefficients. Instead, the author reported that the validity of the WAIS-R could be considered as similar to previous versions of the test.

The Digit Span Forward subtest of the WAIS-R captured patients’ immediate verbal memory while the Digit Span Backward subtest of the WAIS-R assessed patients’ working memory. Both subtests required patients to remember and repeat several trials of a series of numbers of increasing length read to them by the examiner. Digit Span Forward required participants to repeat the numbers as read to them in exactly the same order while Digit Span Backward required participants to repeat the numbers in the opposite order as read to them by the examiner.

*California Verbal Learning Test (CVLT)*

The CVLT, often described as a list-learning task, was used to measure verbal learning and memory (Delis et al., 1987) and was utilized for this study. The test has been
revised since its original publication to accommodate new developments in the field and
to address concerns raised about the first edition (Strauss, Sherman, & Spreen, 2006).
The CVLT was used in the original study as assessments began in 1995, before the
publication of the most current version, CVLT-II. The following information will pertain
to the CVLT because of its use in the original study.

Delis et al. (1987) reported internal consistency and test-retest reliabilities for the
CVLT. Internal consistency was reported for four areas specific to List A and included:
five trial scores “a,” semantic categories “a,” item totals across five trials “a,” and item
totals across five trials “b.” Authors reported internal consistencies of .92 for five trial
scores “a,” .74 for semantic categories “a,” .69 for item totals across five trials “a,” and
.86 for item totals across five trials “b.”

Validity coefficients were not directly reported in the CVLT manual. Rather, the
authors stated that results of factor analyses indicated that the multiple indices cluster into
theoretically meaningful factors and that they are consonant with the constructs they were
designed to measure. Authors addressed criterion-related validity by reporting that the
correlations between the CVLT raw scores and Wechsler Memory Scale (WMS) scores
were significant 64% of the time at the .05 level. Also, Delis et al. (1987) reported that
the total immediate recall of List A across the five trials and the WMS Quotient achieved
a correlation of .66 and in the .’60s” with several other WMS variables.

In the CVLT manual, Delis et al. (1987) reported that the CVLT “measures both
recall and recognition of word lists over a number of trials.” In this study, patients were
presented with 16 words, four from each of four semantic categories, over five trials.
After an interference list was presented, the patient was then asked to recall the first list
of words. There was then a 20 minute delay after which the patient was asked to again recall the first list of words. A form was used by the examiner to administer the test and record answers. This form, along with the manual, facilitated scoring of the test once completed. Scoring of the CVLT involved attention to classification of responses, correct responses, number of correct words, number of intrusions, and correct semantic cluster.

*Benton Visual Recognition Test (BVRT)*

The purpose of the BVRT (Benton, 1981) is to assess visual memory, visual perception, and visuo-constructive abilities. There are several forms of the test, a variety of options for administration (that fall within drawing administration and multiple-choice administration), and several options for scoring, depending on the objective of the assessment (Spreen & Strauss, 1991). Multiple-choice and matching administrations were used in this study.

Swan et al., (1990) and Wahler (1956) reported that for drawing administrations of the test, interscorer agreement for number correct and total error is above .95. Benton (1974) reported that overall, alternate form reliability is good with coefficients ranging from .79 to .84 between the three forms of the test. For multiple-choice administration, Benton (1981) reported that alternate-form reliability is .80 and split-half reliability is .76.

*Wisconsin Card Sorting Test (WCST)*

Finally, the purpose of the WCST is to assess the ability to form abstract concepts and to shift and maintain sets. It was developed by Berg (1948) and Grant and Berg (1948). The test provides information on several aspects of executive functioning including problem-solving behavior and is especially sensitive to lesions of the frontal
lobe. Test instructions and scoring procedures for the long version were formally published as a clinical instrument by Heaton et al. (1981). Milner (1963) reported that clear differences between patients with dorsolateral frontal excisions and those with orbitofrontal and posterior lesions were found in her study. Further, conclusions from several studies have suggested that the WCST is particularly sensitive to frontal lobe function (Bornstein, 1986; Drewe, 1974, Hermann et al., 1988, Robinson et al., 1980).

Heaton (1981) reported interscorer reliability as excellent with correlation coefficients of .93 for Perseverative Responses, .92 for Perseverative Errors, and .88 for Nonperseverative Errors. Heaton (1981) also reported intrascorer reliability to be excellent with correlation coefficients of .96 for Perseverative Responses, .94 for Perseverative Errors, and .91 for Nonperseverative Errors. Heaton (1981) described several studies that have been conducted with the WCST with a variety of populations, concluding that the test is valid and reliable.

The WCST consists of four stimulus cards and 128 response cards depicting figures of varying forms. The forms include crosses, circles, triangles, or stars. The colors include red, blue, yellow, or green. Finally, the number of figures on each card varies between one and four. Administration of the test consists of the patient being presented with four stimulus cards and being given a deck of 64 cards to match with the stimulus cards. The patient is instructed to match the cards from the deck with the stimulus cards. The patient is told only whether each response is right or wrong, but is never told the correct sorting principles, which consisted of color, form, and number. After 10 consecutive correct matches, the sorting principle changes, but with no information to the patient other than that their attempt to match was right or wrong.
Scoring of the WCST was done by following instructions offered in the administration manual and calculating the number of categories completed, trials to complete the first category, percent of perseverative errors, failure to maintain set, and percent conceptual level responses.

*Motor Functioning*

The specific assessment instruments used in this study to assess motor functioning and reviewed below included: the Unified Parkinson’s disease Rating Scale (UPDRS), Hoehn and Yahr Stage of Disease Scale, Schwab and England Activities of Daily Living Scale, and a Global Rating of Motor Functioning.

*Unified Parkinson’s Disease Rating Scale (UPDRS)*

Severity of disease was assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS), which is a standard assessment instrument that was used in the parent study. One of the most important subscales of the UPDRS assesses motor functioning. Both the total score, which covers a wide range of domains, and the motor score were included in analyses. Assessment was done when patients were deemed at their best (“on”) and at their worst (“off”). “On” and “off,” refer to patients being on and off optimal medication levels. For example, when someone is “on,” he or she is functioning as well as possible at his or her particular stage of disease. When a person is “off,” functioning is diminished and he or she may be partly incapacitated until the next dose of medication takes effect. Scores on the UPDRS were averaged over the two assessment periods at baseline. Based on results of previous analyses (Freed et al., 2001; McRae et al., 2004) only scores from practically defined “off” periods were included in analyses.
Assessment periods included baseline, 12 and 24 months for both the real and sham surgery groups. The UPDRS can be found in Appendix B.

_Hoehn and Yahr Stage of Disease Scale_

The Hoehn and Yahr Stage of Disease Scale (Hoehn & Yahr, 1967) was administered to determine the stage of disease. This measure was filled out by patients and medical personnel at each assessment point during the study. Scores of the scale range from 0 (no signs of disease) to 5 (wheelchair bound or bedridden unless aided). Lower scores indicate fewer signs of disease. This scale is considered to be the standard disease staging scale for PD. McRae et al. (1994) found high interrater reliability between neurologists, patients, and caregivers with use of this scale. The Hoehn and Yahr Stage of Disease Scale can be found in Appendix C.

_Schwab and England Activities of Daily Living Scale_

Schwab and England Activities of Daily Living Scale was administered to assess ability to perform ADLs. This scale was designed specifically for use with PD patients and serves as a measure of overall functional ability regarding ADLs (Schwab & England, 1969). The scale ranges from 100% (completely independent) to 0% (bedridden), with each 10% increment having specific definitions. This scale is a common clinical measure of ADLs and has been used in many research studies with PD patients (Goetz et al., 1989; McRae et al., 1989). The Schwab and England Activities of Daily Living Scale can be found in Appendix D.

_Global Rating of Motor Functioning_

The Global Rating measure was designed and utilized as a primary outcome variable by Freed et al., (2001) in the original placebo surgery trial study. The measure
was utilized only at 12 months following the initial real or sham surgery to assess participant perception of clinical improvement or deterioration since the original surgery. The item requests that participants rate their current level of functioning on a scale ranging from -3 to +3, indicating they are markedly worse (-3) than before surgery, to no change (0), to markedly improved (+3) since surgery. The Global Rating Scale can be found in Appendix E.

Quality of life

Quality of life was originally examined as it related to three domains: Physical Functioning, Emotional Functioning, and Social Functioning. For purposes of this investigation, several representative scales from the Emotional and Social Functioning domains were included in the analyses. The selected scales are described below.

Center for Epidemiologic Studies Depression Scale (CES-D)

The Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depression, an aspect of emotional functioning. It is one of the most widely utilized rating scales to assess symptoms of depression (Hann, D., Winter, K., & Jacobsen, P., 1999; Radloff, 1977) The CES-D is a self-report scale consisting of 20 items. The items are focused on emotions felt by respondents “in the past week” prior to filling out the measure. Respondents choose from four response items: 1= Rarely or none of the time (Less than 1 day), 2= Some of the time/little of the time (1-2 days), 3= Occasionally or a Moderate Amount of the Time (3-4 days), 4= Most or All of the time (5-7 days). Total scores, which can range from 20 to 80, are then used to determine the level of depression experienced by the respondent. Radloff (1977) reported reliability of the instrument to range between .85 and .90. In this study the coefficient alpha of the
CES-D at baseline was .89. The CES-D has a substantial research base to support its validity. The CES-D can be found in Appendix F.

*Social Provisions Scale (SPS)*

The Social Provisions Scale is a 24-item scale designed to measure the extent to which an individual’s current relationships provide the six social provisions described by Weiss (1974). The six provisions are: Attachment, Social Integration, Reassurance of Worth, Reliable Alliance, Guidance, and Opportunity for Nurturance. Half of the items describe the presence of a type of support and the others describe the absence of a type of support (Cutrona & Russell, 1987). Each item is rated on a 4-point scale ranging from 1 (Strongly disagree) to 4 (Strongly agree). Cutrona and Russell (1987) reported reliability estimates ranged from .65 to .76 on the subscales measuring each of the social provisions. Cutrona and Russell (1987) also reported reliability of the total Social Provisions score to be .92. Coefficient alpha of the Social Provisions Scale in this study was .91 at baseline. Validity of the instrument has been well established (Cutrona & Russell, 1987). The Social Provisions Scale can be found in Appendix G.

*Short-Form Health Survey*

The Short-Form Health Survey (SF-36) is an instrument utilized to assess patients’ perceived health status (Ware & Sherbourne, 1992). The survey was derived from a large scale (n=20,000) study of medical outcomes. One global health item was utilized as a component of assessment in this study. This item asked patients “In general, how would you describe your health at present?” Patients responded to the item using a five-point Likert-type scale ranging from (1) “Excellent” to (5) “Poor.”
“Free or Restricted” Item

The Neural Implant Questionnaire was designed by McRae (2004) to capture patient and caregiver perspectives of the implications of PD on activity level. One item of this questionnaire is being used in this current study. The item asks participants “Overall, how free or restricted do you feel in doing what you want to do?” Response options are presented with a 1 to 7 Likert-type scale with 1 being “I still do everything I want to do” to 7 being “I can no longer do the things I want to do.” Previous analyses of this single item have provided interesting and significant results (McRae et al., 2004).

Additional focus

In addition to comparing the transplant and sham surgery groups at baseline, 12 and 24 months in regard to neuropsychological functioning, this study also analyzed neuropsychological ability based on perceived treatment at 12 months. Because previous results of analyses using perceived treatment groups have shown such extraordinary results, it was decided to explore neuropsychological data in the same way. Previous results have shown that comparisons of treatment groups based on type of surgery patients thought they received, showed more significant results both in terms of QOL data as well as medical data, than results based on actual treatment (McRae et al., 2004).
Data collection and research questions

Stern and colleagues (Trott et al., 2003) collected the data in the original investigation and this study serves as a collaborative investigation between Dr. Stern’s group and this author.

Research questions relevant to this study are as follows:

1) What are the relationships between neuropsychological functioning and QOL for real and sham surgery groups at baseline, 12, and 24 months post-surgery?

2) What are the relationships between neuropsychological functioning and motor functioning for real and sham surgery groups at baseline, 12, and 24 months post-surgery?

3) Are there any differences at baseline, 12, and 24 months between older (≥61) and younger patients (<60) in the domain of neuropsychological functioning?

4) Are there any differences at 12 months between those who thought they received the fetal cell transplant and those who thought they received the sham surgery in terms of neuropsychological functioning?

Data analysis

Data were analyzed using SPSS. Preliminary analyses examining the neuropsychological measures were conducted. Analyses for the research questions included correlational analyses and analysis of variance (ANOVA).

Correlational analyses were utilized to examine relationships between neuropsychological domains, motor functioning, and quality of life. Analysis of variance (ANOVA) was used to examine differences between older and younger participants and between those who thought they received the real and sham surgeries at 12 months.
Summary of Chapter III

Chapter III outlined the methodology of the study in the areas of participants, procedures, and the measures used in assessing patient functioning in the domains of neuropsychological functioning, motor functioning, and quality of life. Results of these analyses will be reported in Chapter IV.
Chapter IV

Results

Chapter IV presents the results of the data analyses for this study. The chapter is organized by a) explaining the number of real and sham surgery patients at each data collection time point and b) results of preliminary analyses, and c) results of the research questions as they pertain to both the real and sham surgery groups at each data collection time point. Data for the real and sham surgery groups were analyzed separately to most accurately explore relationships and differences over time within the same groups.

This double-blind placebo surgery trial randomly assigned PD patients into real and sham surgery groups. However, at 12 months after the real surgery and after the blind was lifted, participants in the original sham group had the option to undergo the mesencephalic fetal cell transplant surgery. Due to the complex nature of this study and the tracking of participants, Table 2 was created to present the number of participants in the real and sham surgery groups at the different data collection time points.
Table 2

Number of Real and Sham Surgery Participants at Each Data Collection Time Point

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Real Changes to N</th>
<th>Sham Changes to N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>N=20</td>
<td>N=20</td>
</tr>
<tr>
<td>12 Months</td>
<td>N=19</td>
<td>N=20/12 had 2nd surgery</td>
</tr>
<tr>
<td></td>
<td>-1 to death in car accident</td>
<td>-6 to age emotional distress at time of surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 chose not to have the surgery</td>
</tr>
<tr>
<td>12 Months after 2nd surgery</td>
<td>N=12</td>
<td>N=12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Months</td>
<td>N=17</td>
<td>N=10 for Neuropsychological and QOL data N=4 for Motor Functioning *</td>
</tr>
<tr>
<td></td>
<td>-2 to dementia</td>
<td>-1 because did not have data at 24 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1 to dementia</td>
</tr>
</tbody>
</table>

* Due to the small number of sham surgery participants at 24 Months after the 2nd surgery, analyses regarding the relationship between neuropsychological and motor functioning were not completed.

After the 12 month follow-up, several participants did not continue with the study. Six participants in the sham group were advised not to proceed due to their advanced age (being 61 or older). Another participant in the sham group chose not to have the transplant surgery because of family pressure not to have the surgery. One participant became overwhelmed in the operating room during the initial procedure and was not allowed to undergo a second attempt. One person who received the real surgery died in a car accident at seven months post-surgery. Therefore, data from a total of 31 patients were analyzed in the current study.
Preliminary analyses were conducted with the neuropsychological data to examine the mean and standard deviations of the measures over time in both the real and sham surgery groups. Results of the analyses for the real group are presented in Table 2.1. Results for the Sham group are presented in Table 2.2.

Table 2.1: Descriptive Statistics for Neuropsychological Measures Across Time for the Real Surgery Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N= 19)</th>
<th>12 Months (N= 19)</th>
<th>24 Months (N=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>COWAT</td>
<td>69.1 (29.39)</td>
<td>60.00 (38.00)</td>
<td>65.53 (32.34)</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>43.11 (33.60)</td>
<td>34.95 (30.77)</td>
<td>29.18 (32.50)</td>
</tr>
<tr>
<td>WCST</td>
<td>4.84 (2.03)</td>
<td>4.81 (1.94)</td>
<td>4.47 (2.32)</td>
</tr>
<tr>
<td>WAIS-R Digit Span Forward</td>
<td>8.63 (2.31)</td>
<td>7.95 (2.60)</td>
<td>8.35 (2.32)</td>
</tr>
<tr>
<td>WAIS-R Digit Span Backward</td>
<td>7.32 (2.54)</td>
<td>7.47 (2.59)</td>
<td>7.18 (3.05)</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>8.63 (1.77)</td>
<td>7.77 (2.02)</td>
<td>8.31 (1.58)</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>9.53 (1.17)</td>
<td>9.11 (1.94)</td>
<td>9.62 (.50)</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>51.58 (14.10)</td>
<td>48.44 (20.60)</td>
<td></td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>12.21 (3.03)</td>
<td>11.22 (4.12)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.2: Descriptive Statistics for Neuropsychological Measures Across Time for the Sham Surgery Group

<table>
<thead>
<tr>
<th></th>
<th>Baseline (N= 20)</th>
<th>12 Months (N= 20)</th>
<th>12 Months After 2(^{nd}) Surgery (N= 12)</th>
<th>24 Months After 2(^{nd}) Surgery (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
</tr>
<tr>
<td>COWAT</td>
<td>68.00 (26.17)</td>
<td>59.05 (31.34)</td>
<td>60.75 (30.65)</td>
<td>70.70 (27.84)</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>53.15 (26.42)</td>
<td>42.90 (29.69)</td>
<td>37.25 (22.59)</td>
<td>49.70 (33.33)</td>
</tr>
<tr>
<td>WCST</td>
<td>5.67 (.77)</td>
<td>4.68 (2.38)</td>
<td>4.45 (2.84)</td>
<td>5.10 (1.52)</td>
</tr>
<tr>
<td>WAIS-R Digit Span Forward</td>
<td>9.40 (2.68)</td>
<td>8.45 (2.85)</td>
<td>9.33 (2.64)</td>
<td>9.10 (4.84)</td>
</tr>
<tr>
<td>WAIS-R Digit Span Backward</td>
<td>7.40 (3.14)</td>
<td>6.75 (2.15)</td>
<td>7.00 (2.45)</td>
<td>7.00 (3.83)</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>8.70 (1.34)</td>
<td>8.20 (2.01)</td>
<td>8.83 (1.03)</td>
<td>8.90 (1.28)</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>9.75 (.55)</td>
<td>9.50 (1.36)</td>
<td>9.58 (.67)</td>
<td>8.80 (3.12)</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>49.70 (17.07)</td>
<td>50.83 (19.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>11.55 (3.80)</td>
<td>11.11 (3.21)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results and analyses will be presented in the same order as the research questions.

Due to the small sample size and the exploratory nature of this study, the significance level was set at .10.
**Question 1**

What are the relationships between neuropsychological functioning and QOL for each group at baseline, 12, and 24 months post-surgery?

SPSS was used to analyze data from measures across domains of neuropsychological functioning and aspects of QOL. Correlational analyses were used to examine relationships between measures of each type for the real and sham surgery groups at baseline, 12 and 24 months. Results are discussed as they pertain to each group at baseline, 12 and 24 months. The following results were found for the real group, or those who received the actual transplant surgery.

There were no significant relationships at baseline (Table 3).

At 12 months post-surgery, there were three significant relationships at the .05 level and four at the .10 level (Table 3.1). The CES-D was related to four of the nine neuropsychological variables and Digit Span Backward was related to both the CES-D and the Free or Restricted item. Perceived social support was related to BDAE animal naming variable.

At 24 months post-surgery for the real surgery group, significant relationships between neuropsychological functioning and QOL were found at both the .05 and .10 levels. Four relationships were found to be significant at the .05 level and six relationships were found to be significant at the .10 level (Table 3.2). Perceived social support and the Free or Restricted item were both related to four of the seven neuropsychological variables, three of which they had in common; BDAE animal naming, WCST, and BVRT matching. BDAE animal naming was related to three of four
QOL domains while WCST, BVRT multiple-choice, and BVRT matching were related to two QOL variables each.

In summary, results for the real surgery group indicated that BDAE animal naming (verbal fluency) and BVRT multiple-choice and matching (visual memory) emerged as the neuropsychological measures most often correlated with aspects of QOL; significant relationships were found four and five times respectively. The CES-D was significantly related to five neuropsychological variables at 12 months, but only one at 24 months. Conversely, the SPS and the Free or Restricted item were related to only one neuropsychological scale each at 12 months, but four scales each at 24 months.

A summary table of significant relationships for the real surgery group at baseline, 12 and 24 months is presented in Table 3.3 below.
Table 3

Question 1: All Correlations for Neuropsychological and Quality of Life Measures for the Real Surgery Group at Baseline

<table>
<thead>
<tr>
<th>Baseline</th>
<th>SF-36 (1 Item) Health at Present</th>
<th>Free or Restricted</th>
<th>CES-D</th>
<th>Social Provisions Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.013</td>
<td>.051</td>
<td>.464</td>
<td>-.007</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>.464</td>
<td>-.217</td>
<td>.397</td>
<td>-.025</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>.371</td>
<td>-.456</td>
<td>.157</td>
<td>.263</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.077</td>
<td>.272</td>
<td>.252</td>
<td>-.034</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>.205</td>
<td>-.173</td>
<td>.173</td>
<td>.211</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>.144</td>
<td>-.278</td>
<td>.133</td>
<td>.410</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>.244</td>
<td>-.258</td>
<td>.215</td>
<td>-.207</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>-.211</td>
<td>-.387</td>
<td>.272</td>
<td>-.140</td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>.133</td>
<td>-.375</td>
<td>.452</td>
<td>-.212</td>
</tr>
</tbody>
</table>
Table 3.1

Question 1: All Correlations for Neuropsychological and Quality of Life Measures for the Real Surgery Group at 12 Months

<table>
<thead>
<tr>
<th>12 Months</th>
<th>SF-36 (1 Item) Health at Present</th>
<th>Free or Restricted</th>
<th>CES-D</th>
<th>Social Provisions Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.023</td>
<td>.041</td>
<td>-.449</td>
<td>.082</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>.181</td>
<td>-.451</td>
<td>-.432</td>
<td>.640**</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>-.066</td>
<td>.072</td>
<td>-.590*</td>
<td>.023</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>.166</td>
<td>-.164</td>
<td>-.374</td>
<td>.283</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.161</td>
<td>-.558*</td>
<td>-.608**</td>
<td>.469</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>-.083</td>
<td>-.039</td>
<td>-.684**</td>
<td>-.154</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>.041</td>
<td>.183</td>
<td>-.177</td>
<td>-.153</td>
</tr>
<tr>
<td>CVLT: Immediate</td>
<td>-.217</td>
<td>.028</td>
<td>-.592*</td>
<td>.267</td>
</tr>
<tr>
<td>CVLT: Delay</td>
<td>-.396</td>
<td>.397</td>
<td>-.580*</td>
<td>.241</td>
</tr>
</tbody>
</table>

* $p \leq .10$
** $p \leq .05$
Table 3.2

Question 1: All Correlations for Neuropsychological and Quality of Life Measures for the Real Surgery Group at 24 months

<table>
<thead>
<tr>
<th>24 Months</th>
<th>SF-36 (1 Item) Health at Present</th>
<th>Free or Restricted</th>
<th>CES-D</th>
<th>Social Provisions Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.411</td>
<td>-.450</td>
<td>-.024</td>
<td>.399</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.709**</td>
<td>-.586*</td>
<td>-.111</td>
<td>.757**</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>.026</td>
<td>-.616*</td>
<td>-.564</td>
<td>.683*</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.208</td>
<td>-.368</td>
<td>-.368</td>
<td>.616*</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.185</td>
<td>-.302</td>
<td>-.271</td>
<td>.348</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>-.176</td>
<td>-.674**</td>
<td>-.579</td>
<td>.638*</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>-.527</td>
<td>-.666**</td>
<td>-.616*</td>
<td>.419</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT Delay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $p \leq .10$

** $p \leq .05$
Table 3.3

Question 1: Significant Correlations Between Neuropsychological Functioning and Quality of Life Across Time for the Real Surgery Group

<table>
<thead>
<tr>
<th>Scale Names</th>
<th>Specific Domains</th>
<th>Correlation p ≤ .05</th>
<th>Correlation p ≤ .10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>12 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp; SPS</td>
<td>Verbal Fluency &amp; Social Support</td>
<td>.640</td>
<td></td>
</tr>
<tr>
<td>WCST &amp; CES-D</td>
<td>Executive Functioning &amp; Depression</td>
<td>-.590</td>
<td></td>
</tr>
<tr>
<td>WAIS-R: Digit Span</td>
<td>Working Memory &amp; Effect of PD on Activity Level</td>
<td>-.558</td>
<td></td>
</tr>
<tr>
<td>Backward &amp; Free or Restricted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-R: Digit Span</td>
<td>Working Memory &amp; Depression</td>
<td>-.608</td>
<td></td>
</tr>
<tr>
<td>Backward &amp; CES-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>Visual Memory &amp; Depression</td>
<td>-.684</td>
<td></td>
</tr>
<tr>
<td>&amp; CES-D</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT: Immediate &amp; CES-D</td>
<td>Learning and Verbal Memory &amp; Depression</td>
<td>.592</td>
<td></td>
</tr>
<tr>
<td>CVLT: Delay &amp; CES-D</td>
<td>Learning and Verbal Memory &amp; Depression</td>
<td>.580</td>
<td></td>
</tr>
<tr>
<td><strong>24 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp; SF-36</td>
<td>Verbal Fluency &amp; Perceived Health at Present</td>
<td>-.709</td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp;</td>
<td>Verbal Fluency &amp; Effect of PD on Activity Level</td>
<td>-.586</td>
<td></td>
</tr>
<tr>
<td>Free or Restricted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp;</td>
<td>Verbal Fluency &amp; Social Support</td>
<td>.757</td>
<td></td>
</tr>
<tr>
<td>SPS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST &amp; Free or Restricted</td>
<td>Executive Functioning &amp; Effect of PD on Activity Level</td>
<td>.616</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.3: Continued

Question 1: Significant Correlations Between Neuropsychological Functioning and Quality of Life for the Real Surgery Group

<table>
<thead>
<tr>
<th>24 Months: Continued</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WCST &amp; SPS</td>
<td>Executive Functioning &amp; Social Support</td>
<td></td>
<td>.683</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward &amp; SPS</td>
<td>Immediate Verbal Memory &amp; Social Support</td>
<td></td>
<td>.616</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; Free or Restricted</td>
<td>Visuospatial Capabilities &amp; Effect of PD on Activity Level</td>
<td></td>
<td>-.674</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; SPS</td>
<td>Visual Memory &amp; Social Support</td>
<td></td>
<td>.638</td>
</tr>
<tr>
<td>BVRT: Matching &amp; Free or Restricted</td>
<td>Visual Memory &amp; Effect of PD on Activity Level</td>
<td></td>
<td>-.666</td>
</tr>
<tr>
<td>BVRT: Matching &amp; CES-D</td>
<td>Visual Memory &amp; Depression</td>
<td></td>
<td>-.616</td>
</tr>
</tbody>
</table>
Results of correlational analyses for the sham surgery group also resulted in significant relationships between a number of neuropsychological and QOL measures, although there were fewer overall than in the real surgery group.

At baseline, there was one significant correlation at the .05 level and three significant correlations at the .10 level (Table 3.4). Results indicated that BVRT matching was related to two measures of QOL (CES-D and Free or Restricted) while the Free or Restricted item was correlated with two neuropsychological measures (COWAT and BVRT matching).

At 12 months after sham surgery, before the double-blind was lifted, there were two significant relationships at the .05 level and one significant relationship at the .10 level (Table 3.5). The WCST was related to both the CES-D and SPS. Among the four QOL instruments, the SPS was related to two of the nine neuropsychological instruments.

When the blind was lifted for the patients who initially received the sham surgery, 12 patients elected to have the real transplant surgery. At 12 months post-real surgery for the sham group, one relationship was found to be significant at the .05 level and one at the .10 level (Table 3.6). WAIS-R Digit Span Backward was related to the SF-36 (1 item) and BVRT multiple-choice was related to the SPS.

Finally, at 24 months post-real surgery for the sham surgery group, one significant relationship was found between BVRT matching and the SPS (Table 3.7).

Overall results of the sham surgery group at baseline, 12 months post-sham surgery, and 12 and 24 months post-real surgery indicated that the BVRT matching (visual memory) was the neuropsychological measure most often correlated with QOL measures (three times). BVRT matching correlated with the Free or Restricted item, the
CES-D (depression), and with the SPS (social support). The SPS was the QOL measure most often correlated with neuropsychological measures (5 times). The SPS correlated twice with CVLT delay (learning and verbal memory), and once with WCST (executive functioning), BVRT multiple-choice and BVRT matching (visual memory). All of the significant relationships for the sham surgery group at baseline, 12 months post-sham surgery, 12 and 24 months post-real surgery are listed in Table 3.8.
Table 3.4

Question 1: All Correlations for Neuropsychological and Quality of Life Measures for the Sham Surgery Group at Baseline

<table>
<thead>
<tr>
<th>Baseline</th>
<th>SF-36 (1 Item) Health at Present</th>
<th>Free or Restricted</th>
<th>CES-D</th>
<th>Social Provisions Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.267</td>
<td>.461*</td>
<td>.245</td>
<td>.085</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.159</td>
<td>.240</td>
<td>.212</td>
<td>-.040</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>-.367</td>
<td>.170</td>
<td>-.006</td>
<td>.295</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.038</td>
<td>.316</td>
<td>.059</td>
<td>-.011</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.006</td>
<td>-.069</td>
<td>-.344</td>
<td>.187</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>.024</td>
<td>-.061</td>
<td>-.136</td>
<td>.164</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>.019</td>
<td>-.437*</td>
<td>-.600**</td>
<td>.413</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>.000</td>
<td>.239</td>
<td>-.166</td>
<td>.328</td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>-.110</td>
<td>.119</td>
<td>-.053</td>
<td>.445*</td>
</tr>
</tbody>
</table>

* $p \leq .10$

** $p \leq .05$
Table 3.5

Question 1: All Correlations for Neuropsychological and Quality of Life Measures for the Sham Surgery Group at 12 Months

<table>
<thead>
<tr>
<th>12 Months</th>
<th>SF-36 (1 Item) Health at Present</th>
<th>Free or Restricted</th>
<th>CES-D</th>
<th>Social Provisions Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.341</td>
<td>.101</td>
<td>-.162</td>
<td>.255</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.380</td>
<td>.372</td>
<td>.171</td>
<td>.098</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>.121</td>
<td>-.134</td>
<td>-.520**</td>
<td>.476*</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>.000</td>
<td>-.081</td>
<td>-.102</td>
<td>.132</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.246</td>
<td>.070</td>
<td>.144</td>
<td>.159</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>.068</td>
<td>.030</td>
<td>.002</td>
<td>.068</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>.116</td>
<td>-.041</td>
<td>-.123</td>
<td>.008</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>-.042</td>
<td>.354</td>
<td>.134</td>
<td>.145</td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>.144</td>
<td>.160</td>
<td>-.233</td>
<td>.538**</td>
</tr>
</tbody>
</table>

* $p \leq .10$

** $p \leq .05$
### Table 3.6

**Question 1: All Correlations for Neuropsychological and Quality of Life Measures for the Sham Surgery Group at 12 Months after 2nd Surgery**

<table>
<thead>
<tr>
<th>12 Months after 2nd Surgery</th>
<th>SF-36 (1 Item) Health at Present</th>
<th>Free or Restricted</th>
<th>CES-D</th>
<th>Social Provisions Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.440</td>
<td>-.236</td>
<td>-.147</td>
<td>-.038</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.521</td>
<td>.362</td>
<td>.241</td>
<td>-.055</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>-.080</td>
<td>-.363</td>
<td>.274</td>
<td>-.286</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.495</td>
<td>-.233</td>
<td>-.092</td>
<td>-.452</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.699**</td>
<td>.299</td>
<td>.134</td>
<td>-.250</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>-.167</td>
<td>.000</td>
<td>.311</td>
<td>-.610*</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>-.225</td>
<td>.527</td>
<td>.096</td>
<td>-.242</td>
</tr>
</tbody>
</table>

* *p ≤ .10
** *p ≤ .05
Table 3.7

Question 1: All Correlations for Neuropsychological and Quality of Life Measures for the Sham Surgery Group at 24 Months after 2nd Surgery

<table>
<thead>
<tr>
<th>24 Months after 2nd Surgery</th>
<th>SF-36 (1 Item) Health at Present</th>
<th>Free or Restricted</th>
<th>CES-D</th>
<th>Social Provisions Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.291</td>
<td>.431</td>
<td>-.124</td>
<td>-.390</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.142</td>
<td>.061</td>
<td>.053</td>
<td>-.382</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>.483</td>
<td>.427</td>
<td>.453</td>
<td>-.206</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.365</td>
<td>.456</td>
<td>.230</td>
<td>-.146</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.426</td>
<td>.260</td>
<td>-.048</td>
<td>-.048</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>.175</td>
<td>-.228</td>
<td>.469</td>
<td>-.519</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>-.181</td>
<td>.145</td>
<td>.275</td>
<td>-.768**</td>
</tr>
</tbody>
</table>

** p ≤ .05
Table 3.8

Question 1: Significant Correlations Between Neuropsychological Functioning and Quality of Life Across Time for the Sham Surgery Group

<table>
<thead>
<tr>
<th>Scale Names</th>
<th>Specific Domains</th>
<th>Correlation $p \leq .05$</th>
<th>Correlation $p \leq .10$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWAT &amp; Free or Restricted</td>
<td>Verbal Fluency and Effect of PD on Activity Level</td>
<td>.461</td>
<td></td>
</tr>
<tr>
<td>BVRT: Matching &amp; Free or Restricted</td>
<td>Visual Memory &amp; Effect of PD on Activity Level</td>
<td>-.437</td>
<td></td>
</tr>
<tr>
<td>BVRT: Matching &amp; CES-D</td>
<td>Visual Memory &amp; Depression</td>
<td>-.600</td>
<td></td>
</tr>
<tr>
<td>CVLT Delay &amp; SPS</td>
<td>Learning and Verbal Memory &amp; Social Support</td>
<td>.445</td>
<td></td>
</tr>
<tr>
<td><strong>12 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wisconsin Card Sort Test &amp; CES-D</td>
<td>Executive Functioning &amp; Depression</td>
<td>-.520</td>
<td></td>
</tr>
<tr>
<td>Wisconsin Card Sort Test &amp; SPS</td>
<td>Executive Functioning &amp; Social Support</td>
<td>.476</td>
<td></td>
</tr>
<tr>
<td>CVLT Delay &amp; SPS</td>
<td>Learning &amp; Verbal Memory &amp; Social Support</td>
<td>.538</td>
<td></td>
</tr>
<tr>
<td><strong>12 Months after 2nd Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward &amp; SF-36 (1 Item)</td>
<td>Working Memory &amp; Perceived Health at Present</td>
<td>-.699</td>
<td></td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; SPS</td>
<td>Visual Memory &amp; Social Support</td>
<td>-.610</td>
<td></td>
</tr>
<tr>
<td><strong>24 Months after 2nd Surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BVRT: Matching &amp; SPS</td>
<td>Visual Memory &amp; Social Support</td>
<td>-.768</td>
<td></td>
</tr>
</tbody>
</table>
**Question 2**

What are the relationships between neuropsychological functioning and motor functioning for each group at baseline, 12, and 24 months post-surgery?

Several significant relationships were found for the real surgery group at baseline. Four relationships were significant at the .01 level, five were found to be significant at the .05 level, and four were significant at the .10 level (Table 3.9).

Analysis of baseline data revealed that the four relationships found at the .01 level were between BVRT matching and all four motor functioning measures; Hoehn and Yahr, Schwab and England, UPDRS total, and UPDRS Motor “off.

At the .05 level, BVRT multiple-choice was correlated with the same four motor functioning measures. Relationships at the .10 level were not consistent across measures. Thus, BVRT multiple-choice and matching were strikingly consistent in terms of their relationships with motor functioning measures at baseline.
Table 3.9

Question 2: All Correlations for Neuropsychological and Motor Functioning Measures for the Real Surgery Group at Baseline

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Hoehn &amp; Yahr</th>
<th>Schwab &amp; England</th>
<th>UPDRS Total</th>
<th>UPDRS: Motor &quot;off&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.357</td>
<td>.191</td>
<td>-.252</td>
<td>-.230</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.247</td>
<td>.391*</td>
<td>-.236</td>
<td>-.242</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>-.259</td>
<td>.312</td>
<td>-.404*</td>
<td>-.375</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.196</td>
<td>.078</td>
<td>-.148</td>
<td>-.190</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.208</td>
<td>.286</td>
<td>-.280</td>
<td>-.360</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Total</td>
<td>-.227</td>
<td>.210</td>
<td>-.244</td>
<td>-.313</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>-.497**</td>
<td>.462**</td>
<td>-.463**</td>
<td>-.507**</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>-.624***</td>
<td>.603***</td>
<td>-.580***</td>
<td>-.578***</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>-.209</td>
<td>.103</td>
<td>-.410*</td>
<td>-.374</td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>-.362</td>
<td>.278</td>
<td>-.482**</td>
<td>-.427*</td>
</tr>
</tbody>
</table>

* $p \leq .10$

** $p \leq .05$

*** $p \leq .01$
Analyses for the real surgery group at 12 months resulted in three significant relationships at the .05 and six significant relationships at the .10 level between neuropsychological functioning and motor functioning measures (Table 4). The most notable result was that the Hoehn and Yahr, a measure of disease severity, was related to six of nine neuropsychological measures.
<table>
<thead>
<tr>
<th>12 Months</th>
<th>Hoehn &amp; Yahr</th>
<th>Schwab &amp; England</th>
<th>UPDRS Total</th>
<th>UPDRS: Motor “off”</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.430*</td>
<td>.282</td>
<td>-.257</td>
<td>-.256</td>
<td>.151</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.294</td>
<td>.328</td>
<td>-.283</td>
<td>-.324</td>
<td>.200</td>
</tr>
<tr>
<td>Wisconsin Card Sort</td>
<td>-.368</td>
<td>.218</td>
<td>-.145</td>
<td>-.116</td>
<td>.157</td>
</tr>
<tr>
<td>Sort Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-R: Digit Span</td>
<td>-.408*</td>
<td>.182</td>
<td>-.222</td>
<td>-.276</td>
<td>-.115</td>
</tr>
<tr>
<td>Forward</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-R: Digit Span</td>
<td>-.418*</td>
<td>.272</td>
<td>-.359</td>
<td>-.404*</td>
<td>-.037</td>
</tr>
<tr>
<td>Backward</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>-.562**</td>
<td>.422*</td>
<td>-.366</td>
<td>-.287</td>
<td>.088</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>-.553**</td>
<td>.499**</td>
<td>-.272</td>
<td>-.231</td>
<td>.292</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>-.429*</td>
<td>.278</td>
<td>-.223</td>
<td>-.258</td>
<td>.243</td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>-.369</td>
<td>.198</td>
<td>-.148</td>
<td>-.183</td>
<td>.017</td>
</tr>
</tbody>
</table>

*p ≤ .10

**p ≤ .05
Data analyses for the real group at 24 months resulted in three significant relationships at the .05 level and one at the .10 level (Table 4.1). The UPDRS total score was the measure of motor functioning most often correlated with neuropsychological instruments (two times), having significant relationships with WCST and BVRT multiple-choice.

Overall results of correlational analyses for the real surgery group at baseline, 12 and 24 months indicated that BVRT multiple-choice and matching (visual memory), were the measures of neuropsychological functioning that most often and powerfully correlated with motor functioning measures. The Hoehn and Yahr Stage of Disease Scale was the motor functioning measure most often correlated with neuropsychological functioning measures. Results of significant relationships for the real surgery group at baseline, 12 and 24 months post-surgery are listed in Table 4.2.
Table 4.1

Question 2: All Correlations for Neuropsychological and Motor Functioning Measures for the Real Surgery Group at 24 Months

<table>
<thead>
<tr>
<th>24 Months</th>
<th>Hoehn &amp; Yahr</th>
<th>Schwab &amp; England</th>
<th>UPDRS Total</th>
<th>UPDRS: Motor “off”</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.518*</td>
<td>.207</td>
<td>-.448</td>
<td>-.072</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.371</td>
<td>.535*</td>
<td>-.402</td>
<td>-.112</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>-.417</td>
<td>.364</td>
<td>-.575*</td>
<td>-.016</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.193</td>
<td>.318</td>
<td>-.386</td>
<td>-.221</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>.039</td>
<td>-.031</td>
<td>-.157</td>
<td>-.157</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>-.330</td>
<td>.320</td>
<td>-.620**</td>
<td>-.132</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>-.009</td>
<td>.024</td>
<td>-.168</td>
<td>-.084</td>
</tr>
</tbody>
</table>

*p ≤ .10
**p ≤ .05
Table 4.2

Question 2: Significant Correlations Between Neuropsychological Functioning and Motor Functioning Across Time for the Real Surgery Group

<table>
<thead>
<tr>
<th>Scale Names</th>
<th>Specific Domains</th>
<th>Correlation $p \leq .01$</th>
<th>Correlation $p \leq .05$</th>
<th>Correlation $p \leq .10$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp; Schwab and England</td>
<td>Verbal Fluency &amp; Activities of Daily Living</td>
<td></td>
<td></td>
<td>.391</td>
</tr>
<tr>
<td>WCST &amp; UPDRS Total</td>
<td>Executive Functioning &amp; Severity of Illness</td>
<td></td>
<td></td>
<td>-.404</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; Hoehn and Yahr</td>
<td>Visual Memory &amp;Severity of Illness</td>
<td></td>
<td></td>
<td>-.497</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; Schwab and England</td>
<td>Visual Memory &amp; Activities of Daily Living</td>
<td></td>
<td></td>
<td>.462</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; UPDRS Total</td>
<td>Visual Memory &amp; Severity of Illness</td>
<td></td>
<td></td>
<td>-.463</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; UPDRS Motor “off”</td>
<td>Visual Memory &amp; Severity of Illness Off of Medication</td>
<td></td>
<td></td>
<td>-.507</td>
</tr>
<tr>
<td>BVRT: Matching &amp; Hoehn and Yahr</td>
<td>Visual Memory &amp; Stage of Disease</td>
<td></td>
<td></td>
<td>-.624</td>
</tr>
<tr>
<td>BVRT: Matching &amp; Schwab and England</td>
<td>Visual Memory &amp; Activities of Daily Living</td>
<td></td>
<td></td>
<td>.603</td>
</tr>
<tr>
<td>BVRT: Matching &amp; UPDRS Total</td>
<td>Visual Memory &amp; Severity of Illness</td>
<td></td>
<td></td>
<td>-.580</td>
</tr>
<tr>
<td>BVRT: Matching &amp; UPDRS Motor “off”</td>
<td>Visual Memory &amp; Severity of Illness Off of Medication</td>
<td></td>
<td></td>
<td>-.578</td>
</tr>
<tr>
<td>CVLT Immediate &amp; UPDRS Total</td>
<td>Learning and Verbal Memory &amp; Severity of Illness</td>
<td></td>
<td></td>
<td>-.410</td>
</tr>
<tr>
<td>CVLT Delay &amp; UPDRS Total</td>
<td>Learning and Verbal Memory &amp; Severity of Illness</td>
<td></td>
<td></td>
<td>-.482</td>
</tr>
<tr>
<td>CVLT Delay &amp; UPDRS Motor “off”</td>
<td>Learning and Verbal Memory &amp; Severity of Illness Off of Medication</td>
<td></td>
<td></td>
<td>-.427</td>
</tr>
</tbody>
</table>
Table 4.2: Continued

Question 2: Significant Correlations Between Neuropsychological Functioning and Motor Functioning Across Time for the Real Surgery Group

<table>
<thead>
<tr>
<th>Scale Names</th>
<th>Specific Domains</th>
<th>Correlation $p \leq .01$</th>
<th>Correlation $p \leq .05$</th>
<th>Correlation $p \leq .10$</th>
</tr>
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<tbody>
<tr>
<td><strong>12 Months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWAT &amp; Hoehn and Yahr</td>
<td>Verbal Fluency &amp; Stage of disease</td>
<td></td>
<td></td>
<td>-.430</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward &amp; Hoehn and Yahr</td>
<td>Working Memory &amp; Stage of disease</td>
<td></td>
<td></td>
<td>-.408</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward &amp; Hoehn and Yahr</td>
<td>Working Memory &amp; Stage of disease</td>
<td></td>
<td></td>
<td>-.418</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward &amp; UPDRS Motor “off”</td>
<td>Working Memory &amp; Severity of Illness Off of Medication</td>
<td></td>
<td></td>
<td>-.404</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; Hoehn and Yahr</td>
<td>Visual Memory &amp; Stage of disease</td>
<td></td>
<td></td>
<td>-.562</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; Schwab and England</td>
<td>Visual Memory &amp; Activities of Daily Living</td>
<td></td>
<td></td>
<td>.422</td>
</tr>
<tr>
<td>BVRT: Matching &amp; Hoehn and Yahr</td>
<td>Visual Memory &amp; Stage of disease</td>
<td></td>
<td></td>
<td>-.553</td>
</tr>
<tr>
<td>BVRT: Matching &amp; Schwab and England</td>
<td>Visual Memory &amp; Activities of Daily Living</td>
<td></td>
<td></td>
<td>.499</td>
</tr>
<tr>
<td>CVLT Immediate &amp; Hoehn and Yahr</td>
<td>Immediate Verbal Memory &amp; Stage of disease</td>
<td></td>
<td></td>
<td>-.429</td>
</tr>
<tr>
<td><strong>24 Months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWAT &amp; Hoehn and Yahr</td>
<td>Verbal Fluency &amp; Stage of disease</td>
<td></td>
<td></td>
<td>-.518</td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp; Schwab and England</td>
<td>Verbal Fluency &amp; Activities of Daily Living</td>
<td></td>
<td></td>
<td>.535</td>
</tr>
<tr>
<td>WCST &amp; UPDRS Total</td>
<td>Executive Functioning &amp; Severity of Illness</td>
<td></td>
<td></td>
<td>-.575</td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; UPDRS Total</td>
<td>Visual Memory &amp; Severity of Illness</td>
<td></td>
<td></td>
<td>-.620</td>
</tr>
</tbody>
</table>
Results of data analyses for the sham surgery group at baseline, 12 months post-sham surgery, and 12 months post-real surgery varied greatly from the real surgery group. As stated previously, due to the small number of patients for whom we have neurological (motor) data at 24 months post-real surgery, analyses at this data point were excluded.

At baseline, no significant results were found (Table 4.3). Two relationships were significant at 12 months post-sham surgery (Table 4.4).

At 12 months post-real surgery for the sham surgery group, BDAE animal naming was related with all four of the motor functioning instruments (Table 4.5).

In summary, for the sham surgery group at baseline, 12 months post-sham surgery, and 12 months post-real surgery, BDAE animal naming and BVRT matching were the neuropsychological measures that correlated most frequently with motor functioning measures.

A summary of significant relationships for the sham surgery group at baseline, 12 months post-sham surgery and 12 months post-real surgery is presented in Table 4.6.

Overall results of correlational analyses for both real and sham surgery groups across time points indicated that BVRT multiple-choice and matching (visual memory) and BDAE animal naming (verbal fluency) were the measures of neuropsychological functioning that most often correlated with motor functioning measures. The Hoehn and Yahr Stage of Disease Scale was the motor functioning measure most notably correlated with neuropsychological functioning measures.
Table 4.3

Question 2: All Correlations for Neuropsychological and Motor Functioning Measures for the Sham Surgery Group at Baseline

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Hoehn &amp; Yahr</th>
<th>Schwab &amp; England</th>
<th>UPDRS Total</th>
<th>UPDRS: Motor “off”</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.073</td>
<td>-.084</td>
<td>-.159</td>
<td>-.184</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>-.283</td>
<td>.253</td>
<td>-.233</td>
<td>-.205</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>-.105</td>
<td>-.100</td>
<td>-.256</td>
<td>-.195</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>.292</td>
<td>-.260</td>
<td>.056</td>
<td>.003</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>.322</td>
<td>-.166</td>
<td>.122</td>
<td>.109</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>-.271</td>
<td>.263</td>
<td>-.343</td>
<td>-.258</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>.047</td>
<td>.060</td>
<td>-.187</td>
<td>-.169</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>-.170</td>
<td>.152</td>
<td>-.081</td>
<td>.021</td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>-.180</td>
<td>.026</td>
<td>-.169</td>
<td>-.083</td>
</tr>
</tbody>
</table>
Table 4.4

Question 2: All Correlations for Neuropsychological and Motor Functioning Measures for the Sham Surgery Group at 12 Months

<table>
<thead>
<tr>
<th>12 Months</th>
<th>Hoehn &amp; Yahr</th>
<th>Schwab &amp; England</th>
<th>UPDRS Total</th>
<th>UPDRS: Motor “off”</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>-.223</td>
<td>.068</td>
<td>-.242</td>
<td>-.202</td>
<td>-.034</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>.017</td>
<td>-.212</td>
<td>.039</td>
<td>.027</td>
<td>-.119</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>.317</td>
<td>-.543**</td>
<td>-.278</td>
<td>.168</td>
<td>.301</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>-.085</td>
<td>-.053</td>
<td>-.217</td>
<td>-.219</td>
<td>-.054</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>-.152</td>
<td>.045</td>
<td>-.090</td>
<td>-.040</td>
<td>-.085</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>.061</td>
<td>-.277</td>
<td>-.366</td>
<td>-.301</td>
<td>-.041</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>.185</td>
<td>-.214</td>
<td>-.133</td>
<td>-.012</td>
<td>-.198</td>
</tr>
<tr>
<td>CVLT Immediate</td>
<td>.079</td>
<td>-.219</td>
<td>-.015</td>
<td>-.012</td>
<td>.319</td>
</tr>
<tr>
<td>CVLT Delay</td>
<td>.069</td>
<td>-.179</td>
<td>.026</td>
<td>.077</td>
<td>.432*</td>
</tr>
</tbody>
</table>

*p ≤ .10
**p ≤ .05
Table 4.5

Question 2: All Correlations for Neuropsychological and Motor Functioning Measures for the Sham Surgery Group at 12 Months after 2nd surgery

<table>
<thead>
<tr>
<th>12 Months after 2nd surgery</th>
<th>Hoehn &amp; Yahr</th>
<th>Schwab &amp; England</th>
<th>UPDRS Total</th>
<th>UPDRS: Motor “off”</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>.160</td>
<td>-.274</td>
<td>.237</td>
<td>.301</td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td>.557*</td>
<td>-.535*</td>
<td>.654**</td>
<td>.731***</td>
</tr>
<tr>
<td>Wisconsin Card Sort Test</td>
<td>.172</td>
<td>-.178</td>
<td>.080</td>
<td>-.046</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Forward</td>
<td>.039</td>
<td>-.023</td>
<td>.081</td>
<td>.156</td>
</tr>
<tr>
<td>WAIS-R: Digit Span Backward</td>
<td>.258</td>
<td>-.180</td>
<td>.366</td>
<td>.443</td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td>.467</td>
<td>-.611**</td>
<td>.292</td>
<td>.202</td>
</tr>
<tr>
<td>BVRT: Matching</td>
<td>.050</td>
<td>-.312</td>
<td>-.067</td>
<td>-.080</td>
</tr>
</tbody>
</table>

*p ≤ .10
**p ≤ .05
***p ≤ .01
Table 4.6

Question 2: Significant Correlations Between Neuropsychological Functioning and Motor Functioning Across Time for the Sham Surgery Group

<table>
<thead>
<tr>
<th>Scale Names</th>
<th>Specific Domains</th>
<th>Correlation $p \leq .01$</th>
<th>Correlation $p \leq .05$</th>
<th>Correlation $p \leq .10$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST &amp; Schwab and England</td>
<td>Executive Functioning &amp; Activities of Daily Living</td>
<td>- .543</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT Delay &amp; Global Rating of Functioning</td>
<td>Learning and Verbal Memory &amp; Perceived Functioning</td>
<td>- .432</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Months After 2nd Surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp; Hoehn and Yahr</td>
<td>Verbal Fluency &amp; Stage of disease</td>
<td>.557</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp; UPDRS Total</td>
<td>Verbal Fluency &amp; Severity of Illness</td>
<td>.064</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming &amp; UPDRS Motor “off”</td>
<td>Verbal Fluency &amp; Severity of Illness Off of Medication</td>
<td>.731</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BVRT: Multiple-choice &amp; Schwab and England</td>
<td>Visual Memory &amp; Activities of Daily Living</td>
<td>- .611</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Question 3**

Are there any differences at baseline, 12, and 24 months between older (61+) and younger patients (≤60) in the domain of neuropsychological functioning for each group?

Analysis of variance (ANOVA) was used to examine differences between age groups with respect to neuropsychological functioning at each time point. Results are presented for real and sham surgery groups at baseline, 12, and 24 months.

Results of analyses for the real surgery group showed several differences between younger and older participants at each time point (Table 4.8). Younger participants performed better than older participants in each instance.

Results of analyses for the sham surgery group showed differences only at baseline, perhaps because of extremely small sample sizes in the older group, three and one respectively for 12 and 24 months after real surgery. Younger participants performed better than older participants on BDAE animal naming (verbal fluency), BVRT multiple-choice (visual memory), and CVLT delay (learning and verbal memory; Table 4.9).

In summary, differences were seen between younger and older participants in the real surgery and sham surgery groups over time. The majority of the differences were on measures of verbal fluency and verbal memory. In all cases, younger participants performed better than older participants.
Table 4.7

Question 3: Differences Between Older and Younger Participants on Measures of Neuropsychological Functioning at Baseline, 12 and 24 Months for the Real Surgery Group

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2986.901</td>
<td>1</td>
<td>2986.901</td>
<td>4.04*</td>
</tr>
<tr>
<td>Within Groups</td>
<td>12564.889</td>
<td>17</td>
<td>739.111</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>15551.789</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>4558.634</td>
<td>1</td>
<td>4558.634</td>
<td>4.91*</td>
</tr>
<tr>
<td>Within Groups</td>
<td>15767.156</td>
<td>17</td>
<td>927.480</td>
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<tr>
<td>Total</td>
<td>20325.789</td>
<td>18</td>
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<td></td>
</tr>
<tr>
<td><strong>12 Months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COWAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>5203.678</td>
<td>1</td>
<td>5203.678</td>
<td>4.26*</td>
</tr>
<tr>
<td>Within Groups</td>
<td>20790.322</td>
<td>17</td>
<td>1222.960</td>
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<tr>
<td>Total</td>
<td>25994.000</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>11.358</td>
<td>1</td>
<td>11.358</td>
<td>3.52*</td>
</tr>
<tr>
<td>Within Groups</td>
<td>45.079</td>
<td>14</td>
<td>3.220</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56.437</td>
<td>15</td>
<td></td>
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</tr>
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</table>

* \( p < .10 \)

** \( p < .05 \)
Table 4.7: Continued

Question 3: Differences Between Older and Younger Participants on Measures of Neuropsychological Functioning at Baseline, 12 and 24 Months for the Real Surgery Group

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
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<th>Mean Square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 Months</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>4721.582</td>
<td>1</td>
<td>4721.582</td>
<td>5.82**</td>
</tr>
<tr>
<td>Within Groups</td>
<td>12172.889</td>
<td>5</td>
<td>811.526</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16894.471</td>
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<td></td>
</tr>
<tr>
<td>BVRT: Multiple-choice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>7.562</td>
<td>1</td>
<td>7.562</td>
<td>3.54*</td>
</tr>
<tr>
<td>Within Groups</td>
<td>28.875</td>
<td>14</td>
<td>2.134</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>37.438</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p ≤ .10
**p ≤ .05
Table 4.8

Question 3: Differences Between Older and Younger Participants on Measures of Neuropsychological Functioning at Baseline for the Sham Surgery Group

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDAE: Animal Naming</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>2034.368</td>
<td>1</td>
<td>2034.368</td>
<td>3.26*</td>
</tr>
<tr>
<td>Within Groups</td>
<td>11230.182</td>
<td>18</td>
<td>623.899</td>
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</tr>
<tr>
<td>Total</td>
<td>13264.550</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BVRT: Multiple-choice</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>10.766</td>
<td>1</td>
<td>10.766</td>
<td>8.27***</td>
</tr>
<tr>
<td>Within Groups</td>
<td>23.434</td>
<td>18</td>
<td>1.302</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>34.200</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CVLT Delay</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between Groups</td>
<td>65.091</td>
<td>1</td>
<td>65.091</td>
<td>5.58**</td>
</tr>
<tr>
<td>Within Groups</td>
<td>209.859</td>
<td>18</td>
<td>11.659</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>274.950</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* $p \leq .10$
** $p \leq .05$
*** $p \leq .01$
Question 4

Are there any differences at 12 months between those who thought they received the fetal cell transplant and those who thought they received the sham surgery in the domain of neuropsychological functioning?

This question was addressed because of the significant results that were found in previous analyses with these data based on perceived groups, or those who thought they received the real or sham surgery. Analysis of variance (ANOVA) was used to examine differences between groups with respect to neuropsychological functioning one year after surgery, before the blind was lifted. No differences were found between those who thought they received the mesencaphalic fetal cell transplant and those who thought they received the sham surgery one year after the initial surgery.

In summary, this chapter reported results of the preliminary analyses and the research questions. Many significant, although rather inconsistent, relationships were found between neuropsychological, motor, and quality of life variables. There were some differences based on age, with younger patients achieving better results on neuropsychological testing than older patients. There were no significant differences found between perceived real and sham surgery groups on neuropsychological testing 12 months after the initial surgery. Discussion of results is presented in Chapter V.
Chapter V
Discussion

The original study by Stern and colleagues (Trott et al., 2003) evaluated neuropsychological differences between the real and sham surgery groups 12 months following the double-blind sham surgery procedure. Because data were collected for participants up to 24 months and beyond, this study was undertaken to investigate the long-term effects of the transplant on both the original transplant group as well as those who had the sham surgery first and then received the transplant. Although the primary focus of the study was on neuropsychological results, another aim of the study was to examine relationships between neuropsychological functioning, motor functioning, and quality of life.

Preliminary Analyses

Preliminary analyses of neuropsychological measures were conducted for both groups to assess for central tendency and comparability of results over time (see Tables 2.1 and 2.2). Although significance testing was not done to compare means across data collection points because of the small sample size, results will be discussed briefly. Because of the uniqueness of the sample and the study, and because of the exploratory nature of the investigation, this non-traditional approach to discussing non-significant results is being taken. Results that are even suggestive of possible fruitful avenues of further research have been sanctioned by the organization that funded this project, the National Institute of Neurological Disorders and Stroke.
Results of preliminary analyses for the real surgery group showed decline in mean scores on eight of the nine neuropsychological measures from baseline to 12 months. However, there were increases in mean scores on four of the seven neuropsychological measures from 12 to 24 months (only seven measures were administered at 24 months). These increases were seen on tests of verbal fluency, immediate verbal memory, and visual memory. This result seems rather unusual since the typical trajectory of neuropsychological functioning in PD is downward, indicating that patients get worse over time.

There are several potential explanations for these findings. First, two participants in the real surgery group became demented and were withdrawn from the study. Exclusion of data from these two participants at 24 months undoubtedly affected the means of the total scores for the remaining group. Second, increases in mean scores may be suggestive of beneficial treatment effects from the transplant surgery in terms of neuropsychological functioning.

Results of preliminary analyses for the sham surgery group showed decline on eight of the nine neuropsychological measures from baseline to 12 months. The scales that showed an increase were not the same for the real and sham groups. From 12 to 24 months after the second surgery, mean scores increased on four of the seven neuropsychological measures and remained the same for one measure. These increases were seen on tests of verbal fluency, executive functioning, and visual memory while WAIS-R Digit Span Backward, a test of working memory, remained constant. Increases from 12 to 24 months post-transplant were found in both real and sham groups on COWAT and BVRT multiple-choice. It is interesting to observe that mean scores for the
10 patients in the sham group at 24 months following the second surgery were, in most cases, greater than scores of the 20 participants at 12 months and greater than or equal to scores of 12 participants at 12 months after the second surgery.

Much like the real group, exclusion of six participants aged 61 and older 12 months after the initial sham surgery may explain some of the improvement in scores following the second surgery as it left mostly younger participants in the study. In addition, one participant in this group was withdrawn due to dementia and exclusion of these data in all probability also influenced remaining scores. At 24 months following the second surgery there were only 10 participants in the sham to transplant group, apparently comprised of the younger and more able participants whose scores were perhaps higher than those who dropped out of the study. Another explanation of these results may be that improvement was seen after fetal cell transplant surgery. Even relatively stable scores over the period of at least three years in this group is remarkable at such advanced stages of disease.

Overall, scores for both groups appeared to benefit from exclusion of data of demented and older participants. However, it is important to explore the possibility that the relative stability of some scores was related to the positive effects of the fetal cell transplant surgery.

**Question 1**

Correlational analyses of the relationships between neuropsychological functioning and QOL yielded several findings. With respect to the real surgery group, the CES-D, a measure of depression, emerged as a variable that related significantly to several neuropsychological variables at 12 months. Higher depression was related to
lower neuropsychological scores. Depression is known to interrupt attention and concentration and may explain these relationships.

Perceived social support and the Free or Restricted item were both related to several neuropsychological variables at 24 months. Relationships between the SPS and neuropsychological variables were all positive, indicating that more social support was related to better scores. Relationships between the Free or Restricted scores and neuropsychological variables were all negative. However, because of the scaling of the Free or Restricted item, more “freedom” to do what the patient would like to do was related to higher neuropsychological scores.

The fact that the most salient QOL variables changed from the CES-D at 12 months to SPS and Free or Restricted at 24 months may indicate that social support and freedom, or independence may be more valued or desired by participants at 24 months than at baseline and 12 months. This change may also be suggestive of a tendency for participants to transition from primarily individual and internal coping methods to group and external coping methods.

No one neuropsychological test stood out as a correlate with QOL at 12 months post-surgery, suggesting equal performance across domains. Correlations between the WCST, BVRT multiple-choice, and BVRT matching were evenly distributed; relating two times with QOL measures at 24 months post-surgery (see Table 3.2). The most consistent findings at 24 months were the relationships between BDAE animal naming and three of the QOL variables. These results suggest that verbal fluency and visual memory were clearly related to QOL.
With respect to the sham surgery group, there were fewer significant relationships between neuropsychological and QOL measures over time than in the real surgery group. Aside from baseline, when results for the sham surgery group showed more significant correlations than the real surgery group, there were no consistent results across assessment points. This result may be related to a diminishing sample size that began with 20 at baseline and decreased to 10 by 24 months.

Overall results for the sham surgery group indicated that the WCST and BVRT matching were the neuropsychological measures most often correlated with QOL measures. This is consistent with findings for the real surgery group, suggesting that impairments in executive functioning and visual memory significantly impact QOL. Social support was the QOL measure most often correlated with neuropsychological measures, which was also found in the real surgery group.

Overall, for both groups, results were fairly equally distributed among three scales in their relationships with QOL variables: BDAE animal naming (four times), BVRT multiple-choice (four times), and BVRT matching (six times). Two QOL measures stood out in their relationships with neuropsychological measures. Social support was the aspect of QOL that was most consistently (10 times) correlated with neuropsychological measures for both groups over time. Results indicated each time that more support was related to better neuropsychological results. Depression was related to neuropsychological results eight times across groups and assessment points, with more depression related to lower neuropsychological scores.
Question 2

Analysis of the relationships between neuropsychological and neurological functioning for the real surgery group resulted in several significant findings. BVRT multiple-choice and BVRT matching were strongly related to neurological functioning at baseline, with better neuropsychological results linked with better neurological functioning. BVRT matching obtained significance with motor measures at the .01 level, which is particularly powerful when considering the small sample size in this study. These results indicate that BVRT matching, a measure of visual memory, was significantly related to stage of disease, participation in activities of daily living, severity of illness, and motor functioning when off medication. BVRT multiple-choice was consistently related to all four neurological measures at the .05 level. These relationships highlight the apparently parallel declines in visual memory and functioning related to PD experienced by these participants.

UPDRS Total and Motor “off” were both related to neuropsychological measures for the real surgery group at baseline. These results indicate that severity of symptoms and performance on neuropsychological measures were linked before surgery. However, results also raise the question of what happened to these relationships at 12 and 24 months. It may be that sample size, which changed from 20 to 19 to 17 over the period of study, affected the results. It is also possible that relationships among the variables were changing because of effects of the surgery.

A similar result was found at 12 months when the Hoehn and Yahr Stage of Disease Scale correlated significantly with the majority of neuropsychological functioning measures. These results also show the link between neuropsychological
functioning and severity of illness, or stage of disease. Why this should be so apparent at 12 months and not at baseline and 24 months is difficult to determine with these data.

Overall, BVRT multiple-choice and BVRT matching, measures of visual memory, were the neuropsychological functioning measures that were most strongly correlated with motor functioning measures. The Hoehn and Yahr (nine times) and the UPDRS Total (eight times) were the motor functioning measures most often correlated with neuropsychological functioning measures.

Results of analyses of relationships between neuropsychological and neurological functioning in the sham surgery group are remarkable because of their lack of significance. There were no significant relationships at baseline, only two at 12 months, and eight at 12 months after the transplant surgery.

Among the results 12 months after the real surgery for the sham group, BDAE animal naming, a verbal fluency measure, correlated with all four measures of neurological functioning. This result was surprising because it was not found at baseline and 12 months after initial surgery, nor was it found in the real group at any time. The directionality of the relationships are all as expected, with higher neuropsychological scores related to better physical functioning. Keeping in mind that this was a refined group of 12 mostly “younger” participants, it is possible that the animal naming measure was particularly sensitive to the changes resulting from the transplant surgery.

**Question 3**

Younger participants performed better than older participants on several measures across time points in both the real and sham surgery groups. Of the five differences in the real group, four were related to verbal fluency (see Table 4.8). In the sham group one of
three differences was a measure of verbal fluency (see Table 4.9). Two differences (one in both real and sham groups) were found in BVRT multiple-choice, or a measure of visual memory. These differences may be explained by the fact that younger persons typically perform better than older persons on measures of neuropsychological functioning. However, it is noteworthy that such compelling results were found regarding verbal fluency.

**Question 4**

No differences were found between those who thought they received the fetal cell transplant and those who thought they received the sham surgery on measures of neuropsychological functioning. While previous research has shown that the placebo effect influenced ratings of perceived health and QOL among patients and medical personnel, this effect apparently did not extend to neuropsychological test performance. Although it might have been conceivable for the placebo effect to influence measures of attention, (e.g., belief that treatment was received may have increased attention whereas belief that treatment was not received may have decreased attention), it would have been unusual for it to have influenced overall performance. Results of analyses for this question indicated there were no differences between groups.

**Strengths of the Study**

A major strength of this unique study was the opportunity to evaluate longitudinal data of PD patients who participated in a double-blind placebo surgery trial. The original study was complex, and data were collected to capture performance in multiple domains over an extended period of time. The opportunity to analyze longitudinal data is often regarded as a privilege since it allows researchers to consider what happens in various
domains over time. In the realm of this very experimental and esoteric study, this is especially true. The neuropsychological data had only been examined to 12 months and the sample was only regarded as a whole, not two separate groups (real and sham), with possibly two rather different profiles of relationships and change over time. This study allowed for examination of neuropsychological data up to 24 months after surgery and explored reasons for some of the interesting results, including the possibility that the transplant had some effect on the neuropsychological results.

Limitations of the Study

There are several limitations of this study that must be considered. The most obvious is that the sample size was very small, even at baseline. Because archival data were used in this study, there was no way to remedy this difficulty. It is interesting to note that the dilemma of sample size was only magnified over time as participants dropped out of the study because of age or were removed because of dementia. In spite of the small number of participants, there were a remarkable number of significant differences and correlations.

Another limitation specific to this study is that the number of analyses that were conducted increased the possibility of Type I error. Unfortunately, because of the research questions, this approach was unavoidable.

For reasons unknown to the author, the CVLT was not given at each time point for each group. Thus, results of this study cannot be considered to be conclusive over time with respect to this measure of learning and verbal memory. The impact of the data that may have been collected at later time points on this measure is unknown.
Summary

Observations regarding several sets of analyses suggested that changes related to the fetal cell transplant surgery may have been one possible explanation for the results. While further exploration of these data may provide some additional information, a follow-up study with another fetal transplant surgery group will probably not be done to extend and investigate these results in more depth.

Results gave some support to relationships that have been reported in other investigations (e.g., depression and neuropsychological performance). Further exploration of other relationships found in this study (e.g., the relationships between social support and neuropsychological performance) with other samples might be a helpful direction to take for future research.

Finally, it was interesting to observe the development of differences in neuropsychological functioning over time. This result has implications for continuing to test patients receiving other types of surgical interventions for PD such deep brain stimulation. Changes in functioning may take much longer than previously thought, with changes occurring up to 24 months and possibly beyond. In order to really capture differences, it is recommended that control groups of matched patients be tested along with the experimental patients in any intervention in order to consider the normal trajectory of typical decline seen in neuropsychological functioning over time.
References


Appendices

Appendix A:

Figure 2. Change in $^{18}$F-Fluorodopa Uptake in the Brains of Patients with Parkinson’s Disease after Transplantation, as Shown in Fluorodopa PET Scans.

In the panel on the far left, an axial section through the caudate and putamen of a normal subject shows intense uptake of $^{18}$F-fluorodopa (red). On the right side, the upper panels show preoperative and 12-month postoperative scans in a patient in the transplantation group. Before surgery, the uptake of $^{18}$F-fluorodopa was restricted to the region of the caudate. After transplantation, there was increased uptake of $^{18}$F-fluorodopa in the putamen bilaterally. The lower panels show $^{18}$F-fluorodopa scans in a patient in the sham-surgery group. There was no postoperative change in $^{18}$F-fluorodopa uptake.

Images taken from:
Appendix B:

Unified Parkinson Disease Rating Scale (UPDRS)

I. Mentation, Behavior, Mood

Intellectual Impairment
0-none
1-mild (consistent forgetfulness with partial recollection of events with no other difficulties)
2-moderate memory loss with disorientation and moderate difficulty handling complex problems
3-severe memory loss with disorientation to time and often place, severe impairment with problems
4-severe memory loss with orientation only to person, unable to make judgments or solve problems

Thought Disorder
0-none
1-vivid dreaming
2-"benign" hallucination with insight retained
3-occasional to frequent hallucination or delusions without insight, could interfere with daily activities
4-persistent hallucination, delusions, or florid psychosis.

Depression
0-not present
1-periods of sadness or guilt greater than normal, never sustained for more than a few days or a week
2-sustained depression for >1 week
3-vegetative symptoms (insomnia, anorexia, abulia, weight loss)
4-vegetative symptoms with suicidality

Motivation/Initiative
0-normal
1-less of assertive, more passive
2-loss of initiative or disinterest in elective activities
3-loss of initiative or disinterest in day to day (routine) activities
4-withdrawn, complete loss of motivation

II. Activities of Daily Living

Speech
0-normal
1-mildly affected, no difficulty being understood
2-moderately affected, may be asked to repeat
3-severely affected, frequently asked to repeat
4-unintelligible most of time

Salivation
  0-normal
  1-slight but noticeable increase, may have nighttime drooling
  2-moderately excessive saliva, hay minimal drooling
  3-marked drooling

Swallowing
  0-normal
  1-rare choking
  2-occasional choking
  3requires soft food
  4-requires NG tube or G-tube

Handwriting
  0-normal
  1-slightly small or slow
  2-all words small but legible
  3-severely affected, not all words legible
  4-majority illegible

Cutting Food/Handing Utensils
  0-normal
  1-somewhat slow and clumsy but no help needed
  2-can cut most foods, some help needed
  3-food must be cut, but can feed self
  4-needs to be fed

Dressing
  0-normal
  1-somewhat slow, no help needed
  2-occasional help with buttons or arms in sleeves
  3-considerable help required but can do something alone
  4-helpless

Hygiene
  0-normal
  1-somewhat slow but no help needed
  2-needs help with shower or bath or very slow in hygienic care
  3-requires assistance for washing, brushing teeth, going to bathroom
  4-helpless
Turning in Bed/ Adjusting Bed Clothes
0-normal
1-somewhat slow no help needed
2-can turn alone or adjust sheets but with great difficulty
3-can initiate but not turn or adjust alone
4-helpless

Falling-Unrelated to Freezing
0-none
1-rare falls
2-occasional, less than one per day
3-average of once per day
4->1 per day

Freezing When Walking
0-normal
1-rare, may have start hesitation
2-occasional falls from freezing
3-frequent freezing, occasional falls
4-frequent falls from freezing

Walking
0-normal
1-mild difficulty, day drag legs or decrease arm swing
2-moderate difficulty requires no assist
3-severe disturbance requires assistance
4-cannot walk at all even with assist

Tremor
0-absent
1-slight and infrequent, not bothersome to patient
2-moderate, bothersome to patient
3-severe, interferes with many activities
4-marked, interferes with many activities

Sensory Complaints Related to Parkinsonism
0-none
1-occasionally has numbness, tingling, and mild aching
2-frequent, but not distressing
3-frequent painful sensation
4-excruciating pain
III. Motor Exam

Speech
0-normal
1-slight loss of expression, diction, volume
2-monotone, slurred but understandable, mod. impaired
3-marked impairment, difficult to understand
4-unintelligible

Facial Expression
0-Normal
1-slight hypomimia, could be poker face
2-slight but definite abnormal diminution in expression
3-mod. hypomimia, lips parted some of time
4-masked or fixed face, lips parted 1/4 of inch or more with complete loss of expression

*Tremor at Rest
Face
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

Right Upper Extremity (RUE)
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

LUE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

RLE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time
LLE
0-absent
1-slight and infrequent
2-mild and present most of time
3-moderate and present most of time
4-marked and present most of time

*Action or Postural Tremor

RUE
0-absent
1-slight, present with action
2-moderate, present with action
3-moderate present with action and posture holding
4-marked, interferes with feeding

LUE
0-absent
1-slight, present with action
2-moderate, present with action
3-moderate present with action and posture holding
4-marked, interferes with feeding

*Rigidity

Neck
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

RUE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

LUE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe
RLE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

LLE
0-absent
1-slight or only with activation
2-mild/moderate
3-marked, full range of motion
4-severe

*Finger taps*

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

*Hand Movements (open and close hands in rapid succession)*

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform
*Rapid Alternating Movements (pronate and supinate hands)

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

*Leg Agility (tap heel on ground, amp should be 3 inches)

Right
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

Left
0-normal
1-mild slowing, and/or reduction in amp.
2-moderate impaired. Definite and early fatiguing, may have occasional arrests
3-severely impaired. Frequent hesitations and arrests.
4-can barely perform

*Arising From Chair (pt. arises with arms folded across chest)
0-normal
1-slow, may need more than one attempt
2-pushes self up from arms or seat
3-tends to fall back, may need multiple tries but can arise without assistance
4-unable to arise without help

*Posture
0-normal erect
1-slightly stooped, could be normal for older person
2-definitely abnormal, mod. stooped, may lean to one side
3-severely stooped with kyphosis
4-marked flexion with extreme abnormality of posture
*Gait
0-normal
1-walks slowly, may shuffle with short steps, no festination or propulsion
2-walks with difficulty, little or no assistance, some festination, short steps or propulsion
3-severe disturbance, frequent assistance
4-cannot walk

*Postural Stability (retropulsion test)
0-normal
1-reCOVERS unaided
2-would fall if not caught
3-falls spontaneously
4-unable to stand

*Body Bradykinesia/ Hypokinesia
0-none
1-minimal slowness, could be normal, deliberate character
2-mild slowness and poverty of movement, definitely abnormal, or dec. amp. of movement
3-moderate slowness, poverty, or small amplitude
4-marked slowness, poverty, or amplitude

Appendix C: Hoehn and Yahr Stage of Disease Scale

Stage One:
- Signs and symptoms on one side only
- Symptoms mild
- Symptoms inconvenient but not disabling
- Usually presents with tremor of one limb
- Friends have noticed changes in posture, locomotion and facial expression

Stage Two:
- Symptoms are bilateral
- Minimal disability
- Posture and gait affected

Stage Three:
- Significant slowing of body movements
- Early impairment of equilibrium on walking or standing
- Generalized dysfunction that is moderately severe

Stage Four:
- Severe symptoms
- Can still walk to a limited extent
- Rigidity and bradykinesia
- No longer able to live alone
- Tremor may be less than earlier stages

Stage Five:
- Cachectic stage
- Invalidism complete
- Cannot stand or walk
- Requires constant nursing

Appendix D:

Schwab and England Activities of Daily Living

Rating can be assigned by rater or by patient.

* 100%-Completely independent. Able to do all chores w/o slowness, difficulty, or impairment.

* 90%-Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.

* 80%-Independent in most chores. Takes twice as long. Conscious of difficulty and slowing

* 70%-Not completely independent. More difficulty with chores. 3 to 4X along on chores for some. May take large part of day for chores.

* 60%-Some dependency. Can do most chores, but very slowly and with much effort. Errors, some impossible

* 50%-More dependant. Help with 1/2 of chores. Difficulty with everything

* 40%-Very dependant. Can assist with all chores but few alone

* 30%-With effort, now and then does a few chores alone of begins alone. Much help needed

* 20%-Nothing alone. Can do some slight help with some chores. Severe invalid

* 10%-Totally dependant, helpless

* 0%-Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

Appendix E:

Global Rating Scale

Subject’s name: _____________________________ Date:_________________

Number of Months After Surgery:_______________

Please give us your own evaluation of how you are doing compared to what you remember how you were prior to the surgery.

Markedly worse. Very unhappy with results. (-3)

Definitely worse. Unhappy with results. (-2)

Slightly worse, but not significantly. (-1)

No change. ( 0)

Slightly improved, but no significantly. (+1)

Moderately improved. Happy with results. (+2)

Markedly improved. Very happy with results. (+3)

My Score Is:_________

Do you think you received the fetal transplant? Y N Don’t Know
(Circle One)

Any other Comments:____________________________________________________

Appendix F:

Center for Epidemiologic Studies Depression Scale (CES-D)

0= Rarely or none of the time (less than 1 day)
1= Some or a little of the time (1-2 days)
2= Occasionally or a moderate amount of the time (3-4 days)
3= Most or all of the time (5-7 days)

<table>
<thead>
<tr>
<th>During the past week.....</th>
<th>Circle One</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I was bothered by things that usually don’t bother me.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>2. I did not feel like eating; my appetite was poor.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>3. I felt that I could not shake off the blues even with help from my family/friends.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>4. I felt I was just as good as other people.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>5. I had trouble keeping my mind on what I was doing.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>6. I felt depressed.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>7. I felt that everything I did was an effort.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>8. I felt hopeful about the future.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>9. I thought my life had been a failure.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>10. I felt fearful.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>11. My sleep was restless.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>12. I was happy.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>13. I talked less than usual.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>14. I felt lonely.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>15. People were unfriendly.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>16. I enjoyed life.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>17. I had crying spells.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>18. I felt sad.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>19. I felt that people disliked me.</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>20. I could not get going.</td>
<td>0 1 2 3</td>
</tr>
</tbody>
</table>

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

Appendix G:

Social Provisions Scale (SPS)

Instructions: In answering the following questions, think about your current relationships with friends, family members, co-workers, community members, and so on. Please indicate to what extent each statement describes your current relationships with other people. Use the following scale to indicate your opinion:


So, for example, if you feel a statement is very true of your current relationships, you would respond with a 4 (strongly agree). If you feel a statement clearly does not describe your relationships, you would respond with a 1 (strongly disagree).

1. There are people I can depend on to help me if I really need it.
2. I feel that I do not have close personal relationships with other people.*
3. There is no one I can turn to for guidance in times of stress.*
4. There are people who depend on me for help.
5. There are people who enjoy the same social activities I do.
6. Other people do not view me as competent.*
7. I feel personally responsible for the well-being of another person.
8. I feel part of a group of people who share my attitudes and beliefs.
9. I do not think other people respect my skills and abilities.*
10. If something went wrong, no one would come to my assistance.*
11. I have close relationships that provide me with a sense of emotional security and well-being.
12. There is someone I could talk to about important decisions in my life.
13. I have relationships where my competence and skill are recognized.
14. There is no one who shares my interests and concerns.*
15. There is no one who really relies on me for their well-being.*
16. There is a trustworthy person I could turn to for advice if I were having problems.
17. I feel a strong emotional bond with at least one other person.
18. There is no one I can depend on for aid if I really need it.*
19. There is no one I feel comfortable talking about problems with.*
20. There are people who admire my talents and abilities.
21. I lack a feeling of intimacy with another person.*
22. There is no one who likes to do the things I do.*
23. There are people I can count on in an emergency.
24. No one needs me to care for them.*

*Indicates item should be reverse scored before computing scale total.

SPS subscales:
Attachment is emotional closeness from which one derives a sense of security (11, 14, 17, 21)
Social integration is a sense of belonging to a group that shares similar interests, concerns, and recreational activities (2, 5, 8, 22)
Opportunity for nurturance is the sense that others rely upon one for their well-being (4, 7, 15, 24)
Reassurance of worth is recognition of one's competence, skills, and value by others (6, 9, 13, 20)
Reliable alliance is assurance that others can be counted upon for tangible assistance (1, 10,
Guidance is advice or information (3, 12, 16, 19)