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Abstract

Parkinson's disease (PD) is a chronic and progressive neurological disorder that causes both motor symptoms and non-motor symptoms in individuals. Overall, PD impacts the physical, emotional and social functioning in the lives of those impacted by the disorder. In 2001, Freed et al. investigated the effects of fetal tissue transplantation in participants with PD by conducting a double-blind sham-controlled surgery trial. The quality of life (QoL) study was conducted concurrently by McRae et al. (2004) in order to determine whether QoL improved in participants in the transplant group compared to the sham group after the one-year period of the double-blind.

Research regarding the long-term impact of the fetal tissue transplantation on individuals with PD is extremely limited and there is little known regarding the long-term impact of participating in a double-blind sham-controlled surgery trial. This study examined the longitudinal changes, from both a quantitative and qualitative perspective, in QoL after undergoing the fetal tissue transplantation surgery approximately 13-15 years ago. There were a total of five participants who participated in the parent study (Freed et al., 2001) and original QoL study (McRae, 2004). All five participants completed an interview to gather qualitative information regarding their personal experiences over the last 13-15 years and four participants completed a questionnaire that measured several dimensions of QoL as well as optimism. The information gathered in the current study was plotted along with the data collected at baseline, 12, and 24 months after transplantation as well as a previous follow-up in 2008. The change over time in QoL was thus charted for each of the four individuals as well as average scores at each time point on each measure. Interviews were transcribed and coded for themes in order to describe the experiences of the participants in the unique study.

In the current study, the changes on several aspects of QoL were examined over the last 13-15 years. The majority of the participants showed decline on all the measures assessing Physical functioning, Emotional functioning, and Social functioning as well as Optimism between the 10-12-year follow-up in 2008 and the current assessment. However, the decline in functioning on several measures was less than expected given the progression of their illness. The qualitative data (e.g., narratives) provided insight into possible explanations for the resiliency amongst the participants who participated in the transplant surgery trial including the participants' dedication to contributing to our knowledge of PD and treatments of PD, strong social support, and internal drive to continue to live active and meaningful lives.

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PLACEBO SURGERY TRIAL

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Chapter One

Introduction

Description of Parkinson's Disease

Parkinson's disease (PD) is a chronic neurologic disease that impacts the central nervous system. James Parkinson, a British physician, described a complex set of symptoms in 1817 that later became known as Parkinson's disease. PD is characterized by motor symptoms including bradykinesia, resting tremor, stiffness, postural instability, and a broad spectrum of non-motor features including sleep problems, autonomous nervous system dysfunction, depression and dementia (Burch & Sheerin, 2005; Pfeiffer, 2007; Rod, Hansen, Schernhammer & Ritz, 2010).

PD is the result of a loss of dopaminergic neurons in the substantia nigra pars compacta, which causes reduced dopamine release in the striatum (Clark, Reddy, Zheng, Betensky & Simon, 2011). There are multiple genetic and environmental factors involved in PD (Simunovic et al., 2009). Currently, there are two forms of PD recognized: a 'familial' or early-onset PD and an 'idiopathic' or late-onset PD that does not appear to exhibit heritability (Simunovic et al., 2009). The 'familial' or early-onset PD is found in approximately less than 10% of all PD patients and 'idiopathic' or late-onset PD is found in approximately more than 85% of all PD patients. Overall, the pathology of Parkinson's disease is a consequence of a combination of unknown genetic and environmental factors, which leads to a common pathogenic cascade of molecular

events (Maguire-Zeiss & Federoff, 2003; Miller & Federoff, 2005; Simunovic et al., 2009).

PD is currently diagnosed based on clinical criteria, and at this time, there is no definitive test for PD. Diagnosis is generally based on the presence or absence of cardinal motor features associated with PD (e.g., tremors, rigidity, bradykinesia) and response to Levodopa (Rao et al., 2003). The diagnosis of PD can often be challenging, particularly in the early stages of the disease when there is overlap between the symptoms in different syndromes (Jankovic, 2008; Tolosa, Wenning & Poewe, 2006). Persons with PD can sometimes be misdiagnosed for several years before the symptoms become obvious enough for a clear diagnosis.

The treatments for PD include drug therapies and surgical interventions targeted at reducing the symptoms associated with PD. The surgical procedures are implemented when drug treatments are no longer effective in the later stages of the disease. Current surgical treatments for patients with PD include thalamotomy, pallidotomy, and deep brain stimulation. Gene therapy, stem cell transplantation, and fetal tissue transplantation are additional surgical interventions for patients with PD that are in various stages of development and refinement.

Onset and Prevalence

Today, PD is the most prevalent neurodegenerative movement disorder in adults (Borland et al., 2008). PD affects up to one million people in the United States (National Parkinson Foundation, 2010). More specifically, the disease affects approximately 2-3% of individuals over the age of 65 years (Cantuti-Castelvetri et al., 2007). However, in 5-10% of people who develop Parkinson's disease, the condition appears before the age of

40. Overall, age-adjusted prevalence is 1% worldwide, and 1.6% in Europe, rising from 0.6% at age 60-64 to 3.5% at age 85-89 (Clark & Moore, 2007; De Rijk et al., 1997; Zhang & Roman, 1993).

While the progression and symptoms of PD vary significantly among patients, research has found that bradykinesia, rigidity, and activities of daily living deteriorate faster in the earlier stages of the disease (Maetzler, Liepelt, & Berg, 2009). Furthermore, cognitive impairments, speech difficulties, sleep problems and gait difficulties develop throughout the progression of the disease (Maetzler et al., 2009). In the later stages of the disease, orthostatic dysfunction, visual hallucinations, and variability in heart rate develop (Maetzler et al., 2009). The life expectancy of patients with PD has been shown to be lower than the general population (Hobson, Meara, & Ishihara-Paul, 2010). In patients who do not develop dementia, the survival is shown to be similar to the general population (Hobson et al., 2010). In other words, patients with dementia and with a younger onset of PD appear to have shorter life expectancies than other patients with PD (Hobson et al., 2010).

Gender and Ethnicity

Evidence suggests the prevalence of Parkinson's disease is higher in the male population (Cantuti-Castelvetri et al., 2007) with a 60% and 40% male to female ratio. There is limited evidence regarding the prevalence of PD in ethnic minority groups. However, current research found PD impacts diverse racial and ethnic groups worldwide and one-fifth of patients with PD in the United States are from ethnic minority groups (Schneider, et al., 2009). However, more research needs to be conducted regarding the prevalence of PD in racial and ethnic minorities.

Symptoms

There are several cardinal symptoms associated with PD. The most common and recognizable feature of PD is a unilateral rest tremor (Shahed & Jankovic, 2007).

Cardinal symptoms of PD include rigidity, akinesia or bradykinesia, postural instability, flexed posture, and freezing (Jankovic, 2008). In addition, there are several secondary motor symptoms that are present in patients with PD including the re-emergence of primitive reflexes and unintended movements accompanying voluntary activity in homologous muscles (Jankovic, 2008; Thomas, 1994; Li et al., 2007; Wu, Sitburana & Jankovic, 2007). Neuro-ophthalmological abnormalities such as decreased blink rate, ocular surface irritation, altered tear film, visual hallucinations, blepharospasm and decreased convergence also occur in individuals with PD (Biousse et al., 2004; Jankovic, 2008). Individuals with PD experience respiratory disturbances, which can be either restrictive or obstructive (Jankovic, 2008). Non-motor symptoms are present in individuals with PD. These include autonomic dysfunction, cognitive and neurobehavioral abnormalities such as dementia sleep disorders, and sensory abnormalities (Jankovic, 2008). Sensory symptoms include olfactory dysfunction, pain, paresthesia, akathisia, oral pain, and genital pain (Jankovic, 2008).

Drug Treatment

Pharmacological treatments for PD are tailored to the specific needs and circumstances of the patient with PD (Schapira, 2005). As a result, treatments can vary significantly in patients depending on their stage of the disease and response to pharmacologic treatments. Pharmacological treatments are typically introduced to

patients with PD when symptoms interfere with daily activities such as work and social activities (Schapira, 2005).

Currently, pharmacologic treatments primarily focus on improvement of the motor features associated with PD. Other pharmacologic treatments are used to treat non-motor symptoms such as depression, anxiety, hallucinations, sleep disorders, sexual dysfunction, bowel problems and gait, pain, and fatigue given these symptoms can cause significant distress to patients with PD. There have been several pharmacological treatments shown to be effective in treating the non-dopaminergic symptoms of PD.

Surgical treatment

Surgical treatments for PD have been taking place for over 100 years (Bronte-Stewart, 2003). New surgical approaches were developed in the early 1990s as a result of gaining a better understanding of the pathophysiology of PD (Walter & Vitek, 2004). For instance, there have been significant advances in understanding the basal ganglia physiology (Bronte-Stewart, 2003). Thalamotomy was an early surgical procedure used to treat the resting tremor associated with PD. Unfortunately, there were multiple side effects associated with the procedure including an exacerbation of speech and gait disorders (Walter & Vitek, 2004). Thalamotomy was not recommended following the introduction of the pallidotomy procedure and deep brain stimulation (DBS; Walter & Vitek, 2004). One approach to DBS is the stimulation of the thalamus or the ventral intermediate nucleus, which has been shown to be effective in reducing the tremor in patients with PD (Walter & Vitek, 2004). Another DBS procedure that has been implemented in patients with PD is the stimulation of the internal globus pallidus and subthalamic nucleus, which has demonstrated improvement in the cardinal motor

symptoms associated with PD including akinesia and bradykinesia, rigidity, tremor and gait (Walter & Vitek, 2004).

Several other surgical procedures (i.e., neural transplantation) have been implemented in treating patients with PD. There are two types of neural transplantation: stem cell surgery and fetal tissue surgery. While there have been several surgical procedures used in treating PD, this study focused on neural transplantation, and more specifically, fetal tissue transplantation in persons with PD. Fetal tissue transplantation surgery is the stereotactic implantation of human embryonic dopamine neurons into the brain (McRae et al., 2004). In 2001, results of a double-blind, sham-surgery-controlled trial of the implantation of embryonic dopamine neurons in patients with severe PD were reported (Freed et al., 2001). The goals of the study included determining if the implanted neurons survived in patients and if the implanted neurons led to a reduction in symptoms and signs associated with PD. In addition, the study examined the effect of age on the efficacy of the transplantation of embryonic dopamine neurons. The primary aim of the study was to determine whether the transplant group improved more than the participants in the sham group during the double-blind sham-controlled trial (Freed et al., 2001).

The study found human embryonic dopamine neurons survived in patients with severe PD and that younger patients received some clinical benefits (Freed et al., 2001). Along with the neurological investigation of the fetal transplantation surgery trial, there was a concurrent examination of the quality of life among the participants in the double-blind, sham surgery-controlled trial.

Quality of Life Study

The quality of life (QoL) study was conducted by McRae et al. (2004) in order to determine whether QoL improved in participants in the transplant group compared to the sham group following the double-blind, sham surgery-controlled trial. The study was conducted during the first year of double-blind follow-up and the participants were assessed at baseline, 4, 8, and 12 months after surgery. The participants' quality of life (QoL) was assessed by examining three different domains: physical, emotional and social functioning. The physical functioning items assessed the patients' perspectives of ADL's, severity of symptoms, and how "free" or "restricted" participants felt "in doing what you want to do." The emotional functioning set of items assessed depressive symptoms, current and situational aspects of anxiety, stress, and degree to which the chronic illness interferes with usual life activities. The social functioning set of items assessed aspects of both perceived social support as well as the amount of social interaction or activity experienced by each participant.

The researchers found very few differences between the transplant and sham groups at any of the follow-up assessments. Likewise, there were few changes over time. However, there were a number of significant differences between groups as well as changes over time based on perceived treatment or type of treatment participants' thought they received (McRae et al., 2004). Results indicated that those who thought they received the transplant reported improvements and those who thought they received the sham surgery reported a worsening of symptoms and outcomes regardless of actual type surgery they received. As a result, the researchers found the placebo effect greatly impacted the results of the study.

Longitudinal Perspective

As a follow-up to the original QoL study, an investigation of the longitudinal effects of the transplant among those who participated in the unique double-blind surgery trial was conducted by Cole (2009). This study solicited information from the original participants approximately 10-12 years following the transplantation surgery. The individuals were located and agreed to participate. They completed some of the original QoL measures as well as the NEO-FFI, a personality inventory (Cole). There were several significant changes found from baseline to 10-12 years following the procedure regarding the physical functioning, emotional functioning and social functioning of QoL (Cole). In addition, significant changes since baseline were found on the Neuroticism, Extraversion, Openness to experiences, and Conscientiousness factors of the NEO-FFI (Cole). The study conducted by Cole examined the quantitative data to explore the impact of this surgical trial on participants over an extended period of time. However, there has never been an examination of the qualitative aspects of the participants' experiences in this study.

Mixed Methods

A mixed methods approach is the integration of multiple forms of data including both quantitative and qualitative data. More specifically, a mixed method design incorporates real-life understandings, multi-level perspectives and cultural influences along with a collection of quantitative data (Creswell, Klassen, Plano Clark & Smith, 2011). There are many strengths in exploring qualitative data, including the ability to examine different contexts, the meaning of human lives and previously unknown processes (Creswell et al., 2011). This study was designed to take a mixed methods

approach and to integrate the quantitative and qualitative data to use the strengths of both approaches in examining the longitudinal perspectives of participating in a double-blind, sham-controlled surgery trial. However, during the data analysis phase of the study, it became evident that the quantitative data could not be analyzed statistically due to the small sample size and as a result, a qualitative approach was used as opposed to a mixed methods approach.

Statement of the Problem

The research on fetal transplantation in patients with PD is limited. Furthermore, there is limited research pertaining to long-term effects of participating in a double-blind-sham-controlled study. While there has been one long-term follow-up investigation, there has been no qualitative data gathered on the impact of participating in the fetal transplant surgery trial. This study examined the longitudinal impact on QoL of participating in the fetal transplantation study conducted by Freed et al. (2001) from both a qualitative and quantitative perspective. To examine the impact of participating in the study and the course of the disease, the participants' QoL including Physical functioning, Emotional functioning, and Social functioning was assessed along with Optimism. This qualitative and quantitative investigation provided information that is possibly valuable to neurologists and scientists interested in developing effective treatments for PD. The quantitative data explored the current status of the participants approximately 13-15 years following the fetal transplantation. The qualitative data provided a glimpse into the personal experiences of the participants and provided a broader understanding of the impact of participating in this unique double-blind study and the effectiveness of the experimental procedure.

The participants in this study were the surviving participants of the study conducted by McRae et al. (2004). In the study conducted by Freed et al. (2001), there were a total of 40 participants admitted to the Irving Center for Clinical Research at Columbia University for a total of five assessments: two before surgery at baseline, and at 4, 8 and 12 months following the surgery. To examine the effectiveness of the fetal tissue transplantation surgery, 20 participants were assigned to the transplant surgery and 20 participants were assigned to receive the sham surgery. The participants assigned to the sham surgery were given the option to undergo the procedure following revealing of the double-blind. All of the patients and medical staff who were attending the patients were blind to the treatment-group assignments throughout the study. The study was conducted to examine the effectiveness of the fetal tissue transplantation surgery and, more specifically, to determine if the participants in the treatment group demonstrated greater improvements than the participants who received the sham surgery.

The QoL study by McRae et al. (2004) was conducted to assess the QoL in the participants. The researchers assessed the participants' QoL at baseline, 4, 8 and 12 months following surgery (McRae et al., 2004). A total of 30 out of the 40 participants in the study by Freed et al. (2001) agreed to participate in the study and in this group there were 12 participants who received the transplant and 18 participants who received the sham surgery (McRae et al., 2004). The purpose of the study was to determine if QoL improved more in the treatment group than in the sham surgery group (McRae et al., 2004). Furthermore, the researchers investigated whether participants who thought they received the transplant improved more than the participants who thought they received the sham surgery.

The present study used the quantitative data on QoL gathered in the original study at baseline, 12 and 24 months after the transplantation and follow-up data gathered in 2008. The present study involved collecting quantitative and qualitative data regarding QoL and optimism from the surviving patients who participated in the original QoL study by McRae et al. (2004). The study assessed longitudinal changes in QoL and optimism that have taken place over time from both a quantitative and qualitative perspective.

Research Questions

1. What is the trajectory of change in QoL for all the participants in the current study from the baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment? Because of the small sample size, no statistical analyses were performed. Instead, the averages for the participants on each measure were calculated and then plotted to examine the changes over time. In addition, individual scores on each of the measures were plotted over time. Thus, a mixed methods approach could not be used in the current study and as a result, a qualitative approach was used.
2. What are the individual experiences of the participants who participated in the double-blind sham controlled transplantation study and original QoL study?
3. Would the participants, who participated in original transplantation study, volunteer to participate in a future double-blind sham-controlled surgical trial?

Limitations of the Study

There were several limitations present in the current study. The first limitation was the small sample size in the current study. The participants include only a small portion of the participants from the original QoL study (n=30) since several participants from the original QoL study have died and others have perhaps moved to a different location or were not able to be found. As a result, their contact information was no longer valid.

The second limitation was that the data were not generalizable to all patients with PD. There were strict inclusion and exclusion criteria used in the original transplant study and, therefore, the current sample does not include patients with PD who may have other neurological disorders, chronic illnesses, or severe mental health issues. Additionally, the participants in the current study underwent an experimental surgery, 12-month double blind condition and sham-controlled procedure, and as a result, their experiences are unique compared to other patients with PD. The participants of the original transplant study (Freed et al., 2001) and original QoL study (McRae et al., 2004) volunteered to undergo a experimental surgical trial, which may set them apart from other patients with PD who may have declined to participate in a surgery trial. Their experiences are extremely valuable in understanding the impact the original transplant study has had on their lives and different aspects of QoL.

Summary

Chapter One presented an overview of PD, which included the physiology, onset, symptoms, drug and surgical treatments. A detailed discussion of QoL and mixed method research design was also presented. Chapter Two provides a detailed review of the current literature on PD, drug treatments, surgical procedures, QoL and mixed methods.

Chapter 2

Literature Review

Introduction

Chapter Two provides a broad overview of PD along with a discussion of pharmacological treatments, surgical interventions with an emphasis on fetal transplantation, long-term progression of PD, QoL and mixed methods research.

The literature reviewed in this chapter was retrieved using multiple databases. The database MEDLINE was used to provide information on history of PD, onset and prevalence of PD, symptoms of PD, drug treatments, and surgical interventions including the fetal transplantation surgery. A secondary search was conducted using multiple databases including PsycINFO, and PsycARTICLES. Topics in the second search were QoL, mixed methods research and treatment of PD.

Definition of PD

James Parkinson, who wrote the *Essay of the Shaking Palsy* in 1817, was the first person to formally discuss the signs of this unusual disorder. Jean Martin Charcot expanded the early description of PD by separating PD from multiple sclerosis and other disorders characterized by tremors (Goetz, 2011). Moreover, Charcot recognized the work of James Parkinson and termed the disorder “Parkinson’s disease” instead of paralysis agitans (Goetz, 2011). Today, PD is recognized as a progressive neurological disorder characterized by motor and non-motor symptoms. The motor symptoms

include tremor, rigidity, akinesia or bradykinesia, postural instability, fixed posture and freezing (Jankovic 2008). Non-motor symptoms include autonomic dysfunction (orthostatic hypotension, sweating dysfunction, sphincter dysfunction, erectile dysfunction), cognitive and neurobehavioral abnormalities (dementia, affective disorders, obsessive-compulsive and impulsive behavior), sleep disorders and sensory abnormalities (Jankovic, 2008).

The etiology of idiopathic PD is still unknown despite PD being the most common neurodegenerative disorder in elderly populations and representing a considerable personal and societal burden on individuals with PD and their families (Rod, Hansen, Schernhammer, & Ritz, 2011). Currently, there is no one technique or assessment that provides a primary diagnosis of PD. Diagnosis of PD is based on a detailed record of a patient's medical history along with a combination of physical and neurological assessments (Hughes, Daniel, Ben-Shlomo, & Lees, 2002).

Despite the numerous treatment options available to individuals with PD, 40 % of individuals with PD continue to have motor fluctuations and 28% experience Levodopa-induced dyskinesias (Shrag & Quinn, 2000). Currently, PD can not be cured; however, the symptoms of PD can be managed by medications for a number of years.

Symptoms

The three cardinal symptoms of PD are bradykinesia, muscular rigidity and tremor (Pellicano et al., 2007). Bradykinesia, or slowness of movement, primarily contributes to the disability associated with PD progression (Pellicano et al., 2007). Initially, bradykinesia will manifest itself as slow reaction time or planning, initiating, and executing movement (Berardelli, Rothwell, Thompson, & Hallett, 2001; Jankovic,

2008). Muscular rigidity is an increase in resistance among the joints in forming passive movements. Among individuals with PD, muscular rigidity only minimally contributes to disability. Tremor is the most commonly associated symptom with PD. Tremors are the uncontrollable shaking of an upper or lower extremity. Tremors, in persons with Parkinson's disease, can be a rhythmic, involuntary, or an oscillating movement of a body part. Tremors have been shown to worsen as persons with PD focus on the tremor or become increasingly anxious (Dakof & Mendelsohn, 1986). Rigidity is another symptom commonly associated with Parkinson's disease and the presentation of rigidity often manifests itself as muscle stiffness, cramping or soreness. In persons with PD, slowness of movement may also result as the motor program retrieval system becomes impaired, resulting in slowed movements (Marsden, 1989).

In addition to primary symptoms associated with PD, there are multiple secondary symptoms including constipation, decreased sexual libido, insomnia, hot flashes or chills, seborrhea, excessive sweating, conjunctivitis and impairment of visual spatial behaviors (Duvoisin, 1984; Mayeux, 1984). The severity of motor symptoms, including both primary and secondary symptoms, and nonmotor symptoms can fluctuate and vary in individuals. However, all three of the primary symptoms, which include tremors, rigidity and bradykinesia need to be present to make a formal diagnosis of PD (Duvoisin, 1984).

As a result of the debilitating effects of PD and the progressive nature of the illness, there are psychological symptoms associated with PD, which include depression, anxiety, numbness, restlessness, sleep difficulties, fatigue and hypotension (Fahn, 2003). The rates of psychiatric symptoms have been reported to occur in as many as 87% of PD

patients (Kulisevsky, Pagonbarraga, Pascual-Sedano, Garcia-Sanchez, & Gironell, 2008). Depression is the most common psychiatric illness in persons with PD and clinically significant depressive symptoms are present in approximately 35% of persons with PD (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). From the research on the effects of PD on patients, it is evident that PD impacts every aspect of a person's life.

Drug Treatment

Dopaminergic drugs are used in treating PD as they have been found to be effective in improving motor function, reducing morbidity and mortality of PD, and improving overall quality of life (Clarke, Zobkiw & Gullaksen, 1995; Rajput, 2001; Schapira, 2005). Levodopa is the most common drug in this classification and specifically improves bradykinesia and rigidity (Schapira, 2005). Although Levodopa may be effective for a number of years, its potency is modified due to disease progression and the loss of the dopaminergic cells needed to metabolize the drug. As a result, individuals may experience motor complications or a "wearing off" syndrome (Schapira, 2005). Thus, approximately 80% of patients with PD experience motor complications after 5-10 years of Levodopa use (Hammod, Bergman & Brown, 2007). Levodopa may be given in conjunction with a catechol-O-methyltransferase (COMT) inhibitor, which increases the absorption of Levodopa by reducing O-methylation in the gut (Schapira, 2005).

Surgical Treatment of PD

In the past 20 years, there has been an emergence of surgical interventions as a result of the negative effects of the long-term use of Levodopa. Surgical interventions

used in treating PD include ablative surgery, deep brain stimulation, gene therapy, and neural transplantation surgery.

Ablative Surgery

Ablative procedures, also known as lesioning procedures, target areas of the brain that produce tremors (Ahmed, Sheraz, & Ahmad, 2010). In ablative procedures, surgeons create small lesions using high frequency electric currents (Ahmed et al., 2010). There are three types of ablative surgery: thalamotomy, pallidotomy, and subthalamotomy. Thalamotomy is a surgical procedure where the ventral intermediate nucleus is targeted (Walter & Vitek, 2004). Previous research has found the lesions in the ventral intermediate nucleus improve tremors (Ahmed et al., 2010). Patients with asymmetric, severe and medically intractable tremor are recommended to have a thalamotomy (Ahmed et al., 2010). There are several adverse effects as a result of undergoing a thalamotomy, which include paresthesias, motor weakness, dysarthria, disequilibrium and gait disturbance. Bilateral thalamotomy may be conducted on patients with bilateral symptoms; however, there is an increased risk of speech and cognitive difficulties associated with bilateral thalamotomy procedures.

Pallidotomy is another type of ablative surgery where parts of the globus pallidus (GPi), are destroyed (Ahmed et al., 2010). The GPi region of the brain controls movements to restore balance (Ahmed et al., 2010). There have been two single-blind randomized trials completed to compare unilateral pallidotomy with drug treatments. In the first study with a sample of 37 patients, Unified Parkinson's Disease Rating Scale (UPDRS) "off" motor scores showed a 31% improvement from the baseline (Walter & Vitek, 2004; de Bie et al., 1999). A second study involving 36 patients with PD was

conducted and researchers found 32% improvement on the “off” motor UPDRS motor score, which was assessed at 6 months from the baseline (Walter & Vitek, 2004; Vitek et al., 2003). Overall, unilateral pallidotomy has been shown to improve drug induced dyskinesia, bradykinesia, rigidity and tremor (Ahmed et al., 2010). However, the benefits of unilateral pallidotomy vary in long-term follow-ups (Ahmed et al., 2010).

The third type of ablative surgery is subthalamotomy, which has received less attention than thalamotomy and pallidotomy. Subthalamotomy targets the subthalamic nucleus in the brain. While there have been improvements in patients with PD who have undergone a subthalamotomy procedure, surgeons fear performing the procedure due to the risk intractable hemiballism (Walter & Vitek, 2004). However, research has shown subthalamotomy can be completed without concerns of hemichorea. Studies on subthalamotomy showed 15-50% improvement in the “off” medicine UPDRS motor score at a two-year follow-up (Walter & Vitek, 2004). In addition, bilateral subthalamotomy has demonstrated fewer speech and cognitive side effects compared to bilateral pallidotomy or thalamotomy (Walter & Vitek, 2004).

Deep Brain Stimulation

Deep brain stimulation (DBS) is a widely popular therapeutic treatment for PD and has been subject to a significant amount of research. DBS is a surgical technique where continuous electrical stimulation is delivered through implanted electrodes connected to an internalized neurostimulator (Benabid, 2003). Multiple deep brain structures have emerged as potential therapeutic targets in treating PD (Collins, Lehmann, & Patil, 2009). Research in the 1990s and early 2000s suggested the ventral intermediate nucleus (VIM) of the thalamus was the target for DBS therapy in treating

the tremors associated with PD (Collins et al., 2009). However, targeting the VIM in DBS has been shown to have little impact on the other common symptoms associated with PD including rigidity and bradykinesia (Collins et al., 2009). As a result, DBS targeting the VIM is useful in a small percentage of patients where tremors are the predominant symptom. Another area targeted in DBS is the internal globus pallidus (GPi), which has been shown to be effective in treating tremors while also decreasing symptoms of dyskinesia, rigidity and bradykinesia and improving postural stability (Collins et al., 2009; Obeso et al., 2001). Additionally, stimulation of the subthalamic nucleus (STN) is effective for the treatment of rigidity, bradykinesia, and tremor. One study examining the effectiveness of STN stimulation for PD demonstrated improvements of 50% in UPDRS motor scores, with improvements having been observed for periods of 5 years (Krack et al., 2003). In addition, STN DBS allows patients with PD to have a 50% to 60% reduction in dopaminergic agent dosage, which may lead to an improvement in dyskinesias due to Levodopa (Hamani, Richter, Schwalb, & Lozano, 2005; Kleiner-Fisman, Herzog, Fisman, Tamma, Lyons et al., 2006).

A randomized controlled trial of DBS therapy for PD by Weaver et al. (2009) showed patients with PD receiving STN DBS or GPi DBS showed 4 or more hours of additional “on” time per day without the side effect of dyskinesia. Additionally, the “off” time and “on” time with dyskinesias was reduced compared to pre-operative baseline (Weaver et al., 2009).

Gene Therapy

Gene therapy is a promising new experimental treatment for persons with PD. Hopefully it will offer patients an alternative treatment to pharmacologic and surgical

interventions. Gene therapy in patients with PD uses viral vectors to carry out gene transfer (Rodnitzky, 2012). As a result, there is targeted protein expression in different areas of the brain (Rodnitzky, 2012). There are multiple types of gene therapy: AAV-GAD gene therapy in the subthalamic nucleus (SN), AAV2-Neurturin gene therapy (CERE-120), Aromatic L-amino acid decarboxylase (AADC) gene therapy, and prosavin (Rodnitzky, 2012). At this point, it is still continuing to undergo human clinical trials. While gene therapy has shown promise, it has not yet been shown to be superior to surgical or pharmacologic treatments for patients with PD.

Neural Transplantation

An additional experimental treatment for patients with PD is the stereotactic implantation of human embryonic dopamine neurons into the brain (Freed et al., 2001; McRae et al., 2004). Current neural transplantation procedures include stem cell transplantation surgery and fetal tissue transplantation surgery.

Neural Transplantation: Stem Cell Transplantation Surgery

The transplantation of stem cells into the brain has been a procedure used in treating neurodegenerative diseases including PD. The ability for stem cells to differentiate into multiple cell types or all cells of the body makes them beneficial for transplantation (Lindvall, Kokaia, & Martinez-Serrano, 2004). The transplantation of stem cells into the brain has been shown to be possible in several clinical studies (Politis & Lindvall, 2012). Given that PD is the degeneration of nigrostriatal dopaminergic neurons, the transplantation of human fetal mesencephalic tissue, which is rich in postmitotic dopaminergic neurons, has been shown to be effective in neuronal replacement in the brain (Lindvall et al., 2004). The grafted neurons survive and

reinnervate the striatum for approximately 10 years (Kordower et al., 1995; Piccini et al., 1999). Additionally, the grafted neurons have been shown to normalize striatal dopamine release and reverse the progression of the cortical activation underlying akinesia (Lindvall et al., 2004; Piccini et al. 2000; Piccini et al., 1999). As a result, the grafted dopaminergic neurons can be incorporated into the neuronal circuitries in the brain (Lindvall et al., 2004; Piccini et al., 2000).

The results of the stem cell transplantation surgery, however, are mixed (Politis & Lindvall, 2012). One reason for modest effects is the limited amount of surviving grafted dopaminergic neurons (Lindvall et al., 2004). Research also has yet to show that the stem cells can “provide efficient functional reinnervation and behavioral recovery in animal PD models” (Lindvall & Kokaia, 2009). In addition, dyskinesias have been shown to develop following the transplantation, which are believed to result from uneven or patchy reinnervation (Lindvall et al., 2004). More research needs to be conducted on the efficacy of stem cell transplantation in patients with PD. Future research studies will need to “require better criteria for patient selection, improved functional efficacy for grafts by a tailor-made transplantation procedure providing optimum repair of the patient’s DA system and strategies to prevent dyskinesias and tumor formation” (Lindvall & Kokaia, 2009).

Neural Transplantation: Fetal Tissue Transplantation Surgery

Fetal transplantation surgery has been investigated over the last several decades. Fetal transplantation surgery began in 1980’s and 1990’s when human fetal mesencephalic tissue was transplanted in the striatum in patients with PD (Lindvall & Bjorklund, 2004). The initial procedures performed in 1987 demonstrated that cell

replacement works in the human brains of patients with PD (Bjorklund et al., 2003; Lindvall & Bjorklund, 2004). Moreover, the early trials demonstrated human fetal dopaminergic neurons can survive and function in the striatum of patients with PD for more than 10 years (Bjorklund et al., 2003). Following the initial trials of fetal transplantation in humans, the National Institutes of Health (NIH) supported additional efforts to investigate fetal transplantation in patients with PD (Bjorklund et al., 2003). As a result, two double-blind sham-surgery controlled trials were investigated in the 1990's (Bjorklund et al., 2003).

Freed et al. (2001) completed a double-blind, sham surgery controlled trial to examine if the transplant group improved compared to the sham group. The investigators also explored whether the implanted cells survived in the patients who underwent the transplantation surgery and the efficacy of the transplantation on physical symptoms associated with PD (Freed et al., 2001). Additionally, the investigators determined if age was a factor in the efficacy of the transplantation procedure (Freed et al., 2001).

The investigators randomly assigned 40 patients with severe PD to undergo the transplantation of neural cells or a sham surgery; 20 participants received the transplant and 20 participants received the sham surgery (Freed et al., 2001). The participants ranged in age from 34 to 75-years of age and all of the participants were found to have had at least two of the three cardinal symptoms for more than seven years (Freed et al., 2001). The patients were awake during the procedure and given local anesthesia (Freed et al., 2001). The transplantation procedures included a stereotactic ring being affixed to the skull before imaging was conducted to define placement for passes in the axial plane

of the putamen with two needle tracks on each side of the brain. During surgery, four burr holes were made in the patients' forehead and cultured mesencephalic tissue from four embryos was transplanted into the putamen bilaterally (Freed et al., 2001). In the sham surgery, the patients underwent an identical procedure, including drilling holes in the forehead. However, the dura matter was not penetrated and the cultured fetal tissue was not placed in the brain (Freed et al., 2001). All of the fetal transplantation procedures were performed at the University of Colorado Hospital (Freed et al., 2001). Results showed human embryonic dopamine-neuron transplants survived in all patients and there were some clinical benefits in younger participants (Freed et al., 2001). More detailed information regarding the parent study and the fetal transplantation surgery can be found in the report by Freed et al. (2001). The present study will be a longitudinal follow-up of individuals who participated in the study conducted by Freed et al (2001).

An additional double-blind sham-surgery trial was undertaken by Olanow et al. (2003). The study was a 24-month double-blind, placebo controlled trial of fetal nigral transplantation in 34 patients with advanced Parkinson's disease (Olanow et al., 2003). The participating patients with PD received bilateral transplantation with one or four donors per side or a placebo procedure (Olanow et al., 2003). Following the completion of the study, patients showed no significant overall treatment effect. However, patients with milder symptoms of PD at the baseline showed significant improvements (Olanow et al., 2003).

These trials exhibited variable results. Despite several open label trials that showed improvements in striatal uptake of fluorine-18-labelled dopa and UPDRS motor scores, the results have been mixed amongst patients with PD (Bjorklund et al., 2003).

One reason for the varied results in patients with PD is the differences in the survival and growth of the grafted dopaminergic neurons in patients. In addition, the placebo effect may play a stronger role in the results than originally thought.

Original QoL Study

A total of 30 participants out of the 40 from the fetal transplantation study agreed to participate in the QoL study conducted by McRae et al. (2004). The QoL study examined the QoL and medical outcomes of the 30 patients (12 patients who received the transplant and 18 patients who received the sham surgery) at four, eight and twelve months before the double-blind was lifted. The researchers found only one statistically significant difference between the two treatment groups at baseline, 4, 8, and 12 months. However, based on perceived treatment or the type of surgery patients' thought they received, researchers found multiple differences in QoL outcomes. For instance, at the 12-month follow-up, participants who thought they received the transplant reported more positive results regarding physical functioning compared to the participants who thought they received the sham surgery, regardless of the actual type of surgery they received (McRae et al., 2004). The results of this study illustrate the impact of the placebo effect on the fetal transplantation surgery trial.

Longitudinal Follow-up at 10-12 Years After Original Study

Cole investigated the long-term effects of the fetal transplantation surgery on QoL factors on the participants from the parent study (Cole, 2009). A total of 11 participants agreed to participate in the longitudinal follow-up study (Cole, 2009). The patients' physical, emotional and social functioning were assessed and compared to the baseline, one-year and two-year data after transplantation obtained in the original QoL

study conducted by McRae et al. (2004). All participants in the longitudinal follow-up study had received the transplant, either originally or after the blind was revealed and they were allowed to receive the transplant after first being given the sham surgery.

The results from the study showed participants reported improvements in physical functioning between baseline and the two-year follow-up (Cole, 2009). More specifically, the majority of the participants experienced improvements in physical functioning from baseline to the one-year assessment. Following the two-year follow-up, however, participants reported a decline in physical functioning (Cole, 2009). Regarding emotional functioning in the participants, the results showed improvements in emotional functioning between the baseline and two-year follow-up (Cole, 2009). During the two-year assessment and 10-12-year follow-up, however, there was a decline in emotional functioning, which was consistent with physical functioning (Cole, 2009). Social support decreased between baseline and one-year assessment but showed improvements at the two-year assessment (Cole, 2009). Additionally, social support decreased significantly between the two-year assessment and the 10-12-year follow-up (Cole, 2009).

Quality of Life

The exploration of QoL in patients with PD has been researched in recent decades to determine effective treatments in reducing both the motor and non-motor symptoms associated with PD. QoL gives researchers insight into the individual experiences of the patients with PD and the impact of specific treatments on the patients' everyday functioning. In addition, the medical field and medical professionals have begun to look beyond treating only the physical symptoms associated with PD and as a

result, they are beginning to take a multi-dimensional approach to treating patients. In other words, medical professionals are now recognizing the significant impact of non-motor symptoms such as cognitive impairments, sleep problems, dementia and depression on patients with PD. In developing treatments directed at treating both the motor and non-motor symptoms of PD, one of the goals is to improve quality of life.

There are several definitions that exist regarding QoL. Felce and Perry (1995) described QoL as an integration of objective and subjective factors that incorporates a wide range of life domains and individual values (Felce & Perry, 1995). Quality of life (QoL), according to the study conducted by McRae et al., includes three dimensions: Physical, Emotional and Social functioning (2004). WHO defined QoL as ‘an individual’s perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectation, standards and concerns (Ferrara et al., 2010; WHOQOL Group, 1995, p. 1405). Researchers have also used the concepts of health related quality of life (HRQoL) and health status (HS) to examine the benefits of treatments. These concepts have been developed to encompass the impact of a health condition on overall functioning. However, there are no current universal definitions for HRQoL and HS (Ferrara et al., 2010). HS measures focus on the presence of symptoms and their impact on an individual’s ability to perform various daily activities such as leisure activities and housework (Ferrara et al., 2010). In contrast, HRQoL measures explore a patient’s subjective experiences of symptoms and satisfaction with their health condition (Ferrara et al., 2010).

Quality of Life: Importance of the Patient's View in clinical trials

As mentioned previously, the majority of the past research conducted regarding treatments of PD has focused on the medical perspective and the treatment of the physical symptoms of the disease. In recent years, however, research has begun to explore the perspectives of the patients' with PD to gain an understanding of the impact of the disease on the lives of the patients.

One study conducted by Politis et al. (2010), examined the patients' perspectives regarding the symptoms associated with PD. The researchers had the patients rank their three most troublesome symptoms in the last six months (Politis et al., 2010). The results from the study demonstrated diversity in the experiences and perspectives of patients with PD. The study found the lack of response of medication and non-motor symptoms were the most troublesome issues (Politis et al., 2010). The study demonstrated the importance of examining the perspective of the patient with PD to treat both the motor and non-motor symptoms associated with PD (Politis et al., 2010). Moreover, the study conducted by Politis et al. emphasizes the importance of exploring patient's experiences and perspectives to aid in developing patient-centered care and management (Politis et al., 2010).

One method of assessing patients' perspectives is to use QoL as a measure. QoL explores the physical functioning, psychological/emotional functioning, social interaction with others/social support in patients with PD. The assessment of QoL explores a patient's personal experiences and beliefs regarding the progression of the disease and the impact on different domains of daily life. The exploration of QoL in patients with PD allows medical providers to gain a holistic view of how the patients are

functioning and coping with the disease. In taking a more holistic view of patients' functioning, more effective treatments can be developed and designed to address both the motor and non-motor symptoms associated with PD.

One study examined factors that determine QoL in patients with idiopathic PD. Schrag, Jahanshahi and Quinn (2000) examined the impact of PD on QoL in 124 patients with PD using a QoL battery including EuroQoL 5D, the Medical Outcome Study Short Form (SF 36) and the 39-item Parkinson's Disease questionnaire (PDQ-39). In addition, an interview and complete neurologic examination were completed. QoL declined significantly with the progression of the disease and increase in disease severity (Schrag et al., 2000). Physical and social functioning demonstrated the greatest decline (Schrag et al., 2000). Emotional functioning showed results similar to the general population (Schrag et al., 2000).

Given the progression of PD and the chronic nature of the disease, it is essential to explore the patient's perspectives and QoL over a longer period of time to determine the effectiveness of treatments. One study by Karlsen, Tandberg, Arslan & Larsen (2000) examined change in QoL in patients with PD across a four-year follow-up from a community-based 1993 prevalence sample (Karlsen et al., 2000). The results of the study found increased distress during the four-year follow-up period, and increased stress correlated with increased parkinsonism as measured by UPDRS and Hoehn and Yahr stage. Furthermore, pain, social isolation, and emotional reactions in addition to physical mobility were correlated with increased stress (Karlsen et al., 2000). The study demonstrated the importance of examining the long-term effects of the disease on the

QoL of patients and how these findings may assist in targeting and treating distressing symptoms associated with PD that develop over time.

Assessing QoL in the patients in the parent study illuminates the long-term effects of participating in a surgery trial on physical, emotional and social functioning in patients with PD (Cole, 2009). More specifically, continued assessment of QoL in the patients in the parent study could illustrate the long-term impact of neural transplantation on the patients' physical health, severity of symptoms, description of feelings, affective functioning, stress level, social support and interaction with others.

Important Patient Data on Quality of Life

The investigation regarding how QoL has improved, worsened or stayed the same in individuals who underwent the neural transplantation surgery is important. The present study examined the changes in QoL over time from baseline to the current assessment, including one and two years after the transplant surgery, 10-12 years after the transplant surgery in 2008 and the current assessment. The purpose of this study was to examine the long-term effectiveness of fetal transplantation surgery on QoL or patients' physical, emotional and social functioning.

Mixed Methods Approach

To examine the perspectives of the patients who participated in the parent study, a mixed methods approach was used. This topic warrants a qualitative perspective given the importance of understanding the patient's perspectives and personal experiences. Moreover, qualitative research should be conducted when a complex and detailed understanding is warranted (Creswell, 2007). In this study, QoL was assessed in the 13-

15 year follow-up using both quantitative information as well as interviews with the participants.

The concept of mixing different research methods was originated in 1959 by Campbell and Fiske who used mixed methods to study the validity of psychological traits (Creswell, 2007). Following their research study, researchers began combining traditional quantitative surveys with observations and interviews (Creswell, 2007). Researchers also argued that there were inherent biases in using a single method (Creswell, 2007). As a result, the term triangulation was created to describe the convergence of qualitative and quantitative methods (Creswell, 2007). Following the initial exploration of using mixed methods, writers began developing specific procedures for conducting a mixed methods approach to research including multimethod, convergence, integrated and combined approaches (Creswell, 1994; 2007).

Today, there are multiple types of mixed method approaches used in research. However, given the quantitative data could not be analyzed statistically, a qualitative approach was used as opposed to a mixed methods approach. The means scores on the measures for the participants will be connected with the data gathered from the interviews when possible.

Summary

Chapter Two provided a literature review on detailed information on PD, pharmacological treatments, surgical treatments, fetal tissue transplantation surgery, QoL, long-term follow-up, importance of patient views in clinical trials and mixed methods approach.

PD impacts every aspect of a patient's life. There is a significant amount of research regarding PD and treatments for PD; however, there is a limited amount of research on the QoL of patients with PD from both a longitudinal and mixed methods approach. In addition, there is limited information on the QoL of patients who underwent a fetal transplantation surgery trial.

The present study examined QoL in participants who received the fetal tissue transplantation surgery in the parent study approximately 13-15 years ago. The study also examined how the physical, emotional and social functioning changed in the patients over time and from both a quantitative and qualitative perspective. Chapter Three outlines the methods and procedures used in this study.

Chapter Three

Methods

Chapter Three describes the methodology used in the present study, including information on the participants, measures, and data analyses.

Participants in Parent Parkinson's Disease Study

In the parent study, participants were recruited through neurologists from the United States and Canada. A total of 40 patients were accepted into the study. Each participant was evaluated two times for approximately three to four days before being accepted into the study. A total of 20 participants received the transplant and 20 participants received the sham surgery.

Participants in Original Quality of Life Study

A total of 30 participants from the parent study agreed to participate in the concurrent QoL study. Of the 30 participants, 12 originally received the transplant and 18 received the sham surgery (McRae et al., 2004).

Participants in the Longitudinal Follow-up at 10-12 Years After Original Study

A total of 14 participants from the original QoL study were able to be contacted and 11 patients agreed to participate in the longitudinal follow-up study at 10-12 years following the original surgery. In the current investigation, patients who participated in the longitudinal follow-up at 10-12 years were contacted and asked to participate in the present study.

Participants in the current study

In the parent study, there were a total of 40 patients in the parent study and 30 of the participants agreed to participate in the original QoL study. Of the 30 participants from the original study, updated contact information was identified for 7 people. For the remaining participants, either contact information was unable to be found, or some participants had passed away. Of the 7 participants, 5 of them agreed to participate in the current investigation. For the demographic variables of age, gender, ethnicity, duration of disease, and level of education, data were collected from the baseline assessment. For the demographic variables of current living situation, marital status, currently paid for employment, and volunteer work, data were collected from the current assessment.

Inclusion and Exclusion Criteria

Several inclusion criteria had to be met in order to participate in the parent study. The participants were required to be in an advanced stage of idiopathic PD for seven years or longer and needed to demonstrate some responsiveness to L-dopa. All the participants had experienced a reduction in the effectiveness of the L-dopa treatment in addressing their symptoms. Patients have all tried alternative forms of treatment and needed to be medically appropriate for the transplant surgery, including a certification by their attending physician. Patients needed to demonstrate symptoms that were chronic in nature. In other words, the patients needed to show symptoms, including “off” periods and dyskinesias or freezing, which could not be attributed to dopamine agonists. The participants funded expenses not covered by the initial NIH grant for the parent studies. Furthermore, participants could not be diagnosed with depression or report experiencing

hallucinations. In terms of neurocognitive functioning, the patients were required to have a normal MRI scans within the last 18 months of the start of the parent study and undergo a thorough neuropsychological examination (Freed et al., 2001). The participants underwent a fluorodopa PET, which indicated idiopathic PD (Freed et al., 2001). The 40 participants all ranged in age from 34 to 75.

The exclusion criteria for the parent study included: severe or moderately severe depression, gross signs of dementia, previous brain surgery or injury, diabetes, severe cardiopulmonary disease, other severe medical conditions, and MRI evidence of cerebrovascular disease (Freed et al., 2001). In addition, patients who did not receive a medical clearance from their attending physician were unable to participant in the study (Freed et al., 2001).

Procedure

All of the participants in the original QoL study and longitudinal follow-up 10-12 years following the transplant were contacted in order to request their participation in the current study. The contact information, including phone number and current address, was updated via the Internet. Participants were contacted by the researcher via the telephone to discuss the current study and to assess their willingness to participate in the current study. Participants were requested to complete questionnaires delivered in the mail and complete one phone interview. The questionnaires obtained updated information on PD, QoL and Optimism. The phone interview questions were developed to assess the patients' qualitative perspectives on PD, QoL and participating in the original study.

Questionnaires

The questionnaires used in this study were a reduced version of the same questionnaires sent in the original study by McRae et al. (2004). They were sent to the participants in the mail and included instruments to assess QoL while living with PD. Of note, the State-Trait Anxiety Inventory (STAI-State) was not included in the current questionnaire. As a result, the composite variable of Emotional functioning could not be created and the three measures of depression, intrusiveness of illness and stress were analyzed independently. The three measures of Physical Functioning were also analyzed independently. Interview questionnaires were developed to assess the participants' perspectives on participating in a double-blind, sham controlled surgery trial and to assess the impact of the transplant on their lives over time. The questions were developed to assess the participants' individual experiences and perspectives and were administered in one phone conversation. The interview consisted of six questions, which did not overwhelm the participants and allowed adequate time to discuss each question thoroughly. Participants were encouraged to expand upon their answers if they chose to do so.

Measures

The measures can be found in the Appendices B through J. The quantitative measures described below were sent to the participants in the mail to be completed and returned to the investigator. The qualitative interviews were conducted over the phone by this investigator after an introduction by her advisor, Dr. Cynthia McRae, who has known the participants for over 15 years.

Physical Functioning

The participants' level of physical functioning was assessed using the patient version of the *Unified Parkinson's Disease Rating Scale (UPDRS)* developed by Montgomery, Lieberman, Singh, and Fries (1994). The original UPDRS was developed for use by medical personnel to assess the physical capabilities of persons with PD. The patient version of the UPDRS was designed to allow patients to subjectively rate their level of physical functioning and difficulties related to PD (Montgomery, Lieberman, Singh, & Fries, 1994). The patient version used in this study is comprised of two scales, which include Activities of Daily Living (ADLs) at "Worst" (when patients are functioning physically at their "worst") and Severity of Symptoms at "Worst." The Activities of Daily Living subscale is comprised of eight items, which is scored on a Likert scale ranging from 1) Normal, 2) Adequate, 3) Limited, 4) Need Help, to 5) Unable to do. The total score ranges from 8 to 40 points where higher scores are indicative of a lower level of physical functioning and lower scores are indicative of better functioning. The activities assessed on the scale include writing, talking, walking, dressing, hygiene, getting up from a chair, turning in bed, and cutting food.

The Severity of Symptoms Scale is comprised of five items and patients rated each problem at "Worst" functioning. The rating for each item ranges from 1) Normal, 2) Mild, 3) Moderate, 4) Severe, to 5) Very Severe. The total score can range from 5 to 25 with higher scores indicating poor physical functioning and lower scores indicating better physical functioning. The symptoms listed on the scale include: tremor, swallowing, salivation, "freezing" when walking, and falling.

Internal consistency reliability of the subscales of the patient version of the UPDRS ranged from .65 to .90 (McRae et al., 2004). The original UPDRS has demonstrated adequate construct validity across several widely used measures of physical functioning in PD (Ramaker, Marinus, Stiggelbout, & van Hilten, 2002).

An additional scale, the Free or Restricted Scale, was used to assess physical functioning of QoL. The Free or Restricted Scale is a single, global measure that examines how free or restricted the person feels “in doing what you want to.” The item is rated using a Likert-type scale ranging from 1 (I still do everything I want to do) to 7 (I can no longer do the things I want to do). Higher scores indicate lower physical functioning and lower scores indicate better physical functioning.

Emotional Functioning

Several assessments were used to determine the emotional functioning of the participants. The Parkinson’s Disease (PD) Stress Scale was the measure used to assess stress in the participants. The Parkinson’s Disease Stress Scale has a total of 19 items and patients are asked to indicate “yes” or “no” on each item. A sample question is “I am sometimes embarrassed in public because of my symptoms.” The estimated reliability (Cronbach’s alpha) for the scale was .77 (McRae et al., 2004).

The participants in the study were assessed for depressive affect using the Center for Epidemiologic Studies Depression Scale (CESD; Radloff, 1977). The scale has a total of 20- items used to assess the number and frequency of self- reported symptoms of depression. Each item is rated using a 4-point scale, which ranges from 0 to 3 where 0 indicates “less than 1 day” and 3 indicates “5 to 7 days” (Radloff, 1977). Lower scores indicate fewer depressive symptoms and higher scores indicate more depressive

symptoms (Radloff, 1977). A sample item is “I had trouble keeping my mind on what I was doing.” On the CESD, a total score can range from 0 to 60. Scores on the CESD have been shown to have an internal consistency of .89 and test-retest reliability has been found to be satisfactory (Radloff, 1977). Radloff reported the CESD scores have very good concurrent validity according to clinical and self-report criteria and substantial evidence of construct validity. Craig, Richardson, Pass, and Bregman (1985) reported a convergent validity correlation of 0.65, which the researchers compared to Hamilton Rating Scale for Depression. The CESD assesses depressive symptoms and is not used as a tool to diagnose depression.

To assess the degree to which Parkinson’s disease interferes with daily living, the participants completed the Intrusiveness of Illness Scale. The Intrusiveness of Illness Scale is important in this study since illness intrusiveness is a common underlying determinant of quality of life in patients suffering from a chronic illness (Devins, 2010). The Intrusiveness of Illness Scale is a 15-item self-report questionnaire, which measures the impact of an illness on daily living (Devins et al., 1984). The self-report responses presented on a Likert-type scale range from 1 (very little) to 7 (a great deal). A total score on the assessment can range from 15 to 105 (Devins et al., 1984). Total scores in the high range indicate more intrusiveness and total scores in the low range indicate less intrusiveness. One example of an individual item is “my illness interferes with my ability to work.”

The internal consistency reliability has been evaluated for the Intrusiveness of Illness Scale and research has shown internal consistency reliability ranging from .80 to .88 (Devins et al., 1984; McRae et al., 2004). Furthermore, test-retest reliability has

been shown to be high when participants who experience changes in their illness or treatment have been excluded (Devins et al., 1984; McRae et al., 2004). The assessment has been shown to have adequate construct validity amongst groups of participants with a variety of chronic illnesses.

Social Functioning

The Social Provisions Scale (Cutrona & Russell, 1987) assesses social functioning and perceived degree to which participants' social relationships might provide multiple dimensions of social support. The Social Provisions Scale is a 24-item scale and contains a total of 4 items for each of the following subscales: guidance, reliable alliance, attachment, social integration, reassurance of worth, and opportunity to provide nurturance (Cutrona & Russell, 1987). The individual items use a Likert-type scale ranging from 1 (strongly disagree) to 4 (strongly agree) with higher scores indicating more perceived social support. The total score can range from 24 to 96. An example item from the Social Provisions Scale is "I have relationships where my competence and skills are recognized."

Cutrona, Russell and Rose (1984) evaluated internal consistency and test-retest reliability of the Social Provisions Scale and found internal consistency to be above .70 across all provisions amongst a sample of 100 elderly subjects. Furthermore, Cutrona et al. found reliability to be .91 for the total score on the Social Provisions Scale.

Optimism

To assess Optimism in the participants, the Life Orientation Test (LOT) scale was administered. The LOT (Scheier & Carver, 1985) assesses dispositional optimism, which is defined as "a continuum in which pessimism and optimism are polar opposites"

(Scheier & Carver, 1985). Optimism is the tendency to view the world and situations in a positive manner. Several research studies have found that optimism is related to “adequate adjustment to difficult life circumstances in a large number of behavioral contexts (Carver, Scheier, Miller & Fulford, 2009; Chiesi, Galli, Primi, Borgi & Bonacchi, 2013). The LOT is an eight-item measure plus four filler items that is “designed to assess generalized expectations for positive versus negative outcomes (Vassar & Bradley, 2010). The LOT is measured on a 5-point scale ranging from 0 (strongly disagree) to 4 (strongly agree); (Vassar & Bradley, 2010). In order to get a total score, negative items are reverse coded and then added to the total score that ranges from 0 to 32. Higher scores are indicative of greater optimism. According to Scheier and Carver (1985), the LOT has a coefficient alpha estimate of .82 (Vassar & Bradley, 2010). In addition, the LOT was found to have a test-retest correlation of .79 and adequate convergent and discriminate validity (Scheier & Carver, 1985).

Data Analyses

The data analyses in the current study were completed in two stages: preliminary analyses and the primary analyses, which included the quantitative and qualitative data. The preliminary analyses included an investigation of the demographic information and descriptive statistics.

For the primary analysis of the quantitative data, it was anticipated that a repeated measures ANOVA would be used. Unfortunately, all five of the participants in the current study did not complete assessments at all the different time points. Therefore, it was not possible to do the intended primary analysis. For instance, one participant did not participate in 2008 assessment and there was one participant who did

not complete the quantitative questionnaire in the current assessment. In addition, by 24 months after the surgery for those who initially had the sham surgery, data collection had essentially stopped and two participants did not complete the questionnaire. In the current study, averages were calculated and plotted over the last 13-15 years to explore the changes over time. In addition, each participant's score for each measure for all the time points were plotted to examine the changes over time for each participant.

For the primary analysis of the qualitative data, there were 6 questions in the interview, which are presented below.

Qualitative Questions

1. How do you feel when you reflect back on your experiences in participating in the fetal tissue surgery trial?
2. Have your feelings regarding your participation in the surgery trial changed over time?
3. Knowing what you know now, would you volunteer to participate in this study again?
Why or why not?
4. What was the most positive aspect of participating in the study?
5. What was the most negative aspect of participating in the study?
6. What advice would you give to future participants in terms of coping with participating in a double blind placebo surgery trial?

The qualitative interview questions were designed to gain insight into the specific experiences of the participants during their participation in a unique surgery trial. It was important to further explore their personal experiences to better understand why some participants appeared to be doing better than what would be expected given the progression of their PD and in contrast to other participants who had not done as well. In addition, it was helpful to understand what went well in the transplant surgery trial and what did not go well for these participants in order to provide detailed information to future researchers conducting a double-blind, sham controlled surgery trial with patients with PD. The information gathered in the qualitative interview was developed into a narrative for each participant to outline their responses to each question and provide a detailed presentation of their overall experience in the transplant surgery trial over the last 13-15 years.

In a mixed methods approach, there is an attempt to connect several forms of data. However, given the quantitative data could not be statistically analyzed given the small sample size, a qualitative approach was used as opposed to a mixed methods approach. As a result, the plotted changes over time in this study will be integrated with the qualitative data, which explored individual perspectives of the participants. The qualitative data was collected in order to provide a richer, fuller picture of the phenomenon than either approach could provide alone. The plotted results of the quantitative data were followed by qualitative information (i.e., narratives of participants) that added depth and meaning to the quantitative results. In addition, the research questions related to the qualitative information were answered by analyzing the

responses on the qualitative interview and providing these results in both the Results and Discussion section.

Summary

Chapter Three outlined the methodology used in the current study. More specifically, a description of the participants, procedures, QoL measures, and data analyses were provided. Chapter Four presents the preliminary and primary results of the current study.

Chapter Four

Results of the Study

Overview

This chapter presents the results of both the quantitative and qualitative data aspects of the current study. First, the preliminary analyses are reviewed and then the results of the primary analyses are reviewed in the context of the research questions. All the preliminary statistical analyses were performed using the Statistical Package for the Social Sciences version 20.0 (SPSS 20.0).

Participants of the current study originally represented two treatment groups; those who initially received the fetal tissue transplant (n=2) and those who initially received the sham surgery (n=3) and then later received the fetal tissue transplant in the parent study (Freed et al., 2001). The primary analyses in the current study examined several domains of QoL and Optimism of participants at baseline, 12, and 24 months after the fetal tissue transplant, along with data from the 10-12 year follow-up assessment in 2008 and current assessment. Because of the one-year period of the double-blind, participants who received the sham surgery initially did not receive the fetal tissue surgery until more than a year after the baseline assessment. Thus, it was decided to use the 12-months assessment as the new baseline for those who first received the sham surgery and then the transplant. Likewise, scores for the 12 and 24-month assessment used in this study were those following the actual fetal transplant.

Preliminary Analyses

This section of the chapter is organized in the following manner: a) participant response to questionnaires and interview; b) missing data; c) participants' demographic information; d) descriptive statistics related to the variables included in the study; e) comparison of current participants to the rest of the cohort from the parent study; f) reliability of variables.

Participant Response to Questionnaires and Qualitative Interview

Participants in the 2008 follow-up study were contacted via phone to assess their willingness to participate in the current study, which consisted of an interview and questionnaire. There were a total of five interviews completed; however, only four completed questionnaires were returned.

The questionnaires measured several domains of QoL and Optimism that had been assessed at previous time periods. Aspects of Physical functioning, Emotional functioning, and Social functioning as well as Optimism were included in the questionnaire.

The Physical functioning dimension of QoL was assessed using the patient version of the Unified Parkinson's Disease Rating Scale (UPDRS), including the Activity of Daily Living, Severity of Symptoms, and the Free or Restricted scales. It was intended that Physical Functioning would be analyzed as a composite variable, which is consistent with previous analyses. However, the scales for Physical Functioning were analyzed independently. The Emotional functioning dimension of QoL was assessed by using the Center for Epidemiological Studies- Depression Scale (CESD), the Intrusiveness of Illness Scale, and the Parkinson's Disease Stress Scale.

The State-Trait Anxiety (STAI-State) was not included in the current questionnaire. As a result, the scales for Emotional Functioning (Center for Epidemiological Studies-Depression Scale (CESD), the Intrusiveness of Illness Scale, and the Parkinson's Disease Stress Scale) were analyzed independently. Social functioning (Social Provisions Scale) and Optimism (Life Orientation Test Scale) were also analyzed independently. The four questionnaires that were received in the current study were then examined in contrast to data collected previously at different time periods, including baseline (prior to surgery), 12 and 24-months after the transplant surgery and the 10-12 year follow-up assessment conducted in 2008.

Missing Data

There were very little missing data in the questionnaires; however, there was one questionnaire that was missing the Parkinson's Disease Stress Scale. Most likely, the participant simply skipped the page accidentally. With the exception of the one questionnaire missing the Parkinson's Disease Stress Scale, there were no other missing data on the questionnaires.

Demographic Information

In the current questionnaire, there were several demographic questions (Appendix J) that were used to collect information on the participants' present status. Information from the baseline questionnaire was also examined. The data is presented in Table 1. While the majority of the participants do not currently work (four out of five), three of the participants who completed the questionnaire are volunteering despite being diagnosed with PD approximately 25-35 years ago (Table 1). Overall, the study was

based on participants with PD who received fetal tissue transplantation surgery approximately 13-15 years ago.

Table 1

Demographic Information of Participants in the Current Investigation

Demographic Variables	Demographic Information
Gender:	
Male	0
Female	5
Age (from baseline assessment)	
Mean years	46.00 ± 6.98
Range	40-56
Duration of disease	
Mean years	28.20 ± 4.49
Range	25-35
Ethnicity - number	
Native American	0
African American	0
Caucasian	5
Hispanic	0
Asian	0
Other	0
Duration of education completed (from baseline assessment)	
Mean years	16.8 ± 2.75
Range	13 - 19
Current living situation - number (from current assessment)	
Living with family	3
Living with friend or roommate	0
Living alone	1
Living in residential setting	1
Marital Status - number (from current assessment)	
Never been married	0
Married or living with partner	3
Separated or divorced	0
Widowed	2
Currently paid for employment (from current assessment)	
No	4
Part-time	1
Full-time	0
Volunteer work (from current assessment)	
No	2
Yes	3
I used to, but no longer do	0

Descriptive Statistics

In the current study, the descriptive analyses of the QoL measures were performed (see Table 2). The descriptive analyses consist of the number of respondents at each time period along with the means and standard deviations of each measure. For each QoL dimension in the current study, there are five time periods representing baseline (adjusted to reflect the assessment period immediately prior to surgery), 12 months after the transplant surgery, 24-months after the transplant, 10-12 year follow-up conducted in 2008 and the current assessment.

Table 2

Descriptive Statistics of QoL Variables for Baseline, 12-Months, 24-Months, 10-12 year follow-up assessment in 2008 and Current Assessment

QoL Variable (includes time of assessment)	N	Mean	S.D.
Physical Functioning			
Activities of Daily Living at Worst Scale			
Baseline	5	32.00	3.67
12 Months	5	26.20	9.20
24 Months	3	16.30	2.08
2008	4	25.25	6.29
Current	4	30.50	5.26
Severity of Symptoms at Worst Scale			
Baseline	5	14.60	2.51
12 Months	5	13.00	4.36
24 Months	3	9.70	2.31
2008	4	13.00	2.00
Current	4	17.50	0.58
Free or Restricted Scale			
Baseline	5	4.40	1.34
12 Months	5	3.20	1.64
24 Months	4	2.00	0.82
2008	4	2.63	0.48
Current	4	4.25	1.71
Emotional Functioning			
Center for Epidemiological Studies – Depression Scale			
Baseline	5	7.40	4.98
12 Months	5	8.00	6.21
24 Months	4	6.25	5.91
2008	4	9.50	5.45
Current	4	16.25	7.80
Intrusiveness of Illness Scale			
Baseline	5	59.40	23.80
12 Months	5	64.00	22.76
24 Months	3	50.00	17.78
2008	4	61.25	22.85
Current	4	74.25	17.50

Table 2

Descriptive Statistics of QoL Variables for Baseline, 12-Months, 24-Months, 10-12 year follow-up assessment in 2008 and Current Assessment

Parkinson's Disease Stress Scale			
Baseline	5	6.4	2.7
12 Month	5	8.4	4.22
24 Month	3	4	3.61
2008	4	5.63	3.95
Current	3	7.67	5.03
Social Functioning			
Social Provisions Scale			
Baseline	5	83.4	8.71
12 Months	5	80.8	6.5
24 Months	4	86	12.49
2008	4	79.25	11.59
Current	4	75.5	6.81
Optimism			
Baseline	5	21.8	6.61
12 Months	5	22.6	4.1
24 Months	4	23	3.92
2008	4	22	4.55
Current	4	21.75	1.71

Differences Between Current Participants and Rest of Cohort in Parent Study

McRae et al. (2014) investigated the differences between the participants in the current 13-15 year follow-up and the rest of the cohort that participated in the parent study at baseline and 12 months. The results of the study are included in Table 3. Of note, the baseline and 12 month assessment data was not shifted in the investigation by McRae et al. (2014). The results of the investigation found that four participants reported worse scores on the Activities of Daily Living Scale and Severity of Symptoms Scale at baseline compared with the other 26 participants (McRae et al., 2014). Scores of measures including Optimism, Perceived Social Support, Depression, Intrusiveness of Illness and Stress improved over the 12 months for the four participants in the current study and declined for the other 26 participants (McRae et al., 2014).

Table 3

Differences between the Four Participants in the Current Study that Completed the Questionnaire and the Rest of the Cohort from the Original Parent Study at Baseline and 12 months.

	<u>N=4</u>	<u>N=36</u>
<u>Demographics</u>	<u>Mean (SD)</u>	<u>Mean (SD)</u>
Age	46.8 (6.3)	58.3 (9.7)*
Gender	F=4	F=15, M=20
Duration	11.4 (4.0)	14.1 (5.7)
<u>Quality of Life</u>	<u>N=4</u>	<u>N=26</u>
ADL's @ Worst 0	33.6 (2.1)	28.4 (6.8) ***
ADL's @ Worst 12	29.8 (5.6)	26.3 (6.6)
Severity @ Worst 0	15.6 (3.4)	13.5 (2.3) *
Severity @ Worst 12	14 (3.7)	12.5 (3.2)
Depression 0	38 (10.9)	31.9 (8.7)
Depression 12	26.2 (5.3)	33.7 (8.6) *
Intrusiveness 0	73.8 (21.9)	64.6 (16.3)
Intrusiveness 12	52.4 (20.6)	67.0 (13.8)*
Stress 0	7.4 (3.0)	6.1 (3.6)
Stress 12	6.4 (4.2)	7.2 (3.4)
Perceived Support 0	80.4 (10.7)	80.3 (9.0)
Perceived Support 12	88.6 (2.1)	77.7 (10.4)****
Optimism 0	20.2 (5.9)	22.5 (5.5)
Optimism 12	23.4 (4.6)	19.9 (3.9)*

* ≤ 0.10

** ≤ 0.05

*** ≤ 0.01

**** ≤ 0.001

Reliability of Measures

Because of the small sample size in the current study, estimates of reliability (Cronbach's alpha) of all measures were obtained from the previous follow-up analysis conducted at 10-12 year follow-up assessment (see Table 4; Cole, 2009). The Free or Restricted variable of the UPDRS is a single item and no reliability coefficient was calculated.

Table 4

Reliability of QoL Measures for Current Assessment

QoL Measure at Current Assessment	Cronbach's Alpha
Physical Functioning	
Activities of Daily Living at Worst Scale	.88
Severity of Symptoms at Worst Scale	.68
Emotional Functioning	
Center for Epidemiological Studies - Depression Scale	.84
Intrusiveness of Illness Scale	.94
Parkinson's Disease Stress Scale	.67
Social Functioning	
Social Provisions Scale	.95

Primary Analyses

The previous section outlined the demographic information as well as other preliminary analyses. The current section focuses on the analyses and results for the research questions of the study.

Research Question #1

What is the trajectory of change in QoL for all the participants in the current study from the baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment?

After examining the data, it was evident that with such a small sample size and some missing data over the five time periods, using statistical analyses was not the most effective way to approach the data. Instead, the means and standard deviation for each variable at each time point were calculated and the means were plotted in order to illustrate changes in the means across the five time points.

The profile plot presented in Figure 1, which shows the means of Activities of Daily Living at Worst Scale at baseline, 12, and 24 months after the transplant surgery, 10-12 year follow-up assessment conducted in 2008 and current assessment (13-15 years after the real surgery). There was an improvement in Physical functioning between baseline assessment and 24-month assessment and then a decline in Physical Functioning following the 24-month assessment.

Figure 2 demonstrates the line of progression of Activities of Daily Living at Worst Scale for each participant at baseline, 12 and 24 months after the transplant surgery, 2008 assessment and current assessment. Activities of Daily Living at Worst Scale scores showed that the majority of the participants showed improvements in

Physical functioning between baseline and the 24-month assessment and then a decline following the 24-month assessment.

Figure 1

Trajectory of Change in Activities of Daily Living at Worst Scale for Baseline to the Current Assessment. (lower scores mean improved functioning)

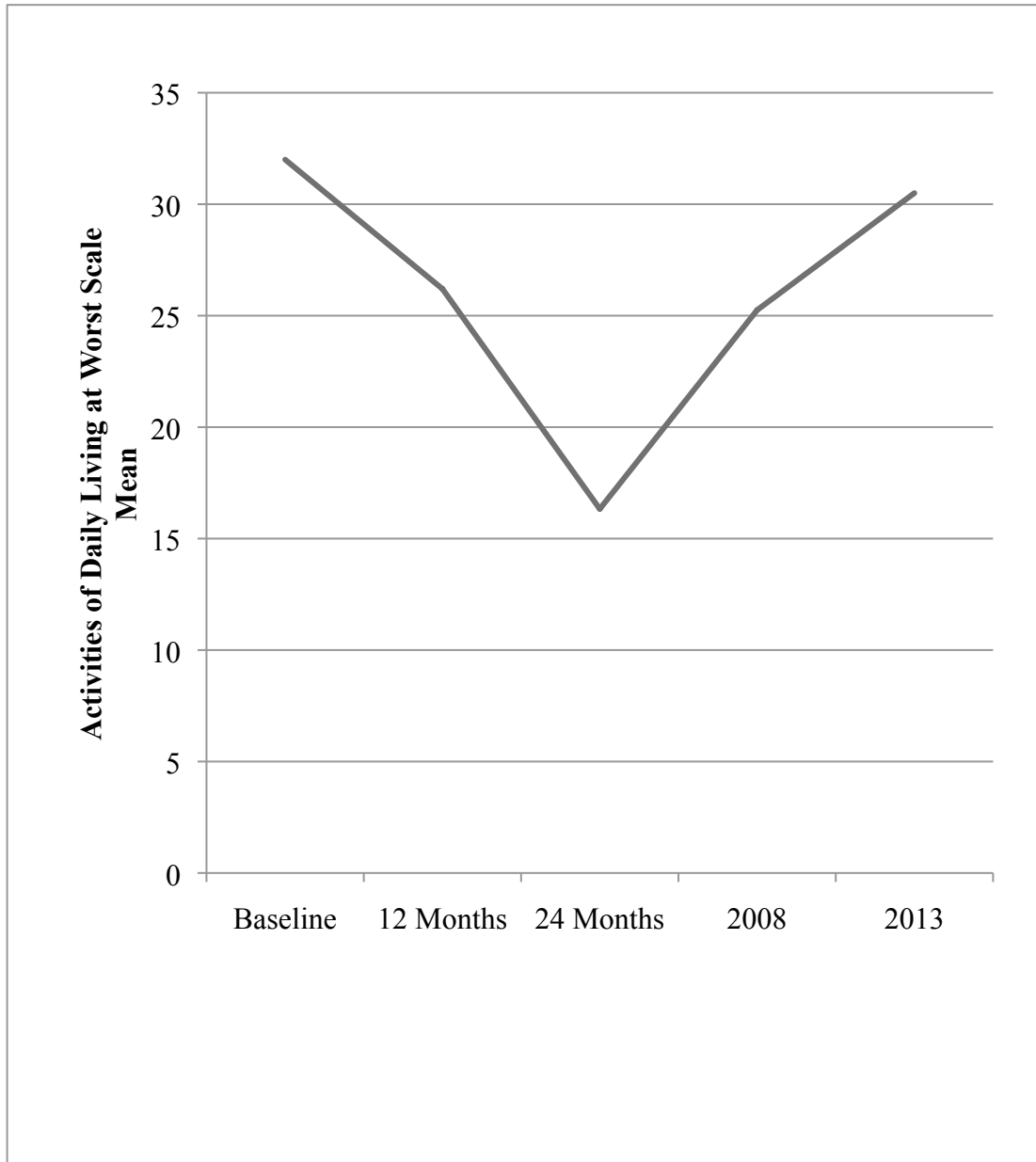
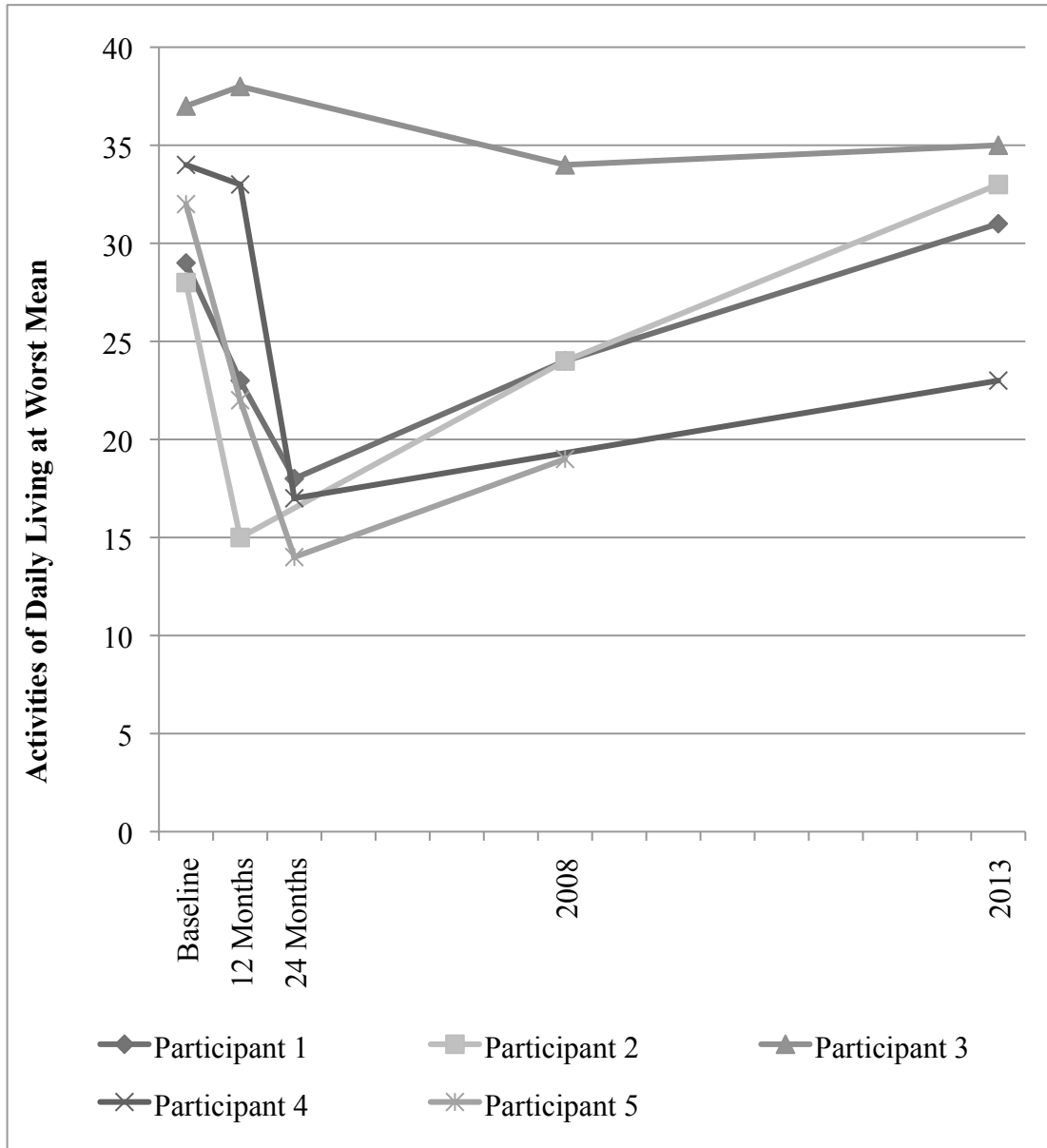


Figure 2

Changes in Activities of Daily Living at Worst Scale over time for Five Participants.

(lower scores means improved functioning)



To examine changes on another aspect of Physical functioning, the means for the Severity of Symptoms at Worst Scale are shown in the profile plot presented in Figure 3, which shows the mean values of the Severity of Symptoms Scale at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. The means for the Severity of Symptoms Scale showed improvements between baseline and the 24-month assessment and then a decline following the 24-month assessment.

Figure 4 demonstrates the line of progression of the Severity of Symptoms at Worst Scale for each participant at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. Three participants showed an improvement in Physical functioning between baseline and the 12-month assessment; however, there was one participant that showed no change in Physical Functioning and one participant that showed a decline in Physical Functioning between baseline and the 12-month assessment. The majority of participants showed a decline in Physical Functioning between the 24-month assessment and the current assessment.

Figure 3

Trajectory of Change in Severity of Symptoms at Worst Scale for Baseline to the Current Assessment. (lower scores mean improved functioning)

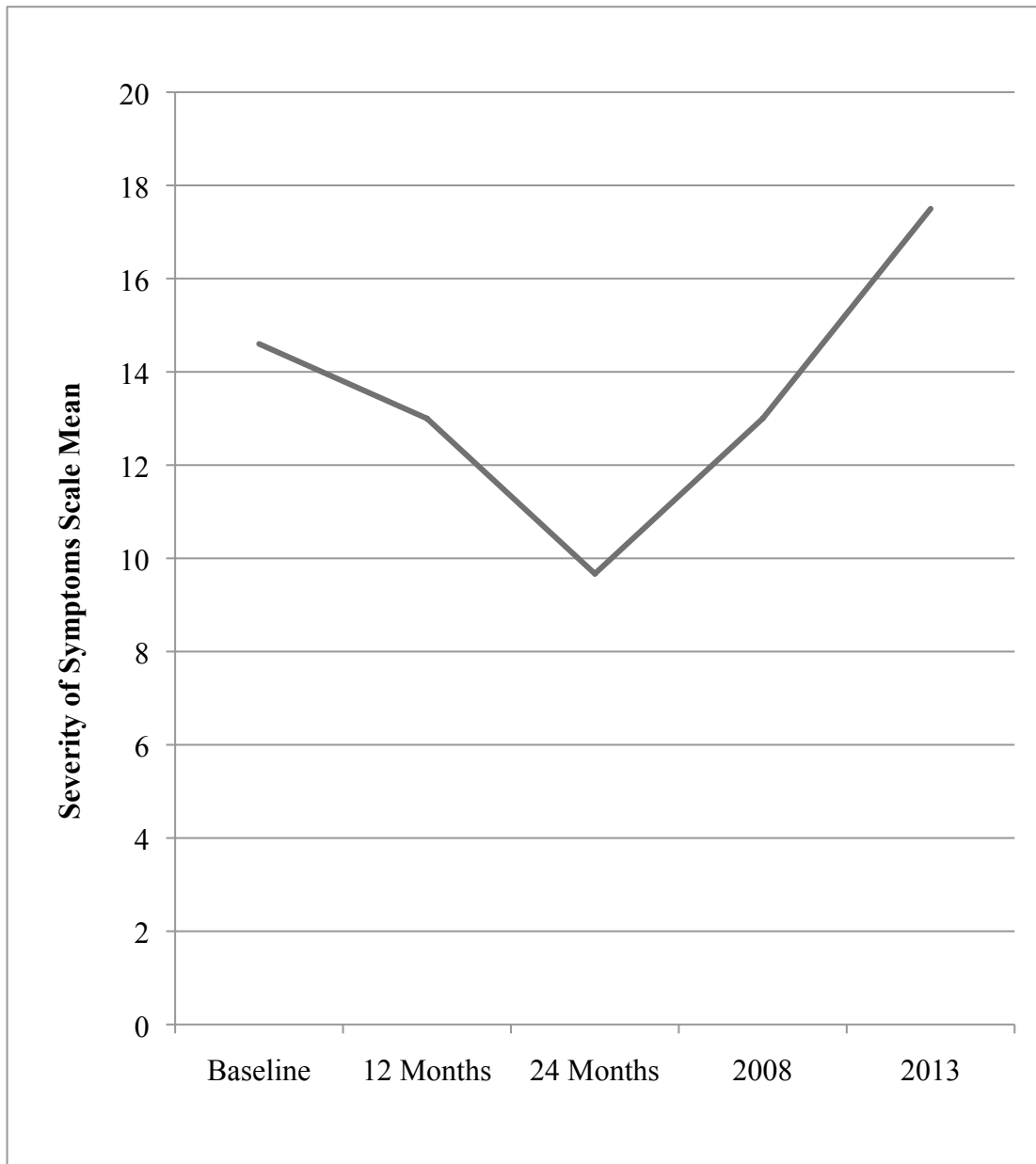
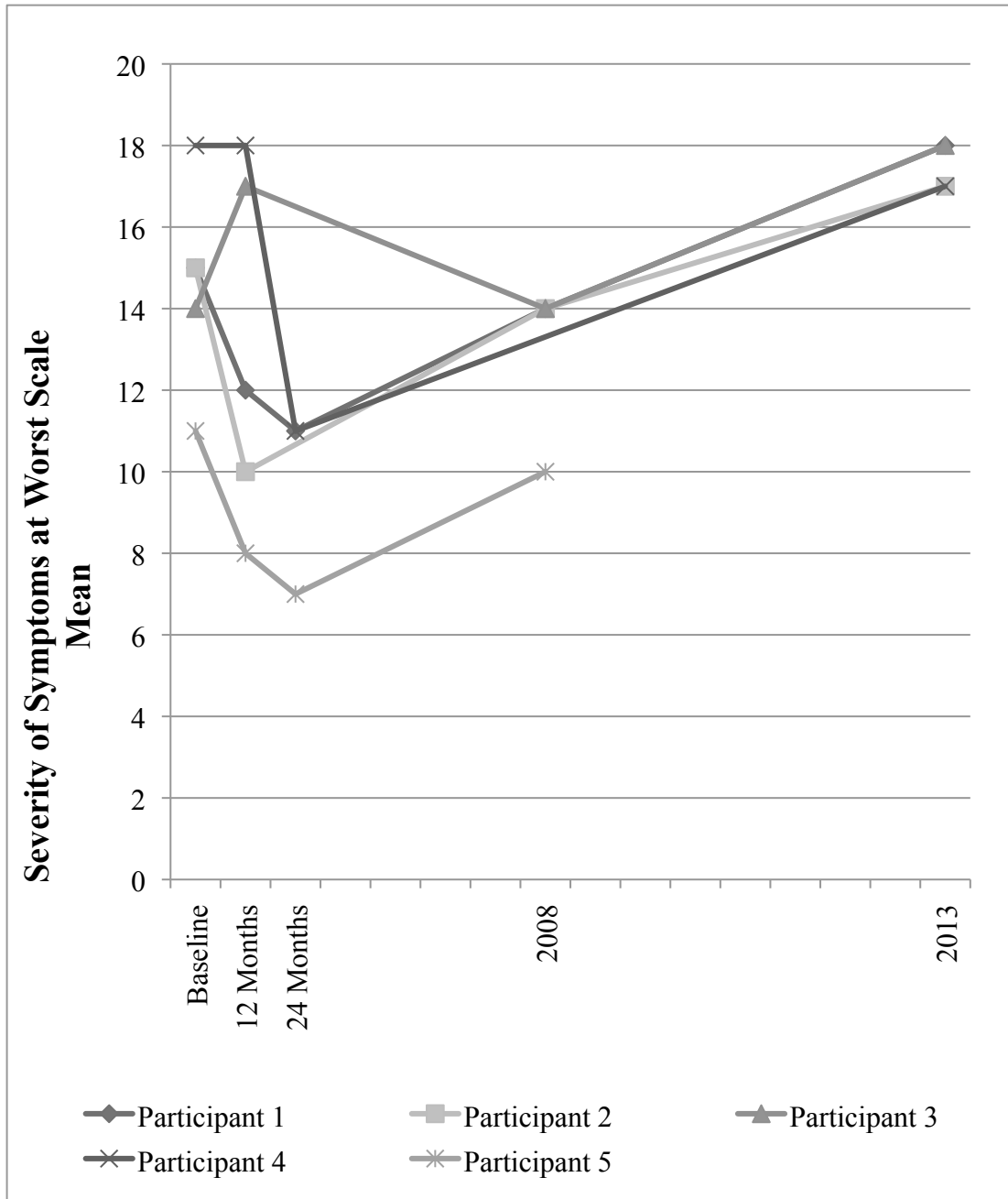


Figure 4

Changes in Severity of Symptoms at Worst Scale over time for Five Participants.



To examine changes on another aspect of Physical functioning, the means for the Free or Restricted Scale are shown in the profile plot presented in Figure 5, which shows the mean values of the Free or Restricted for baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. The means for the Free or Restricted Scale showed an improvement in Physical Functioning between baseline and the 24-month assessment and then a decline between the 24-month assessment and current assessment.

Figure 6 demonstrates the line of progression of the Free or Restricted Scale for each participant for baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. Most of the participants showed an improvement or no change between the baseline assessment and 12-month assessment; however, there was one participant that was an outlier and showed worse Physical functioning. The majority of the participants showed a decline in physical functioning between the 24-month and current assessment. However, there was one outlier (i.e., participant 2) who self-reported an improvement in physical functioning between the 10-12 year follow-up assessment in 2008 and the current assessment.

Figure 5

Trajectory of Change in Free or Restricted Scale for Baseline to the Current Assessment.

(lower scores mean improved functioning)

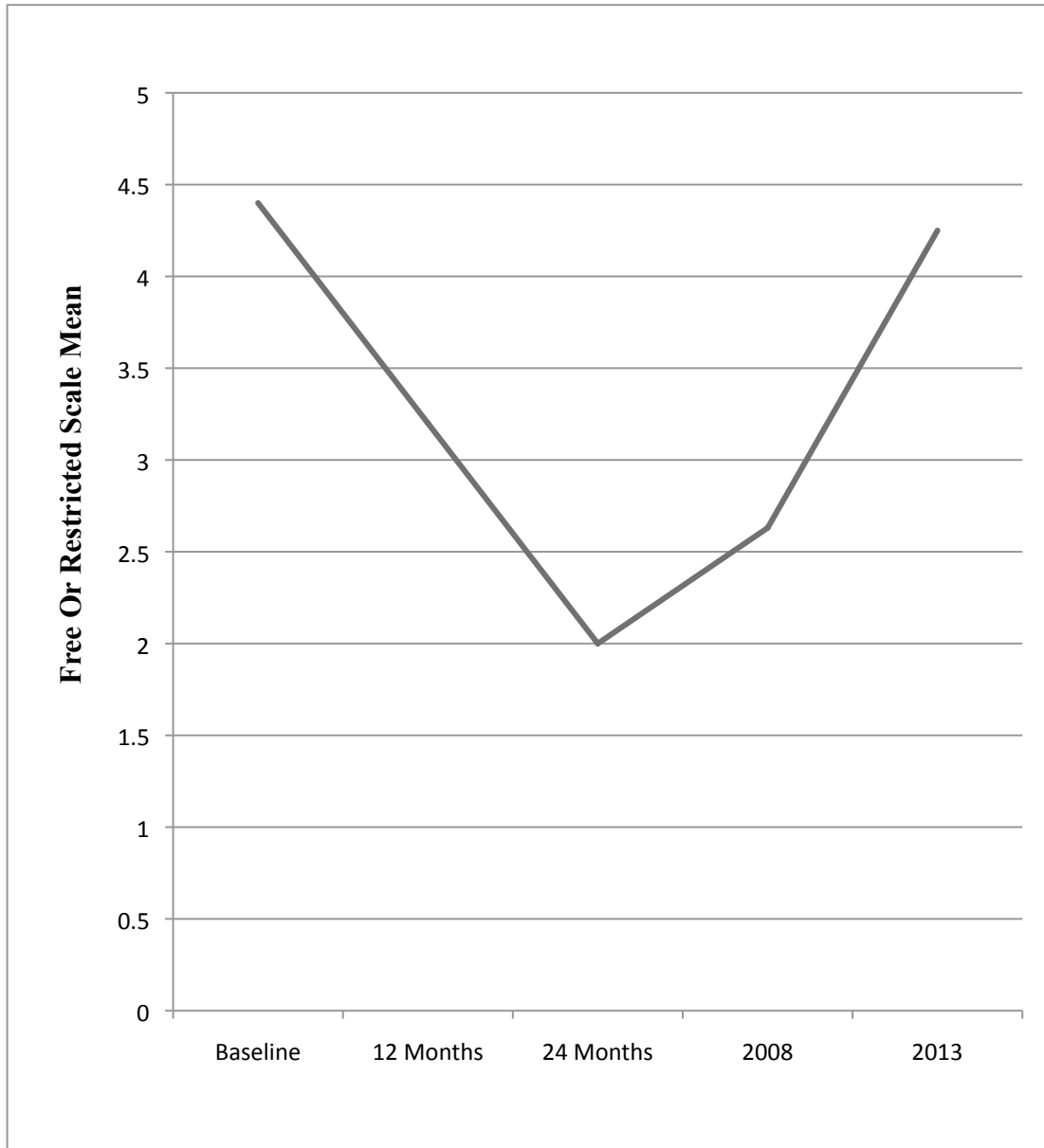
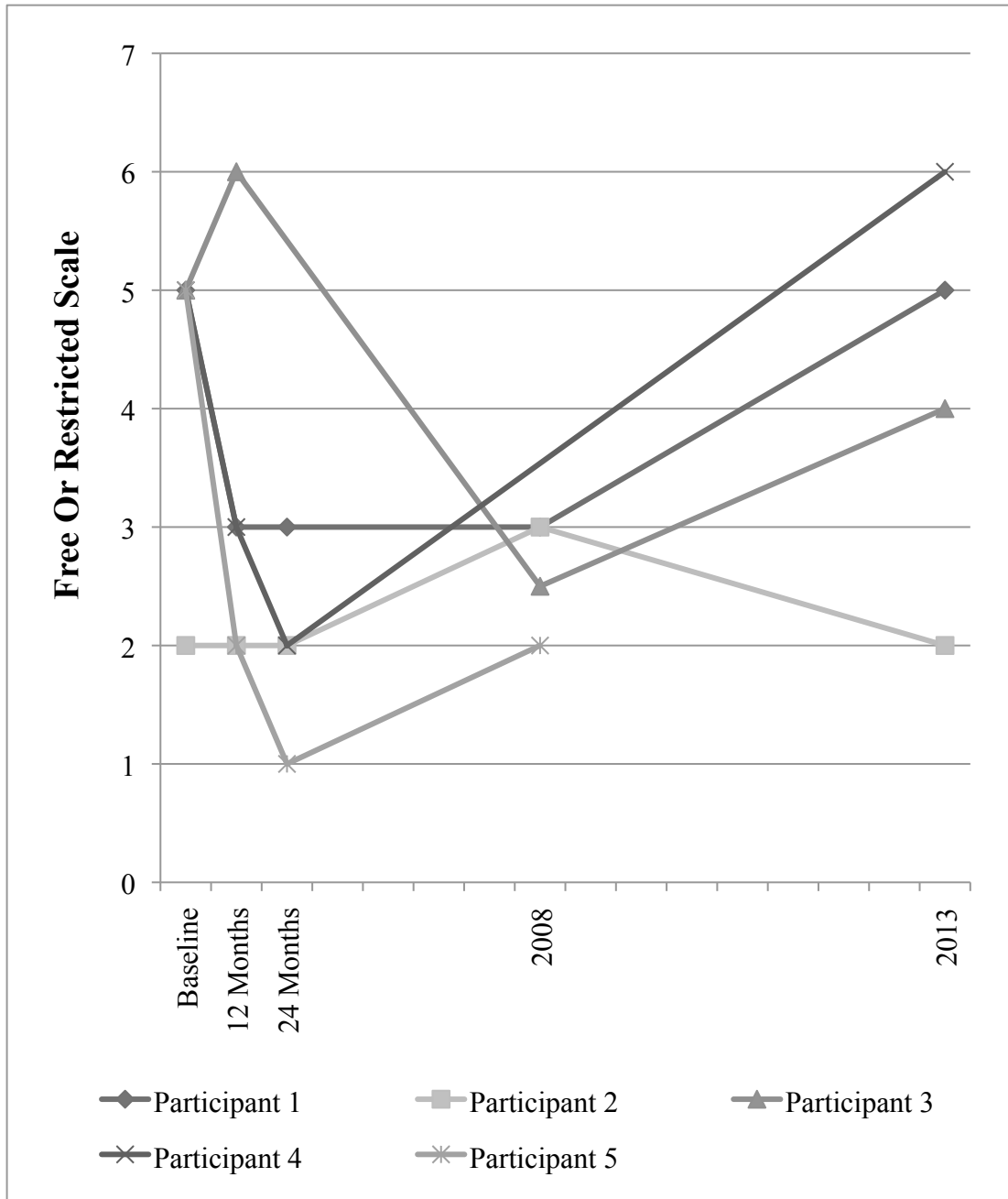


Figure 6

Changes in Restricted or Free Scale over time for Five Participants.



To examine the changes in Emotional functioning over the last 13-15 years, the means and standard deviations were computed for each time period to examine changes on three scales used to assess aspects of Emotional functioning includes the CESD, the Intrusiveness of Illness Scale, and the Parkinson's Disease Stress Scale across the five time points (baseline, 12 and 24 months after the transplant surgery, 2008 and current assessment).

A profile plot is presented in Figure 7, which shows the mean values for all participants on CESD at baseline, 12 and 24 months after transplant, 2008, and current assessment. There was a mild increase in depressive symptomology from baseline to 12 months and then decline in depressive symptomology between the 12-month assessment and the 24-month assessment. From the 24-month assessment to the current assessment, there was an increase in depressive symptomology.

Figure 8 demonstrates the line of progression of depression for each participant for the baseline, 12 and 24 months after transplant, 2008, and current 13-15 year follow-up assessment. Across the first three time points, there were mixed results amongst the participants with some participants experiencing an increase in depressive symptomology and some participants experiencing a decrease. For three of the four participants, there was an increase in depressive symptomology between the 2008 and current assessment; however, there was a decrease in depressive symptomology for one participant.

Figure 7

Trajectory of Change in CESD for Baseline to the Current Assessment. (lower scores mean fewer depressive symptoms)

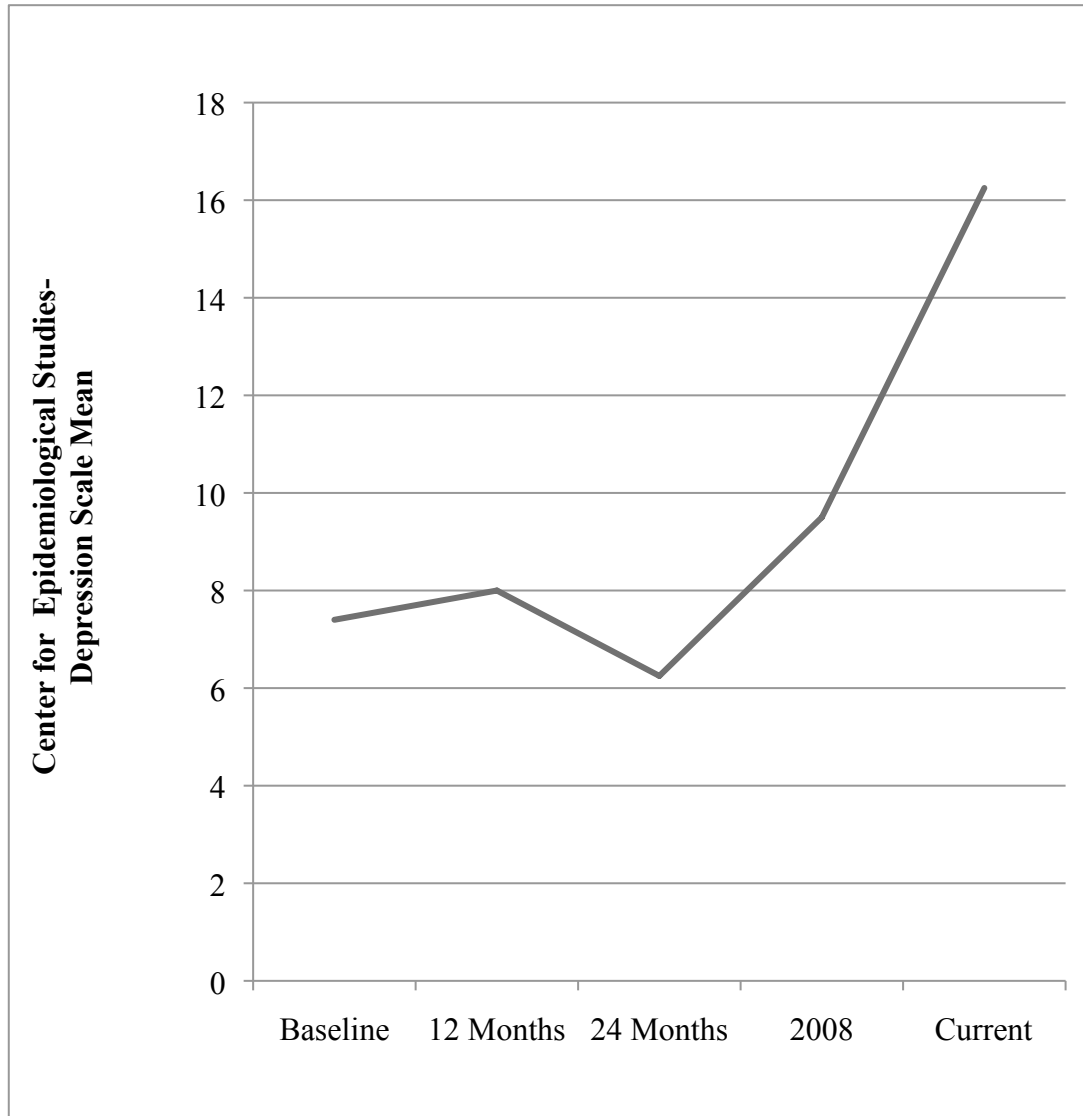
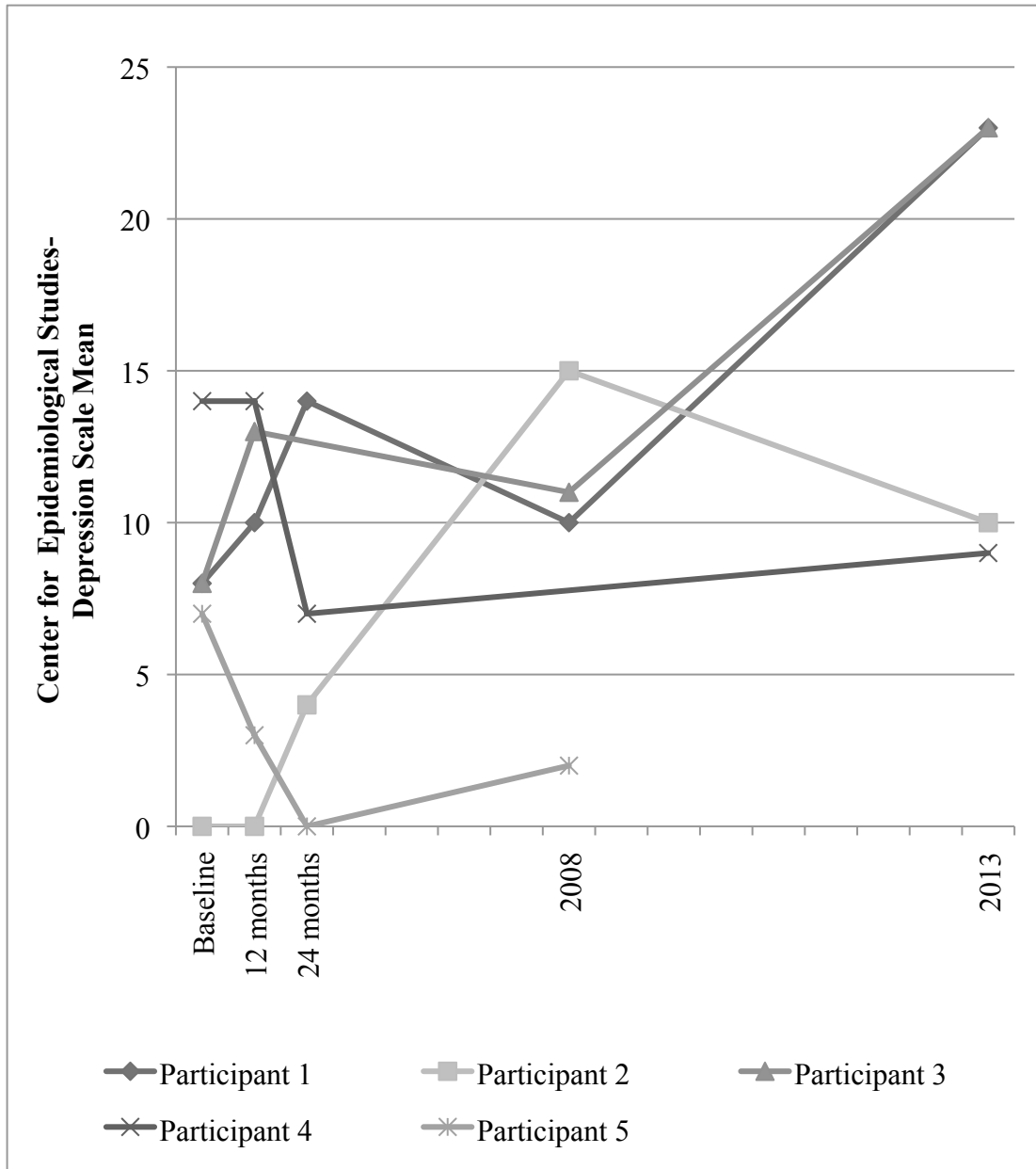


Figure 8

Changes in CESD over time for Five Participants.



To examine changes on another aspect of Emotional functioning, the means for the Intrusiveness of Illness Scale are shown in the profile plot presented in Figure 9, which shows the mean values of the Intrusiveness of Illness at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. There was an increase in the Intrusiveness of Illness Scale between baseline and 12-month assessment as well as the 24-month assessment and current assessment. There was a decline in the Intrusiveness of Illness Scale between the 12-month assessment and 24-month assessment.

Figure 10 demonstrates the line of progression of the Intrusiveness of Illness Scale for each participant for the baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. Intrusiveness of Illness Scale increased in the majority of the participants between baseline and the 24-month assessment. The Intrusiveness of Illness Scale increased following the 24-month assessment in the majority of the participants.

Figure 9

Trajectory of Change in the Intrusiveness of Illness Scale for Baseline to the Current Assessment. (lower scores mean less intrusiveness)

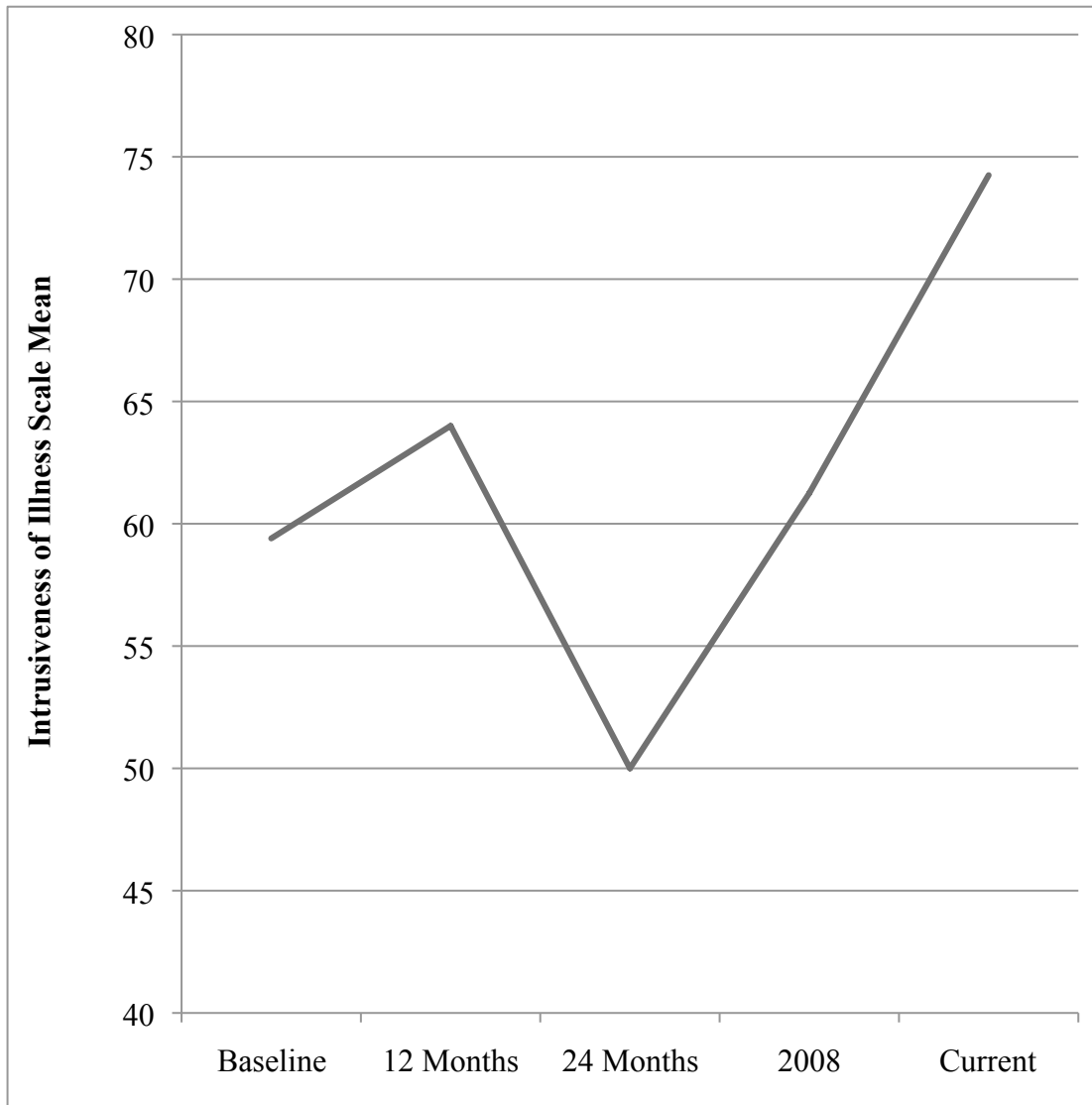
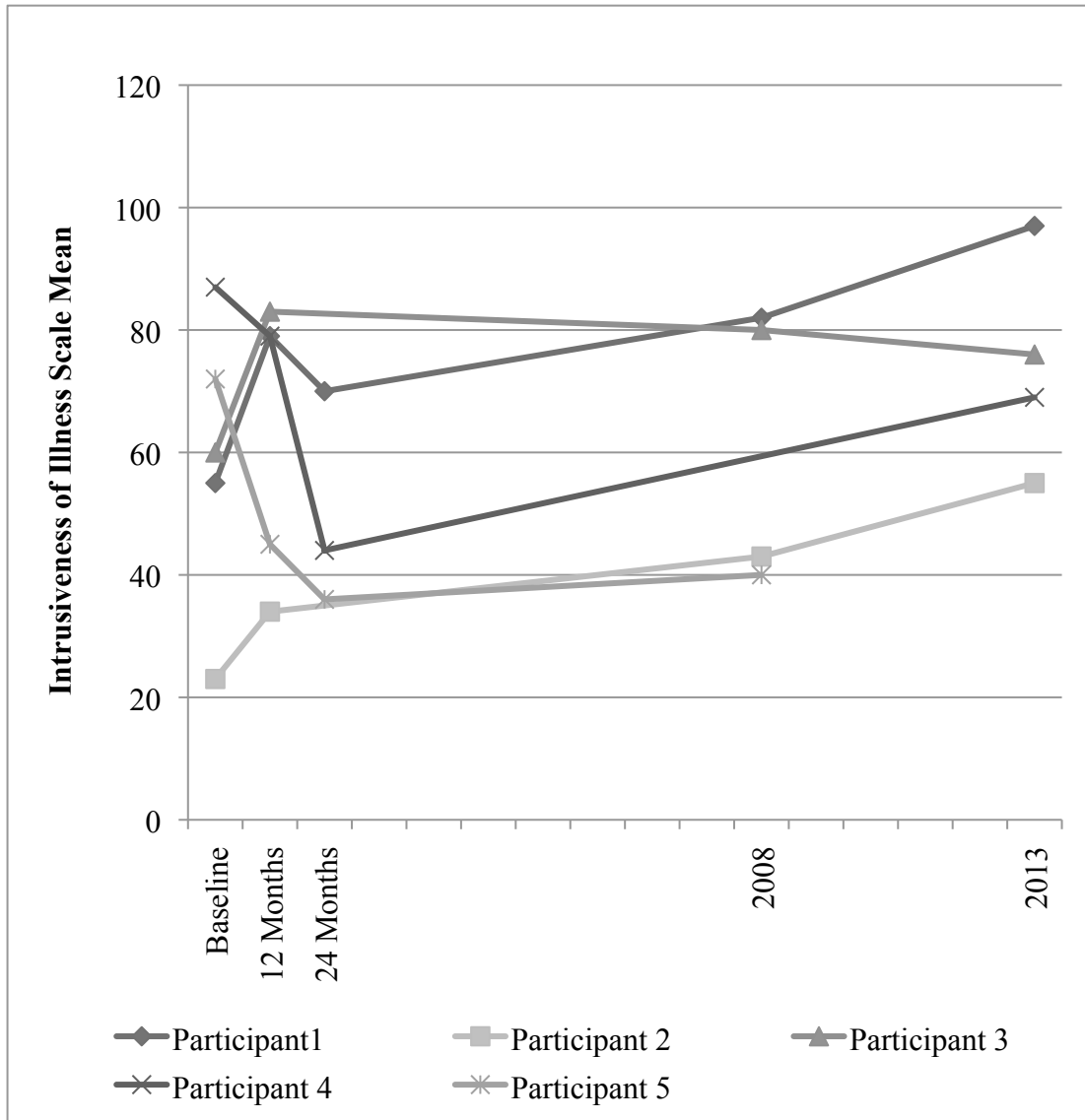


Figure 10

Changes in the Intrusiveness of Illness Scale over time for Five Participants.



To examine change on another aspect in Emotional functioning, the means were computed for the Parkinson's Disease Stress Scale for each time period. A profile plot is presented in Figure 11, which shows the mean values of the Parkinson's Disease Stress Scale at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. There was an increase between baseline and 12-month assessment and then a decline between 12-month and 24-month assessment. There was an increase in stress between the 24-month assessment and the current assessment.

Figure 12 demonstrates the line of progression of the Parkinson's Disease Stress Scale for each participant at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. The Parkinson's Disease Stress Scale increased for three participants and decreased for one participants between baseline and the 12-month assessment. There was a decrease in the Parkinson's Disease Stress Scale between the 12-month and 24-month assessment for the majority of the participants. There was an increase in Parkinson's Disease Stress Scale between 24-month assessment and the current assessment for two participants. Overall, there were mixed findings on this scale for the participants over the last 13-15 years.

Figure 11

Trajectory of Change in the Parkinson's Disease Stress Scale for Baseline to the Current Assessment. (lower scores mean less stress)

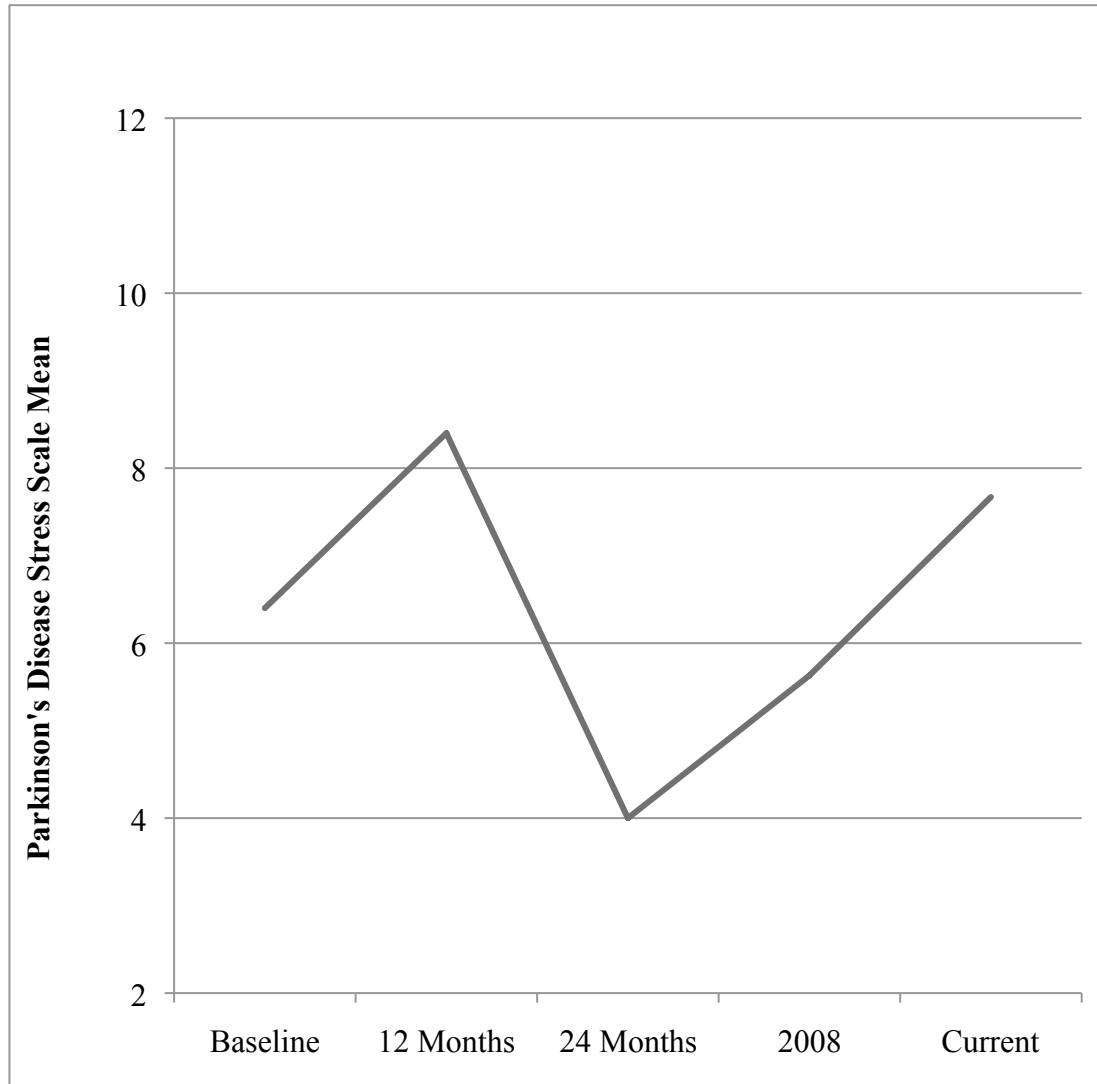
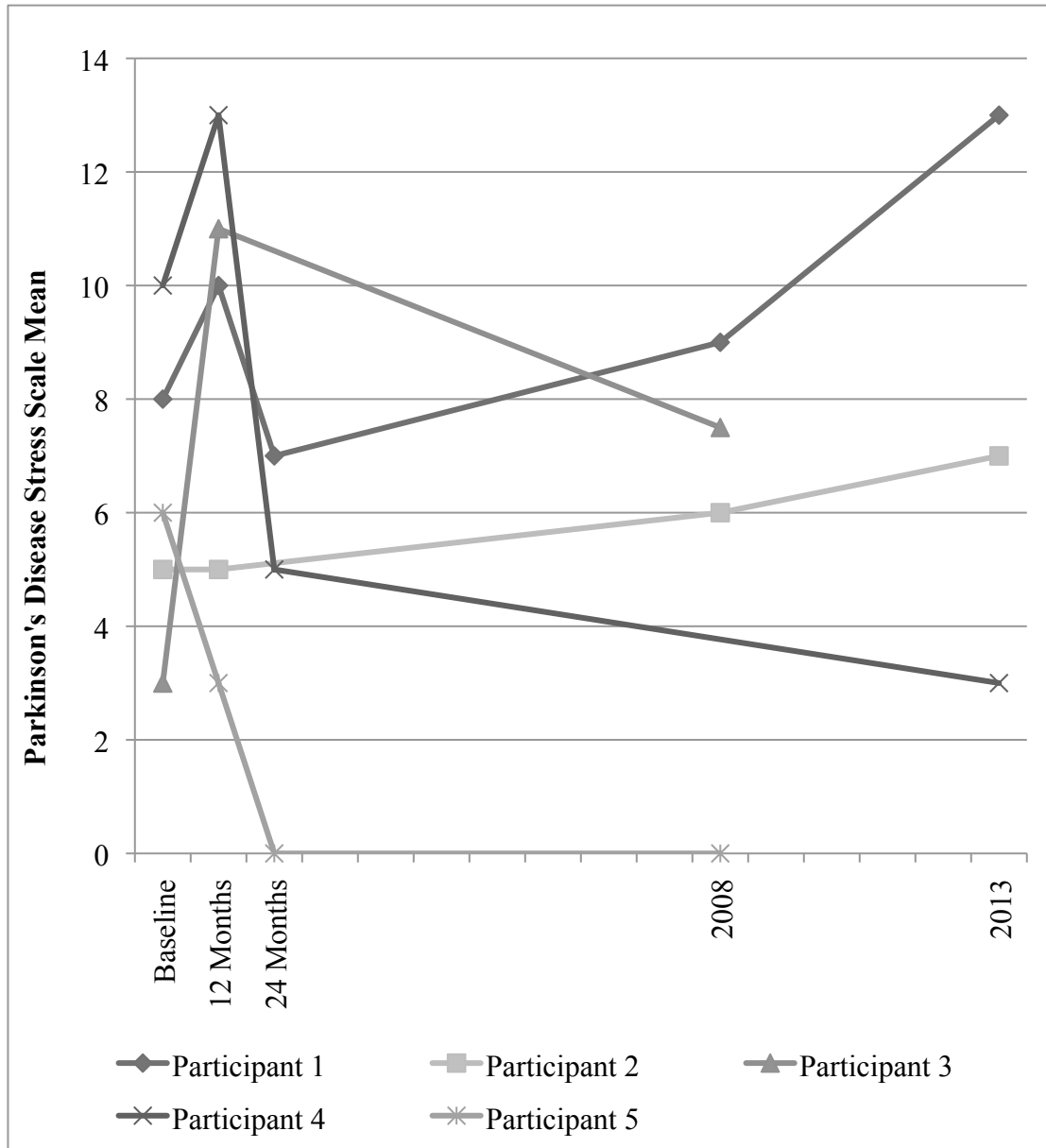


Figure 12

Changes in the Parkinson's Disease Stress Scale over time for Five Participants.



To examine the changes in the perceived social support over time, the means were computed for the Social Provisions Scale for each time period. A profile plot presented in Figure 13 shows the mean values of the Social Provisions Scale at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current assessment. There was a decline in perceived social support between baseline and 12-month assessment, an increase between 12-month assessment and 24-month assessment and then decrease between 24-month assessment and the current assessment.

Figure 14 demonstrates the line of progression of Social Provisions Scale for each participant at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current assessment. There was a decrease in Social Functioning for three participants between baseline and the 12-month assessment. Social Functioning remained relatively stable between the 12-month assessment and the current assessment with the exception of a decline in Social functioning for two participants between the 10-12 year follow-up assessment and the current assessment. Higher scores on the Social Provisions Scale indicate more perceived social support.

Figure 13

Trajectory of Change in the Social Provisions Scale for Baseline to the Current

Assessment. (lower scores mean less perceived social support)

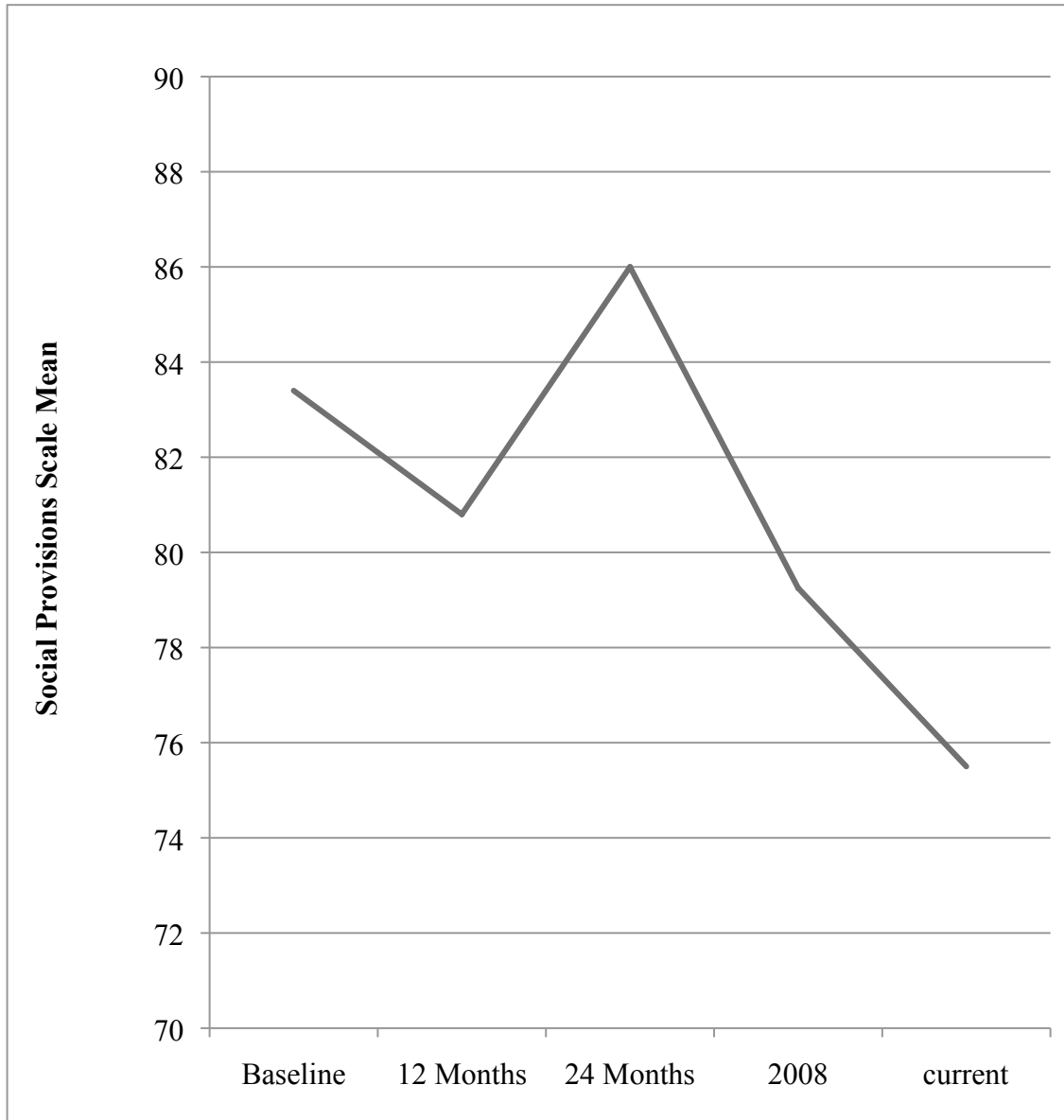
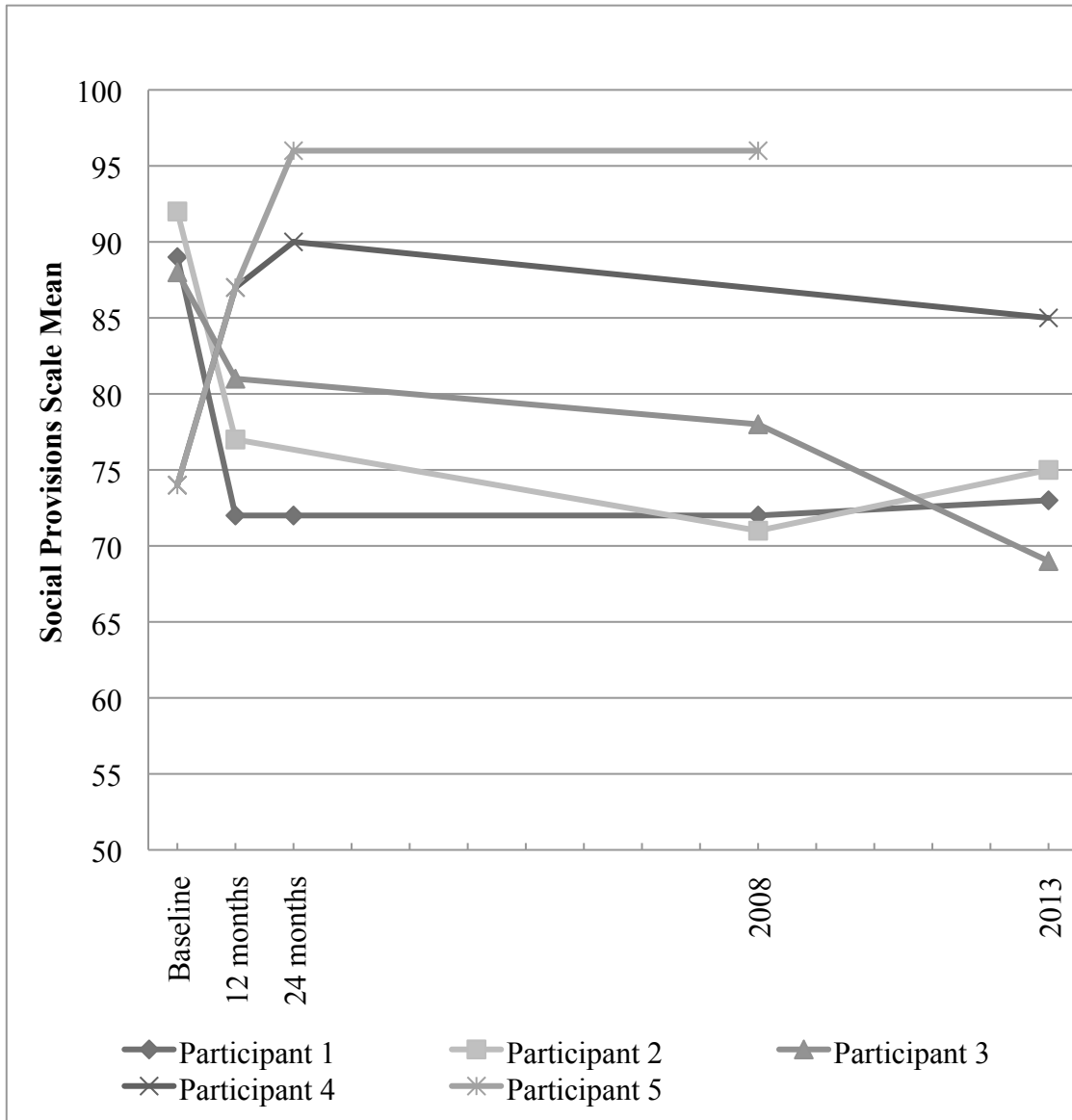


Figure 14

Changes in the Social Provisions Scale over time for Five Participants.



To examine changes in the Life Orientation Test (Optimism), the means were computed for the Life Orientation Test for each time period. A profile plot presented in Figure 15 shows the mean values of the Life Orientation Test Scale at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. There was an increase in Optimism between baseline and the 12-month assessment. Then there was a decline between the 12-month assessment and 24-month assessment. There was an increase between the 24-assessment and the 2008 assessment. There was a decline between the 2008 assessment and the current assessment. Scores range from 0-32 with higher scores indicative of more optimism (Scheier & Carver, 1985). The scale has a mean score of 21 (Scheier & Carver, 1985).

Figure 16 demonstrates the line of progression of the Life Orientation Test Scale for each participant at baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment. There was no consistent pattern of change between baseline, 12-month assessment and 24-month assessment. Optimism stayed relatively stable between the 24-month assessment and current assessment. However, there was a decline in Optimism for one participant between the 2008 assessment and the current assessment.

Figure 15

Trajectory of Change in the Life Orientation Test Scale (Optimism) for Baseline to the Current Assessment. (lower scores mean less Optimism)

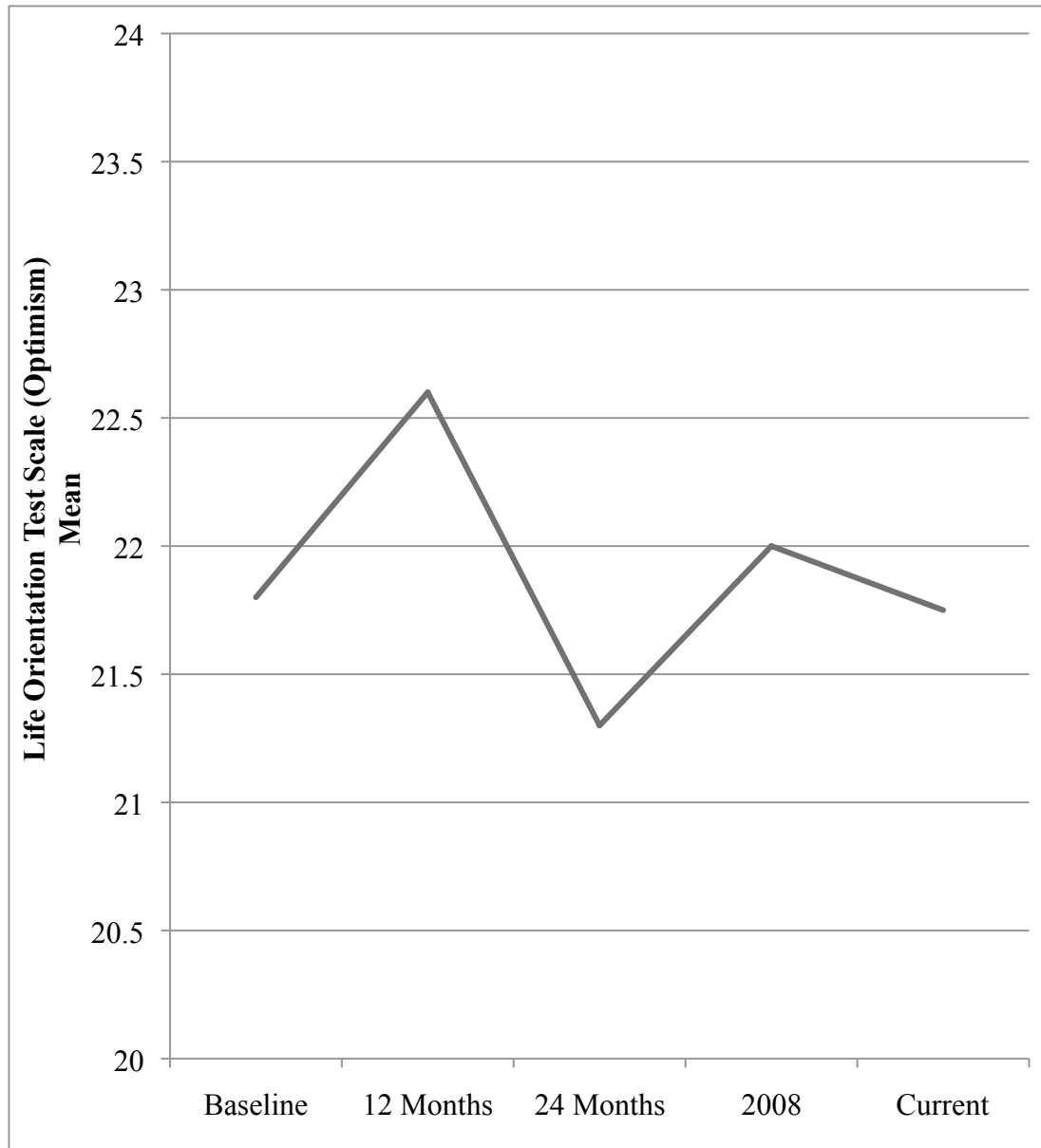
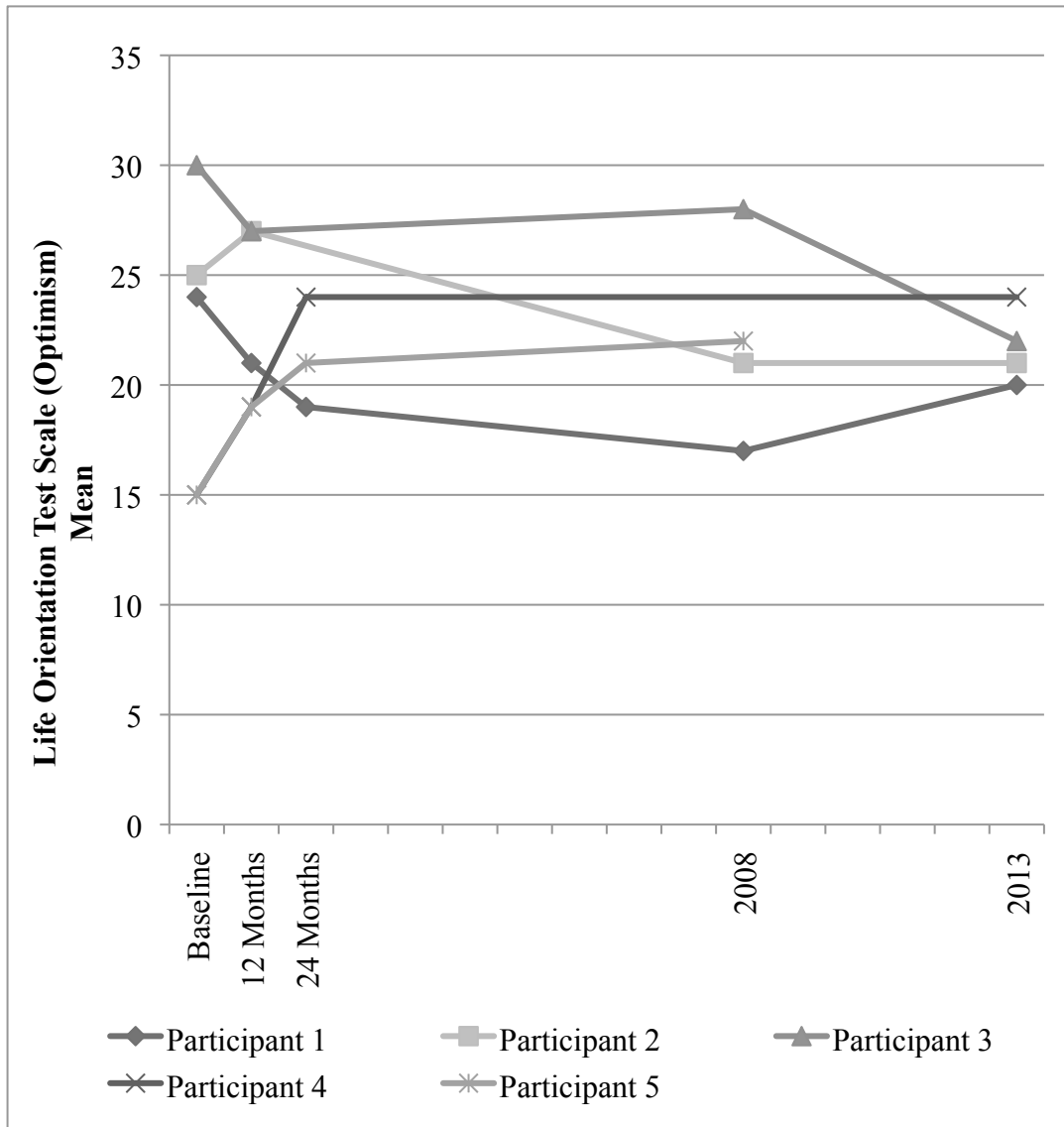


Figure 16

Changes in the Life Orientation Test Scale (Optimism) over time for Five Participants.

(lower scores mean less Optimism)



Research Question #2 and #3

What are the individual experiences of the participants who participated in the double-blind sham controlled transplantation study and original QoL study? Would the participants, who participated in original transplantation study, volunteer to participate in a future double-blind sham-controlled surgical trial?

To examine the personal experiences of the participants and to explore if they would participant in a future surgery trial, participants were interviewed and recorded. Transcripts of the recordings were made by the investigator and narratives based on the interviews were developed for each participant. Individual stories for each participant were developed. Each story was created by combining the individual responses to the qualitative questions. Pseudonyms were given to each participant for confidentiality.

Narrative for Susan (pseudonym)

When asked to reflect on her experiences in the surgery trial in the beginning of the discussion, Susan explained that she has had Parkinson's disease for 40 years now and she was diagnosed at the age of 35. She stated that "for [her], [the surgery] was extremely successful" and she feels "very positive" about the experience. She explained that she "was violently dyskinetic before the surgery so afterwards [she] got great relief." She then added that she stills gets dyskinetic but "not nearly to the extent that [she] had been earlier." She then explained important activities she has been able to do in the years following the surgery, including developing a workshop for police officers following an incident where she was almost arrested due to individuals in a mall perceiving her as intoxicated or high on drugs. She explained how she and her husband enjoy educating others about PD, and that it is a great passion for them.

When asked how her feelings have changed over the years, she mentioned that “she felt she didn’t have any other avenue “ for treatment at the time, and she was really “down” after she got the first surgery because she wasn’t doing well. At that time, she prayed that she didn’t get the real surgery because she wasn’t doing well. She reported she did receive the placebo surgery initially and she had some “placebo benefits but nothing [she] could dig [her] teeth in.” She reported, “That is one thing the transplant did is restore some regulatory ability to my body” and she expressed that “even if you can stop where you are, that is a huge improvement with a chronic illness.” She then explained how the surgery gave her “a second chance” in life. She noted that she was able to sleep more than two hours per night, eat and gain weight, talk on the phone without dropping it or flinging it around the room, and walk to the end of the driveway and back. She acknowledged that she was not able to do these activities previously. She discussed how being able to “make [friends] a cup of tea” was a big improvement. She stated she overall felt as though “life was starting over again” after the transplant surgery.

After discussing her experiences, she was asked if she would participate in a similar surgery trial in the future and she stated, “[She] absolutely would! I learned a lot.” She went on to say that “the major problems were cured and new problems arose that come with a chronic illness.” She then described the surgery as “some new defense that you didn’t have before.” Her husband expressed more fear regarding the process and indicated how it was a dangerous process because once the cells are implanted, there is no control over them. He also noted he worried regarding his wife experiencing adverse effects. With that said, he stated he would agree that he would recommend she

do a similar surgery trial in the future given that it would be intended to combat the illness, which is always beneficial.

Susan was then asked what were the positives of participating in the surgery trial and she stated the “outcome” and “knowing there was an opportunity to get better.” But when asked the negative aspects of participating in the surgery trials, she noted the negative was “not knowing [if it would be beneficial].”

While discussing what advice would she give to future participants of a surgery trial, she stated to “make sure you understand the risks” associated with the study and then “don’t be afraid to speak up.” She explained further that there is “nothing that is too little to be dealt with.” She explained that when people enter into a surgery trial, they need to “trust [the researchers].” Her husband stated that one should understand what the doctors want before you enter into the surgery trial. He also explained how important it is to accept that things may go wrong during the surgery trial and he emphasized the importance of preparing the other people in your life regarding why the participant is participating in the study and what the outcome may be at the end.

At the end of the interview, Susan stated she never got to speak with other participants and how it would have been helpful to speak with them following the trial.

Narrative for Nancy (pseudonym)

The interview began with a discussion regarding reflecting back on her experiences in the surgery trial and she quickly stated that she felt the surgery was “a work in progress” and explained that the surgery didn’t improve her symptoms of PD past the first month. Whether or not she had the real or sham surgery was discussed and she indicated she had the sham surgery first. She acknowledged benefits from the sham

surgery for one month including improvements in her balance and her overall tightness. She explained that her benefits following the real surgery were no better than with the sham surgery.

The discussion then went on to explore the negatives of the surgery trial and she stated she felt as though the physicians were “done with [the participants]” at the end. She indicated that it was a real sacrifice to participate in the study, especially with three young children. As soon as her children entered the conversation, her mood shifted a bit and she became positive as she expressed great pride in how her children turned out.

She then explained she was diagnosed at age 26 and she had the surgery when she was 38 years old. She indicated that she has been able to keep going as a result of having deep brain stimulators (DBS) inserted in 2005 or 2006. She reported that she has found DBS helpful in addressing her worst symptom, which she stated is walking. She stated DBS has “given [her] a whole new start.”

She was asked if her feelings regarding her participation in the surgery trial have changed over the last 13-15 years and she stated “not really.” She explained that it was a trial and explained how it is important to remember that. She acknowledged that she was glad she went through the trial since there was an opportunity to have input if it worked. She was then asked if she would do it again. She explained that she is older now and doesn’t know if it would be worth it.

While discussing if there were any positive aspects of participating in the study, she noted she enjoyed “seeing other people at the level they were at.” In other words, she found it helpful to see others with the disease but at different stages of the disease. There was then an inquiry regarding the worst aspects and she stated it was the time

when she was waiting to find out why it didn't work for her and the overall results of the study.

The discussion ended up with a reflection on regarding what advice she would give to future participants, and she said, "Go and have it done. If it helps, you are lucky. If it doesn't help, maybe there is something else down the road."

Narrative for Piper (pseudonym)

In looking back on her experiences in the surgery trial, Piper stated that she believes it is something she would do again overall and that she has no regrets. In the surgery trial, she acknowledged that she had the sham surgery initially and then underwent the real surgery.

Towards the end of the surgery trial, however, she felt "abandoned" and went on to explain that everything was moving so quickly and then all of a sudden, there was nothing. While she was grateful for the care of the nurses and physicians, at the end of the study, she felt as though "all of sudden [the participants] were nothing."

She went on to explain how it would have been helpful to have support towards the end of the trial due to her experiencing ups and downs in regards to her symptoms. She stated it would have been helpful to know what was expected and if her symptoms were normal. She pointed out that there was no one to guide her towards the end of the trial and give her any information. She stated she could feel the medical staff "losing interest." She expressed sadness and stated, the participants "put time and energy into it, too."

Regarding whether she would be willing to go through a similar surgical trial for a second time, she stated yes and explained that she felt like she was a small part of

future technology that would one day find a cure. In regard to personal benefits to her own health, she stated “I don’t know what I would be like if I didn’t have it.” She also stated she had DBS surgery approximately 8 years ago as well. She explained that it is hard to tell the benefits for her since her dyskinesias are different; she experiences both dyskinesia and dystonia at the same and experiences more of a rolling than a jerking movement.

Over the last 13-15 years, she stated her feelings regarding participating in the trial have not changed and she has always been glad she participated in the trial stating, “I wanted to be on the cutting edge.” She explained further that she is a “risk taker,” which she attributed to being a single parent and taking on new endeavors in her work life. She explained that the experiences she had in the trial were unique and she would have never had those opportunities without the trial.

The discussion then turned to the waiting period between the sham surgery and the real surgery, which lasted approximately one year for her. She stated it was “difficult” to wait that long. She explained that every Monday she thought the phone call would come telling her she could undergo the transplant surgery. However, she stated that instead of receiving a call from them, she had to follow-up with the doctors, only to find out that she need to wait several more months. She explained that time as “living week to week.”

She went on to recall the weeks following the sham surgery and how she was convinced she had the real surgery initially due to “feeling better.” She stated that when she found out she got the sham surgery, she “kept on because [she] felt [she] was

representing people with Parkinson's." She went on to say, "I had to stay positive even though deep down, I didn't believe it."

During the last part of the interview, she was asked what advice she would give to future participants who would participate in a surgery trial. She stated "you can't do it if you don't believe in it. You have to really believe in it. You have to be positive about it." She went on to say that, "a lot of Parkinson's has to do with your attitude" and stated that if you don't make the most out of your situation, "you only hurt yourself."

Narrative for Melissa (pseudonym)

The interview began with her feelings regarding her experiences in participating in the fetal tissue surgery trial. She noted that at the beginning, she was "full of hope." At that time, she was "hopeful that it would be a cure but it wasn't." She went on to explain her symptoms three years post-surgery and stated she did pretty well. She was walking and she felt "in control of [herself]." Furthermore, she stated she was "full of pep" and her "tremors weren't too bad." However, she acknowledged wearing off effects around three years. More specifically, she noticed her left side was getting affected and up until that point, her left side was not affected by her PD. She stated at this time, she realized that the "Parkinson's wasn't wearing off, [she] was wearing off."

The conversation then explored her feelings in the beginning of the surgery trial. She stated that in the beginning, "[she] felt very special." She explained that she and her husband were recently married at the start of the study and stated they worked hard to join the study. She acknowledged that during the period following surgery, there were several follow-up appointments where she explained how she felt "very challenged and [she] wanted to do well." She then found out that she had the real surgery; however, she

found out the fetal tissue cells in one part of her brain “didn’t take.” She also stated that she had some medical complications including hypertension and it was unclear at that time if her health issues were related to having the fetal tissue cells implanted. She explained that she had to be taken off of her PD medications, which caused her functioning to decline and explained that as a result, the effects of the surgery didn’t last long. When the effects of the surgery wore off, she explained that she experienced mild depression and began searching feverishly for new treatments. At that time, she felt as though she was “back to square one.”

She was then asked how her feelings of participating in the surgery trial have changed over time. She acknowledged that at the beginning, she was filled with hope and she felt as though she was “dedicating [herself] to science.” She then stated she does not regret being a volunteer when she reflects back on her experiences. She also stated that if there were any real prospects for improvements, she would participate in a similar study again.

While inquiring regarding the most positive aspect of participating in the study for her, she stated it was the attention she got during the study. When she was queried further, she stated she was compared to other individuals and she was invested in doing well. She stated she wanted the study “to be a success.” The discussion was then directed to the negative aspects of participating in the study and she stated the most negative aspect was having her symptoms return and then become worse.

Regarding advice for future participants, she stated individuals frequently come to her for advice regarding PD and what medications they should take since she has had PD for 28 years. For instance, she has a friend who resides near her who comes to her

for advice and she told her that you have to tell the doctor what you feel and you need to be honest with the medical providers. She also told her friend that if you are not ready to take medications and if you feel you can cope without the medications, then tell the medical providers you are not ready. She placed importance on being true to yourself and standing up for yourself.

She then went on to explain that she enjoys pushing herself and explained that she will push herself to walk outside when she is getting picked up by friends instead of waiting inside. She expressed that pushing herself gives her a “sense of importance.”

At the end of the interview, the discussion turned to her support system during the surgery trial and she explained that her husband was “a terribly good sport.” She explained that he was “about helping me” and she didn’t think she “could have done it without his help.” She explained that when he died, she felt “abandoned,” but she has good friends and she is now in a new romantic relationship.

The final question discussed was what she would tell someone else going through a similar surgery trial. She stated she would “ask them if they have close friends and family.” She then went on to say, “they would need people they care about being on their side” and explained that they would need to have “a conviction about helping others and science.”

Narrative for Jenny (pseudonym)

While reflecting back on her overall experience in the surgery trial, she stated she feels “very positive” regarding her experience in the transplant surgery trial. She then went on to say that she had “a very good result” from the transplant surgery trial and she explained that she was able to resume her life as a practicing neurologist as a result of

the transplant surgery. She then went on to discuss her medical history and she noted she was diagnosed with PD around 1989. She stated she is currently experiencing balance difficulties and she is unclear if her balance difficulties are related to her PD or her history of scoliosis.

The discussion then turned to the next question regarding how her feelings have changed about her participation in the surgery trial over time. She indicated she has been “confident about it since the very beginning.” She went on to explain that she knew she received the real transplant surgery initially because the doctors were “spending more detail” than they would if they weren’t putting something in her brain. She also noted she felt the needle pass the blood-brain barrier due to experiencing pain. When asked if she would participate in the surgery trial again, she quickly said yes. When asked to elaborate, she stated “there is nothing out there that could have given me as good of results or any results at all.” She noted that she doesn’t believe the neurostimulators are ideal for her type of Parkinson’s. She explained that the year following the transplant surgery, she was off all her medications and she was able to “feel like [herself].”

The next question explored the negative aspects of participating in the transplant surgery trial. She initially stated, “I don’t know.” She then was probed to explore the question further by exploring the attention she received since she was the patient that experienced a brain hemorrhage as a result of the transplant surgery. She indicated the attention she received was “bothersome.” The discussion then turned to when the study ended and how some participants felt forgotten. She stated that was true for her as well. She explained further that it was “sad the study did not go any place.”

She was then asked what advice she would give to future participants who participate in a fetal tissue surgery trial. One piece of advice was that if you decide to do it, “act like a patient and do what you are told.”

Towards the end of the interview, the discussion turned to a more personal topic, her experiences when she was first diagnosed. She stated her relationships have been “formed and deformed by Parkinson’s.” She noted that her children had to cope with a “mother who moved funny.” But she says she is grateful she is still working and she was able to get married again. She also noted she was able to watch her children grow up. She stated regarding friendships, “it is not generally up to me, it is up to those who socialize with me.” She explained that people look differently at those with chronic illness. She explained that she “never felt totally comfortable with my friends and colleagues. They looked at [her] as a person with Parkinson’s’ not a person.” She then went on to explain how she was recently introduced by a student at a symposium and the student stated she was a fabulous teacher and she explained how wonderful it was for someone to acknowledged her as a person and teacher, rather than to see her primarily as someone with PD.

Summary

Chapter Four presented the results of the preliminary and primary analyses associated with the current study. In the beginning of the chapter, the results of the preliminary analyses were discussed, which was followed by the results of the primary analyses.

To answer the first research question, the means of all the measures were computed over five time points: baseline, 12 and 24 month following the transplant

surgery, 10-12 follow-up assessment in 2008 and current assessment and then plotted to determine changes in the means over the last 13-15 years. The means for each participant were also computed and plotted to assess the changes from baseline through the current assessment. In response to the second and third research questions, the information gathered from the qualitative interviews was presented in narratives that described the participants' individual experiences in regard to the surgical trial.

Chapter Five discusses the results presented in Chapter Four as well as connecting both the quantitative and qualitative data. Additionally, the limitations associated with this study and recommendations for future research are discussed.

Chapter Five

Discussion

Overview

Chapter Five presents the following topics: a) summary of the current study, b) discussion of the overall findings from the primary analyses, c) connecting of the qualitative and quantitative data) d) limitations of the study, e) recommendations for future research, and f) conclusions.

Summary of the Study

Parkinson's disease (PD) is a chronic illness that impacts every aspect of an individual's life including emotional, physical and social functioning. There have been significant improvements in the treatments for PD including the introduction of surgical treatments over the last few decades. In 2001, Freed et al. investigated the effects of fetal tissue transplantation in participants with PD by conducting a double-blind sham-controlled surgery trial. Results showed human embryonic dopamine-neuron transplants survived in all patients and there were some clinical benefits in younger participants (Freed et al., 2001). While the parent study was being conducted by Freed et al. (2001), there was also a study that was conducted by McRae et al. (2004) that examined if QoL improved in participants in the transplant group compared to the sham group after the 1-year period of the double-blind was lifted in the study conducted by Freed et al. (2001). However, there has been limited research examining the long-term impact of these

surgical treatments on QoL in persons with PD. In addition, there is little known regarding the long-term impact on QoL in the participants that participated in the double-blind, sham controlled transplant surgery trial from a qualitative perspective.

In the present study, the longitudinal changes in QoL in the participants after undergoing the fetal tissue transplantation surgery approximately 13-15 years ago were examined from both a quantitative and qualitative perspective. There were a total of five participants who participated in the parent study (Freed et al., 2001) and original QoL study (McRae, 2004). All five participants completed the interview to gather qualitative information regarding their personal experiences over the last 13-15 years and four participants completed the questionnaire that measured several dimensions of QoL as well as optimism. The information gathered in the current study was plotted along with the data collected at baseline, 12 and 24 months after transplantation as well as the previous 10-12 year follow-up conducted in 2008. The change over time in QoL was then charted for each participant as well as average scores at each time point on each measure. Interviews were transcribed and narratives were developed to present the data gathered in the qualitative interview. In addition, the narratives of the participants' were coded for themes in order to describe the experiences of the participants in the unique study. The following research questions were addressed in the current study:

1. What is the trajectory of change in QoL for all the participants in the current study from the baseline, 12 and 24 months after transplant, 10-12 follow-up assessment conducted in 2008 and current 13-15 year follow-up assessment?

Because of the small sample size, no statistical analyses were performed. Instead, the averages for the participants on each measure were calculated and then

plotted to examine the changes over time. In addition, individual scores on each of the measures were plotted over time.

2. What are the individual experiences of the participants who participated in the double-blind sham controlled transplantation study and original QoL study?
3. Would the participants, who participated in original transplantation study, volunteer to participate in a future double-blind sham-controlled surgical trial?

Discussion of Overall Findings

In the current study, the first research question examined the trajectory of change in QoL (Emotional, Social and Physical functioning) and Optimism over the last 13-15 years in the participants in the fetal tissue transplantation surgery trial conducted by Freed et al. (2001). The average scores were first plotted on the three measures of Physical functioning: Activity of Daily Living at Worst Scale, Severity of Symptoms at Worst Scale and Free or Restricted Scale across the five time points including baseline, 12 and 24 months after the transplant surgery, 10-12 year follow-up assessment in 2008 and the current assessment. The results of the quantitative investigation showed that the means for the Activity of Daily Living Scale showed improved Physical functioning from baseline to the 24-month assessment and then a decline in Physical functioning between the 24-month assessment and the current assessment. In addition, the individual scores for each participant were plotted for the Activity of Daily Living Scale. The individual scores on the Activity of Daily Living Scale revealed that the majority of the participants demonstrated improvements between baseline and the 24-month assessment. In addition, the majority of the participants showed worsening physical functioning between the 24-month assessment and the current assessment.

The mean scores on the Severity of Symptoms Scale showed a similar pattern to the Activities of Daily Living Scale and there was an improvement in Physical functioning from the baseline assessment to the 24-month assessment followed by a decrease in Physical functioning between the 24-month assessment and the current assessment. The individual scores revealed that there was one participant that self-reported worsening physical functioning at the 12-month assessment followed by an improvement at the 10-12 year follow-up assessment in 2008. The majority of the participants demonstrated improvements in functioning between baseline and the 24-month assessment. All of the participants self-reported worsening functioning following the 24-month assessment. The qualitative interviews revealed that while several participants have undergone additional procedures (e.g., DBS), they continue to experience a decline in their physical functioning.

The mean scores for the Free or Restricted Scale showed an improvement between the baseline assessment and the 24-month assessment and decline in physical functioning between the 24-month and the current assessment. The individual scores on the Free or Restricted Scale showed that the majority of participants demonstrated an improvement in physical functioning between the 12-month and 24-month assessment. In addition, the majority of the participants showed a decline in how free or restricted they felt between the 24-month and current assessment. However, there was one outlier (i.e., participant 2) who self-reported an improvement in physical functioning between the 10-12 year follow-up assessment in 2008 and the current assessment. The qualitative data for participant 2 revealed that she had DBS surgery performed in 2005 or 2006, which may explain the improvements in her physical functioning.

The means of all the measures of Emotional Functioning (Center for Epidemiological Studies-Depression (CESD) Scale, Parkinson's Disease Stress Scale and Intrusiveness of Illness) were then compared over the five time points as well as the individual scores across all five time points. On the CESD, participants experienced a slight decrease in depressive symptomology between the 12 and 24-month assessment and then a gradual increase in depressive symptomology following the 24-month assessment. On the CESD, possible scores range from 0-60 with higher scores being more indicative of depressive symptomology (Radloff, 1977). The average score in the current assessment on the CESD Scale was 16.25 for the current assessment. It is important to note that higher scores do not indicate that an individual meets the clinical criteria for depression. In other words, a higher score on the CESD is indicative of more depressive symptoms. In reviewing the individual scores at the current assessment, two participants obtained scores of 9 and 10 and the other two participants received a score of 23. Overall, it is surprising that the level of depressive symptoms was not higher across time given the progressive nature of their illness and declining physical health.

The average scores were analyzed for the Parkinson Disease Stress Scale across the five time points, which revealed a gradual increase in stress from the 24-month assessment to the current assessment. Notably, there was a decrease in stress between the 12- and 24-month assessments. It was interesting that the stress level was higher at 12-months compared to the current assessment despite the increase following the 24-month assessment. The individual scores showed that an increase in stress for three participants at the 12-month assessment. In addition, the individual scores of the Parkinson Disease Stress Scale revealed that two participants showed an increase in stress following the 24-

month assessment, while one participant showed a decrease in stress between the 10-12 year follow-up assessment and the current assessment. The qualitative data allowed for insight into the high level of stress at the 12-month assessment. At the 12-month assessment, many participants indicated they felt abandoned by the researchers, which may explain the high level of stress.

The participants' level of Intrusiveness of Illness was assessed and there was a similar pattern with the other two measures of Emotional functioning. The level of Intrusiveness of Illness decreased between the 12 and 24-month assessments and then increased following the 24-month assessment. The individual scores on the Intrusiveness of Illness scale revealed that the majority of participants reported an increase in Intrusiveness of Illness between the 2008 and current assessment. Of note, there was a decrease in Intrusiveness of Illness for three participants between the 12-month and 24-month assessment. Overall, the measures of Emotional functioning showed a worsening in Emotional functioning (e.g., depression, stress and intrusiveness of illness) between 2008 and the current assessment. However, the degree to which their Emotional functioning declined is less than expected given the progression of the participants' PD. Several participants noted in the qualitative interviews that they continue to be active in their lives and contribute society in different ways such as volunteering. These factors may explain why the decline is less than what would be expected.

Social functioning was assessed using the Social Provision Scale and the average score for each time period was plotted to determine changes over the last 13-15 years. The results showed that at 24-months, the participants showed the highest degree of

perceived support. Following the 24-month assessment, there was a decline in the level of perceived support amongst the participants. Prior to the 24-month assessment, there was a decline in perceived social support at the 12-month assessment. The individual scores for the participants on the Social Provision Scale revealed a significant decline in perceived social support between the baseline and 12-month assessment. There were two participants who reported a decrease in perceived social support between the 10-12 year follow-up assessment in 2008 and the current assessment. Two participants showed a slight increase in social support.

The trajectory of change in Life Orientation Test Scale (Optimism) was examined over the five time points: baseline, 12 and 24-month assessments, 10-12 year follow-up conducted in 2008 and the current assessment. The average scores for each time point were computed. There was an increase in Optimism between baseline and the 12-month assessment. Then there was a decline between the 12-month assessment and 24-month assessment. There was an increase between the 24-assessment and the 2008 assessment. There was a decline between the 2008 assessment and the current assessment. A higher score is indicative of greater Optimism. Overall, the average scores of Optimism are higher than might be expected given the circumstances. The individual scores on the Life Orientation Test Scale over the five time points revealed that Optimism fluctuated between the baseline assessment and 24-month assessment. There were some participants who showed an increase in Optimism while others showed a decrease. Between the 24-month assessment and the current assessment, Optimism has remained relatively stable with the exception of one participant who exhibited a decline in Optimism and one participant who exhibited a slight increase in Optimism.

There is very limited research on the longitudinal impact on Quality of Life in individuals with Parkinson's over time. Thus, there is very little to compare the current quantitative findings to in the literature. There was one study conducted by Lezcano et al. (2004) that investigated the improvement in quality of life in individuals with Parkinson's disease after undergoing bilateral deep-brain stimulation in subthalamic nucleus. The study found improvement in Quality of Life in 62 percent of the participants following two years after surgery (Lezcano et al., 2004). However, the study did not extend beyond two years and thus, it is difficult to compare the current findings to the study conducted by Lezcano et al. (2004). More research needs to be conducted on the long-term impact of undergoing a surgery trial on Quality of Life in individuals with PD.

In addition, a separate analysis of the data, where the current four participants who completed the questionnaire were compared to the rest of the cohort at baseline and 12 months, revealed that the participants in the current assessment showed improvements on several measures over the 12 months (McRae et al. 2014). The rest of the cohort; however, showed a decline on several measures including optimism, perceived support, depression, intrusiveness and stress (McRae et al., 2014).

While the quantitative data demonstrated change in QoL over the five time points, the quantitative results does not provide any context or possible explanations for changes on the different dimensions of QoL. Qualitative interviews were conducted in order to gain insight into the individual lives of the participants who participated in the unique double-blind, sham controlled surgery trial. The responses of the participants were then coded for themes and narratives were created to present the findings of the

qualitative interviews. The qualitative data are rich with life experiences of these individuals and give a unique look into their individual lives during the last 13-15 years. The participants spoke candidly regarding the surgery trial and how their feelings have changed over the years as well as some of the most negative and positive aspects of participating in the surgery trial.

There were several themes that emerged during the qualitative interviews. The first theme that emerged was the feeling of being “dropped” or “abandoned” following the surgery trial. Several participants reported that while they received benefits from the surgery trial, their experiences were not validated due to the overall results of the study not being what was expected. Several participants also discussed the time and energy they dedicated to the study and how it was disappointing to feel “abandoned” at the end. For instance, one participant reported that she and her husband spent hours filming her current functioning in order to be accepted into the study and then spent numerous hours flying and traveling to participate in the surgery trial. The feeling of being “abandoned” may explain the high level of stress at the 12-month assessment, which was essentially the end of the study for her.

A second theme that emerged from the data was the feeling of contributing to a larger cause and feeling as though as their participation in the surgery trial was one step closer to finding a cure for PD. The individuals in the current study expressed a strong desire to participate in research and to help contribute to the body of knowledge on PD. It was that desire that appeared to help participants be resilient when they experienced difficulties during the trial. This was evident by the fact that many of them stated they

would participant in the surgery trial for a second time and the majority of them felt positive overall regarding their experiences in the surgery trial.

The third theme that emerged from the data was the fact that the participants in the current study demonstrated a strong desire to live their lives to the fullest despite coping with PD for a long time. One participant (current age is 74) stated that she recently began dating again and she makes herself walk to the sidewalk when her friends pull up in their car to pick her up. Several other participants continue to volunteer and several indicated they participate in activities in order to educate others on PD.

Connecting of the Quantitative and Qualitative Data

The qualitative and quantitative data allows a unique insight into the lives of the participants who participated in the fetal tissue surgery trial conducted by Freed et al. (2001) approximately 13-15 years ago. The qualitative data can provide possible alternative explanations for changes in QoL beyond the scope of the fetal tissue surgery trial. For instance, many of the participants have experienced loss of loved ones, changes in social support, changes in employment, additional procedures in order to alleviate symptoms of PD, and changes in how they view the trial and their current functioning.

In examining the level of depressive symptoms in the participants, it was interesting that several participants self-reported a minimal level of symptoms despite having a chronic and progressive illness and decline in physical functioning. The qualitative interviews revealed that many of the participants continue to be active in society and contribute to the world's knowledge regarding PD. Despite many of the participants not currently being employed, the majority of the participants are

intrinsically motivated to be active and contribute to society. In future studies, including individuals who are intrinsically motivated to contribute to society through their lives, their work or volunteer activities would most likely help participants be resilient in the face of adversity during surgery trials. These common factors amongst the group of participants in the current assessment may also explain that minimal decline in other scales such as the Intrusiveness of Illness Scale and Optimism Scale. These findings in the interview are also consistent with the findings that the four participants in the current assessment showed improvement on several measures between baseline and 12 months compared to the rest of the cohort that participated in the parent study conducted by Freed et al. (2001). These individuals appear to be functioning better than the rest of the cohort on several emotional and social measures, which may serve as a protector factor for them over a long period of time despite having a chronic and progressive illness.

Another interesting finding in the data gathered was the importance of social support in coping with the surgery trial. Many participants stated they relied heavily on their significant others or extended family members during the initial stages of the surgery trial. In addition, at the current assessment, many of the participants continue to have strong support despite a decrease since previous time points in the quantitative data. Several participants have had significant others pass away since the start of the surgery trial. However, many of them have gone on to find new partners or remarry. In addition, it was evident in the interviews where the significant others were present that they also had a desire to increase knowledge regarding PD and exhibited a large investment in research. In future studies, it will be pertinent to not only assess the participant's ability to go through a surgery trial, but also assess their family members'

willingness and ability to participate in the surgery trial. Furthermore, social support is also crucial for the period of time following the surgery trial, where participants may feel “abandoned.”

Overall, the participants in the current study are remarkable human beings who have contributed significantly to our body of knowledge regarding PD and they are an inspiration in their ability to overcome adversity and live very meaningful lives especially after living so many years with a chronic and debilitating illness. The data obtained in qualitative interviews gives the quantitative information a context and assists in understanding the quantitative data more holistically.

Recommendations for Future Research

Recommendations for future research include establishing a comparison group. As future surgery trials with participants with PD take place, it will be helpful to compare the participants in the current assessment with participants who receive “standard” treatment. The comparison will allow an investigation into similarities and difference amongst those who received the transplant and another group of participants. This research will assist in furthering our knowledge regarding why participants did well in this surgery trial and why other participants did not do well. The findings in the current surgery trial suggest that the motivation to contribute to research regarding PD was helpful in coping with adversity and difficulties during the transplant surgery trial. It would be interesting to examine if this was true in similar research trials with persons with PD. In addition, perceived social support worsened at the 12-month assessment, which may be related to the feeling of being abandoned. It would be interesting to compare this to similar trials to see if perceived social support shifted at the end of the

study. The investigation in our social support changes as the study comes to an end might help researchers establish more effective ways of terminating surgery trials with participants.

Another area for future research would be to assess changes in QoL from both a quantitative and qualitative perspective with a larger sample, which would allow for the quantitative data to be analyzed statistically to determine the changes in QoL are statistically significant. However, this may be difficult given the limited amount of research in this area.

Future research in this area is needed to further identify factors that help participants do well in surgery trials in order to possibly adjust or focus the recruitment of participants on those with certain characteristics. More in depth analysis of available data at all the time points may allow for the specific identification of factors that exist amongst the participants who did well in the overall study. Another area of future research would be to examine all the transcripts from the different time points to further assess changes in QoL amongst the participants. This would allow for further examination into how their perspectives have changed over the last 13-15 years. Furthermore, it would be interesting to compare the quantitative data using the original baseline with the shifted baseline in order to gain an additional perspective.

Conclusions

The objective in the current study was to examine changes in QoL over the last 13-15 years in participants who participated in the fetal tissue transplant surgery trial. The current study is unique in regards to the longitudinal perspective from both a quantitative and qualitative perspective with individuals who participated in a unique surgery trial approximately 13-15 years ago.

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Appendix A

Letter Sent to Participants with Questionnaire

Dear [name],

Thank you so much for participating in the 13-15 year follow-up to the original fetal tissue implant study for the treatment of Parkinson's Disease. It was such a pleasure to meet you during the phone interview. I have enjoyed learning about your experiences of participating in the double-blind, placebo surgery trial and the impact your participation has had on all the different aspects of your life as well as lives of your family members.

During the phone interview, Cyndy McRae and I discussed the questionnaire that would be sent in the mail. I apologize for the delay in getting the questionnaire to you. I recently got married and moved to a different state to start my pre-doctoral internship. I have enclosed the questionnaire for you to complete. The questionnaire is to help us gather additional information about you and your participation in the fetal implant surgery trial. Please complete all the questions on the questionnaire. Please return the questionnaire in the postage paid envelope.

Thank you so much for your time and willingness to share your experiences with Cyndy and I. Your contributions are incredibly beneficial to our knowledge regarding Parkinson's Disease and the treatments of Parkinson's Disease.

Please feel to email Cyndy McRae at Cynthia.McRae@du.edu or Jessica Kuhne at jessicakuhne@hotmail.com if you have any questions or concerns.

Again, thank you so much for your time. I have really enjoyed speaking with you and I look forward to receiving your completed questionnaires.

Sincerely,

Jessica Kuhne

Appendix B

Unified Parkinson's Disease Rating Scale (UPDRS) – Patient Version

How well can you perform these daily activities AT YOUR WORST?

(check one for each row)

	<u>Normal</u>	<u>Adequate</u>	<u>Limited</u>	<u>Need Help</u>	<u>Unable To Do</u>
Walking	_____	_____	_____	_____	_____
Dressing	_____	_____	_____	_____	_____
Cutting food	_____	_____	_____	_____	_____
Hygiene	_____	_____	_____	_____	_____
Getting up from chair	_____	_____	_____	_____	_____
Turning in bed	_____	_____	_____	_____	_____
Writing	_____	_____	_____	_____	_____
Talking	_____	_____	_____	_____	_____

Appendix C

Severity of Symptoms

Please rate the severity of each of the following problems AT YOUR WORST.

(check one for each row)

	<u>Normal</u>	<u>Mild</u>	<u>Moderate</u>	<u>Severe</u>	<u>Very Severe</u>
Tremor	_____	_____	_____	_____	_____
Swallowing	_____	_____	_____	_____	_____
Salivation	_____	_____	_____	_____	_____
Freezing when walking	_____	_____	_____	_____	_____
Falling	_____	_____	_____	_____	_____

Appendix D

Free or Restricted Scale

Overall, how free or restricted do you feel in doing what you want to do?
(check or circle the appropriate number)

1 2 3 4 5 6 7

I still do everything
I want to do

I can no longer do the
things I want to do

Appendix E

Parkinson's Disease Stress Scale

Below you will find a list of stressful situations that may occur because of your physical symptoms. Please check "Yes" or "No" to indicate whether or not an item causes you considerable stress, or clearly bothers you.

- | <u>Yes</u> | <u>No</u> | |
|------------|-----------|---|
| ___ | ___ | 1. Sometimes I am embarrassed in public because of my symptoms. |
| ___ | ___ | 2. I attract attention in public because of my symptoms. |
| ___ | ___ | 3. Friends and acquaintances do not take my symptoms seriously. |
| ___ | ___ | 4. I cannot make new friends because of my disease. |
| ___ | ___ | 5. I am anxious about the uncertainty of the future of my disease. |
| ___ | ___ | 6. I worry a great deal about my symptoms. |
| ___ | ___ | 7. I worry so much about my disease that all other things become unimportant. |
| ___ | ___ | 8. My physical condition tends to determine all that I think and do. |
| ___ | ___ | 9. I feel like a disabled person. |
| ___ | ___ | 10. I feel a sense of helplessness and anger because I cannot influence my disease. |
| ___ | ___ | 11. The lives of my loved ones have changed because of my disease. |
| ___ | ___ | 12. Even members of my family cannot really understand the difficulties I face. |
| ___ | ___ | 13. My partner and my family take too little notice of my disease. |
| ___ | ___ | 14. I am concerned that my family members restrict themselves too much because of my disease. |
| ___ | ___ | 15. Sometimes I think my partner may leave me because of my disease. |

Appendix E, continued

Parkinson's Disease Stress Scale

Below you will find a list of stressful situations that may occur because of your physical symptoms. Please check "Yes" or "No" to indicate whether or not an item causes you considerable stress, or clearly bothers you.

Yes No

- | | | |
|-------|-------|---|
| _____ | _____ | 16. Because of my disease I have had to give many personal responsibilities over to my partner or family members. |
| _____ | _____ | 17. Because of my disease I have had to give up my job. |
| _____ | _____ | 18. I have the impression that my disease is not being treated properly by my doctor. |
| _____ | _____ | 19. I often cannot ask all my questions when I am with the doctor. |

Appendix F

The Center for Epidemiologic Studies Depression Scale (CESD)

Below is a list of ways you might have felt during the past week. Please indicate how often you felt or acted the way each statement suggests by using the following scale:

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

	<u>Rarely</u>	<u>Some of the Time</u>	<u>Moderate Amount of Time</u>	<u>Most of the Time</u>
1. I was bothered by things that usually don't bother me.	_____	_____	_____	_____
2. I did not feel like eating; my appetite was poor.	_____	_____	_____	_____
3. I felt that I could not shake off the blues even with help from my family or friends.	_____	_____	_____	_____
4. I felt that I was just as good as other people.	_____	_____	_____	_____
5. I had trouble keeping my mind on what I was doing.	_____	_____	_____	_____
6. I felt depressed.	_____	_____	_____	_____
7. I felt that everything I did was an effort.	_____	_____	_____	_____
8. I felt hopeful about the future.	_____	_____	_____	_____
9. I thought my life had been a failure.	_____	_____	_____	_____
10. I felt fearful.	_____	_____	_____	_____
11. My sleep was restless.	_____	_____	_____	_____

Appendix F, continued

The Center for Epidemiologic Studies Scale (CESD)

Below is a list of ways you might have felt during the past week. Please indicate how often you felt or acted the way each statement suggests by using the following scale:

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

	<u>Rarely</u>	<u>Some of the Time</u>	<u>Moderate Amount of Time</u>	<u>Most of the Time</u>
12. I was happy.	_____	_____	_____	_____
13. I talked less than usual.	_____	_____	_____	_____
14. I felt lonely.	_____	_____	_____	_____
15. People were unfriendly.	_____	_____	_____	_____
16. I enjoyed life.	_____	_____	_____	_____
17. I had crying spells.	_____	_____	_____	_____
18. I felt sad.	_____	_____	_____	_____
19. I felt that people disliked me.	_____	_____	_____	_____
20. I could not get "going."	_____	_____	_____	_____

Appendix G

Intrusiveness of Illness Scale

Using the scale below, check or circle the number that expresses how much you feel your Parkinson's disease interferes with the following aspects of your life.

My illness interferes with my...

	<u>Very Little</u>							<u>A Great Deal</u>
Body Image	1	2	3	4	5	6	7	
Eating Habits	1	2	3	4	5	6	7	
Ability to Work	1	2	3	4	5	6	7	
Financial Security	1	2	3	4	5	6	7	
Preferred Recreation/Leisure	1	2	3	4	5	6	7	
Responsibility in the Family	1	2	3	4	5	6	7	
Family Relationships	1	2	3	4	5	6	7	
Marital Relationships	1	2	3	4	5	6	7	
Sexual Relationships	1	2	3	4	5	6	7	

Appendix G, continued

Intrusiveness of Illness Scale

Using the scale below, check or circle the number that expresses how much you feel your Parkinson's disease interferes with the following aspects of your life.

My illness interferes with my...

	<u>Very Little</u>				<u>A Great Deal</u>		
Personal Relationships with Friends	1	2	3	4	5	6	7
Plans for the Future	1	2	3	4	5	6	7
Freedom to Choose Time Alone	1	2	3	4	5	6	7
Ability to Express My Personality	1	2	3	4	5	6	7
Sense of Independence	1	2	3	4	5	6	7
Self-Esteem	1	2	3	4	5	6	7

Appendix H

Social Provisions Scale (SPS)

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 (check one answer for each item).

	<u>Strongly</u> <u>Disagree</u>	<u>Disagree</u>	<u>Agree</u>	<u>Strongly</u> <u>Agree</u>
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 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 rescue.	_____	_____	_____	_____
11. I have close relationships that provide me with a sense of emotional security and well-being.	_____	_____	_____	_____

Appendix H, continued

Social Provisions Scale (SPS)

	<u>Strongly Disagree</u>	<u>Disagree</u>	<u>Agree</u>	<u>Strongly Agree</u>
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.	_____	_____	_____	_____

Appendix I

Life Orientation Test (Optimism)

Indicate the extent to which you agree with each of the items below. Be as accurate and honest as you can. There are no right or wrong answers (check one for each item).

	<u>Strongly Agree</u>	<u>Agree</u>	<u>Neutral</u>	<u>Disagree</u>	<u>Strongly Disagree</u>
1. In uncertain times, I usually expect the best.	_____	_____	_____	_____	_____
2. It's easy for me to relax.	_____	_____	_____	_____	_____
3. If something can go wrong for me, it will.	_____	_____	_____	_____	_____
4. I always look on the bright side of things.	_____	_____	_____	_____	_____
5. I'm always optimistic about my future.	_____	_____	_____	_____	_____
6. I enjoy me friends a lot.	_____	_____	_____	_____	_____
7. It's important for me to keep busy.	_____	_____	_____	_____	_____
8. I hardly ever expect things to go my way.	_____	_____	_____	_____	_____
9. Things never work out the way I want them to.	_____	_____	_____	_____	_____
10. I don't get upset easily.	_____	_____	_____	_____	_____
11. I'm a believer in the idea that "every cloud has a silver lining."	_____	_____	_____	_____	_____
12. I rarely count on good things happening to me.	_____	_____	_____	_____	_____

Appendix J

Participant Demographics

INFORMATION ABOUT YOU

1. What is your current living situation? (check one)

- Living with a partner or family member
- Living with a friend or roommate
- Living alone
- Living in a residential setting

2. What is your current marital status? (check one)

- Never been married
- Married or living with partner
- Separated or divorced
- Widowed

3. If you are married to your partner, how long have you been married? _____

4. If you are married, is this your: (check one)

- first marriage
- second marriage
- third marriage

5. Do you have paid employment right now? (check one)

- No
- Yes, part-time
- Yes, full-time

6. Do you currently do any volunteer work?

- Yes
- No
- I used to, but no longer do

Appendix J, continued

Participant Demographics

7. If not currently employed, what is the main reason? (please check one box only)

- Temporarily laid off
- Retired by my own choice
- Forced to retire by my employer
- Retired on physician's advice
- Homemaker
- Poor health
- My job was too stressful, or physically demanding
- Other reason (specify): _____

8. Do you have any other chronic health problems (e.g., diabetes, heart condition, high blood pressure)? (check one)

- Yes If yes, please describe: _____
- No

Appendix K

Qualitative Interview

1. How do you feel when you reflect back on your experiences in participating in the fetal tissue surgery trial?
2. Have your feelings regarding your participation in the surgery trial changed over the last 13-15 years?
3. Would you volunteer to participate in a future study? Why or why not?
4. What was the most positive aspect of participating in the study?
5. What was the most negative aspect of participating in the study?
6. What advice would you give to future participants in terms of coping with participating in a surgery trial?