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Comorbid Symptom Treatment in Parkinson's Disease Using Neurofeedback

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COMORBID SYMPTOM TREATMENT IN PARKINSON'S DISEASE USING NEUROFEEDBACK

by

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DEDICATION

We should not judge people by the peak of their excellence
but by the distance they have traveled …

~ Henry Ward Beecher

I dedicate this effort to the memory of my sister, Christine McFarland Price and all those who face illness and injury with a ceaseless fighting spirit, who carry on with hope, dignity, and humor, and no matter their own hardships, who take time to encourage others along the way.

Acknowledgments

As parents, we take our kids along on our journeys, without them exactly knowing what they are getting into. I began my Ph.D. when my son, John, was 7 and he is now 12. Much of his life thus far has involved sacrifice so that I could finish this degree. He was always cheerful, helpful, entertaining, and understanding. The greatest cost was his, I am forever indebted, and I pledge to make it count.

My study participants were a constant source of inspiration and I am very grateful for their willingness to participate, for their faith in me, and for the intervention participants, their resolve to attend sessions during Michigan's polar vortex.

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Finally, I would like to thank my parents, Art and Maxine McFarland, who supported me from the very beginning in all my pursuits and who provided an exemplary model of compassion and commitment, which I hope this work reflects.

JoAnne McFarland O'Rourke

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JOANNE MCFARLAND O'ROURKE, PH.D.

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The purpose of this research was to determine the impact of neurofeedback (NFB) on Parkinson's symptoms that patients identify as priorities. First, a focus group of patients helped identify priority symptoms, then a pilot study tested protocols resulting from the focus group, and finally, an intervention study using a single subject design was conducted.

In the focus group, tremor and activity planning were identified as issues affecting every group member. The pilot study was conducted with three mid-stage Parkinson's patients, who received a sensory motor (SM) protocol to address tremor, a SM plus cognition protocol (SM+Cog) for tremor and planning (cognition), or no protocol. Theta and high beta were inhibited, while SMR/beta were rewarded in 12 sessions. The chief outcome measure was overall disability percentage using World Health Organization Disability Assessment Scale (WHODAS).

Participants who received either protocol reported less disability posttest and one-month followup. The person in the control group reported increased disability across measurements. Analysis of pre- and posttest quantitative electroencephalogram (QEEG) showed posttest reductions in delta, theta, and high beta, as well as increases in beta for participants in the intervention groups. QEEGs also demonstrated variation in brain disregulation, even among participants in the same disease stage.

Next, an intervention study was conducted with seven participants with varying levels of affectedness from the disease. Outcome measures were self-reported tremor using the Unified Parkinson's Disease Rating Scale (UPDRS) and cognition using the WHODAS; and a single protocol that included both the SM+Cog conditions was used in 20 sessions. Two baseline EEG measures were taken to document pre-intervention status, and a qualitative component was added to document changes that participants noticed.

For the three participants who were the furthest away from initial diagnosis, tremor scores improved at posttest, and EEG measures showed desired reductions in theta and high beta. Tremor improvement was sustained at follow-up for two of these three participants. Tremor improved per verbal report, but not quantitative score, for an additional 2 participants. Cognition scores improved at posttest for four of seven participants and for an additional participant at follow-up. Of the participants who reported improvement at posttest, cognition scores returned to pretest levels at the one-month follow-up for three participants and worsened for the fourth, but not back to pretest levels. Cognition improved per verbal report for one additional participant. Qualitative reports of improvement during the intervention included motor symptoms of tremor, walking and balance; cognitive symptoms of memory, focus, word-finding, and holding a train of thought in spite of tremor; and other symptoms of sleep, restless leg syndrome, anxiety/agitation, fatigue, and light-headedness upon standing.

Recommendations were: 1) including self-report and more precise, objective measures and 2) conducting studies to more accurately delineate changes based on pre-

intervention functioning and attempt to capture symptom delay. The study adds to the evidence that NFB can be a useful therapy in alleviating motor symptoms of Parkinson's, as well as cognitive issues, which are not typically addressed with medication.

Table of Contents

List of Tables

List of Figures

Chapter 1. Introduction

Significance

Parkinson Disease (PD) affects an estimated 1 million people in the U.S., is slowly progressive, and can affect a broad range of functioning for 20 or more years (Kowal, Dall, & Chakrabarti, Storm & Jain, 2013). In addition to the human cost of PD, economic costs of medical care and disability were estimated at $14.4 billion annually in 2010 (Parkinson Disease Foundation, 2016). Functional areas affected may include physical movement (tremor, balance), emotionality (mood, anxiety), and cognition (memory, planning) (Getz & Levin, 2017). Research has shown that motor symptoms decline more in the early stages of the disease than in the later stages (Maetzler, Liepelt, & Berg, 2009). Research has also shown that the later a person is diagnosed with PD, as well as the comorbid presence of dementia and psychosis, the more quickly the disease progresses. Recent studies have linked the use of anti-PD medications with dementia (Gray & Hanlon, 2018; Coupland, Hill, Dening, Morriss, Moore, & Hippisley-Cox, 2019), underscoring the importance of delaying medication initiation, reducing dosages to the extent possible, and exploring alternatives to drug therapy. Conclusions suggest "treatments to prevent or delay the progression of movement problems, psychosis and dementia in people with Parkinson's disease could help people live longer" (American Academy of Neurology, 2010).

Neurofeedback (NFB) is one option that has shown promise in slowing the progression of Parkinson Disease. The brain's electrical activity, shown as brainwaves on the electroencephalogram (EEG), was hypothesized by Hans Berger beginning in 1924 to change according to the functional state of the brain while awake, asleep, or in various

states of diseases or injury affecting the brain (Wiedemann, 1994; Gruzelier, 2014; Robbins, 2000).

NFB is a form of biofeedback that regulates the electrical activity of the brain. NFB is based on operant conditioning, or positive reinforcement of behavior (Strehl, 2014). Electrodes attached to the head monitor electrical currents produced in the brain, and subjects watch a computer game. The computer game provides auditory and visual "rewards" (more beeps, faster movement) when the brain is producing the desired signals and thus the individual "learns" to modify her or his brainwaves (Davelaar, 2018). This creates a reinforcement loop that over time helps normalize brain waves and improve functioning. That is, the brain responds to the positive feedback by producing more of the desired brain wave, thus regulating the brain and improving functioning (Marzbani, Marateb, & Mansourian, 2016). NFB is also referred to as *EEG biofeedback* and *neurotherapy*.

The slowly progressive nature of PD combined with the multiple facets of life affected by the disease, as well as the benefit of early diagnosis and treatment, create the need for finding ways to alleviate and delay symptoms for as long as possible, with the goal not only of improving the quality of life (QOL) but extending life.

Theoretical Basis

The purpose of NFB is to adjust brain wave frequencies that have become disregulated. Frequencies are divided into bands defined as delta, theta, alpha and beta. Delta (0-4 hertz) production increases when sleeping, theta (4-8 hertz) production is associated with the state between sleeping and waking or deep meditation, alpha (8-12 hertz) is associated with low activity while awake, and beta (12-36 hertz) is divided

between lower bands associated with being alert and higher bands associated with anxiety and anger. The optimal amplitude – or intensity – of each brain wave frequency (i.e., delta, theta, and so on) at each site of the brain is necessary for peak functioning. Studies have shown particular types of disregulation in PD and that NFB may help address this disregulation and thereby, improve functioning.

The study began with the central premise of determining how PD patients would prioritize treatment for symptoms that could be alleviated with NFB and then designing and testing NFB protocols to address those symptoms. This arose from my clinical experience treating PD patients using NFB. For example, when I asked one PD patient "what currently gets in the way of enjoying life?", she responded "drooling". Drooling is a common symptom of PD, interfering with social interactions and self-concept (Nóbrega, Rodriques, Torres, Scarpel, Neves, & Melo, 2008; Srivanitchapoom, Pandey, & Hallett, 2014). Though NFB can address balance, gait, tremor, and other symptoms one might commonly assume patients would prioritize for treatment, this patient prioritized a symptom that she felt was interfering with her ability to attend social events and interact with other people.

Three inter-related studies comprise the overall research. First, I conducted a focus group of PD patients to assess how they would prioritize symptoms for treatment. Next, I conducted a pilot study to test the NFB intervention and procedures based on the focus group discussion. Finally, I refined the NFB design based on the pilot study results and conducted a larger intervention study.

Focus Groups

The study began with a focus group in order to obtain firsthand information from PD sufferers about how they would prioritize treatment for PD and to document these priorities. The goal of the focus group was to help ensure that the final protocols for the NFB component of the project align with the issues PD patients find most challenging and to address their real life concerns. Focus groups are well suited for hypothesis testing and forming a final framework for a quantitative study. The focus group process allows participants to clarify their own thinking by comparing and contrasting their thoughts and experiences with other group members (Axinn & Pearce, 2006). The point of the focus group was not necessarily to quantify responses, nor to direct the conversation regarding symptoms, but rather to more deeply understand and delineate core concerns of PD sufferers that can be addressed by NFB.

Neurofeedback

A number of research studies have demonstrated the effectiveness of NFB for many different issues, including Attention Deficit / Hyperactivity Disorder (ADD/ADHD) (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009; Gevensleben, Holl, & Albrecht, Vogel, C., Schlamp, D., Kratz, O., ... & Heinrich, H., 2009; Steiner, Frenette, Rene, Brennan, & Perrin, 2014), migraine (Walker, 2011), depression (Raymond, Varney, Parkinson, & Gruzelier, 2005), and optimal performance (Gruzelier, 2014), among many other issues. A smaller number of studies have shown positive results on degenerative diseases, including PD (Azarpaikan, Torbati, & Sohrabi, 2014; Erickson-Davis, Anderson, Wielinski, Richter, &

Parashos, 2012; Esmail & Linden, 2014) and Alzheimer's Disease (Berman & Frederick, 2009).

Several definitions and concepts are important for understanding the mechanics of NFB. *Frequency* refers to the rate at which a brainwave repeats its cycle within one second. *Hertz* (Hz) refers to the number of cycles per second. All areas of the brain express all frequencies, or brain states. However, predominance of certain frequencies at each area of the brain is desirable. A person with a healthy brain will shift through the different frequencies depending on the task-at-hand. Most of the electrical activity from scalp EEG, or the signal that can be obtained by placing an electrode on the scalp, falls in the range of 1 to 50 Hz. *Amplitude* refers to the magnitude of the various frequencies. There is general agreement regarding the following frequencies for each state:

- *Delta* (0-4 Hz): Delta is a slow, sleep wave that is present to various degrees throughout normal brains when awake. It tends to be the highest in amplitude of all states, with a normal amplitude range in adults of 15-18 (Demos, 2005).
- *Theta* (4 to 8 Hz): Theta is slow waves that are often associated with drowsiness such as that between sleep and wakefulness, with a normal amplitude range in adults of 7-12 (Demos, 2005).
- *Alpha* (8 and 12 Hz): Alpha is characterized by calm, relaxed, wakeful, and meditative feelings, and is also associated with day dreaming and unfocused thought, with a normal amplitude range in adults of 7.5-10.5 (Demos, 2005).
- *Beta* (12-36 Hz): Beta is the most active brainwave and is associated with focus, attention, and concentration. It dominates the normal waking state and is subdivided into the following:

- *Sensory Motor Rhythm* (SMR, 12-15 Hz): SMR waves are relaxed, but alert; SMR is a specific type of low beta activity observed over the sensorimotor cortex, and the normal amplitude in adults is 4-6 (Demos, 2005).
- *Beta* or *Beta1* (15-18 Hz): Beta is associated with active attention, with a normal amplitude range in adults of 3.5-4.5 (Demos, 2005).
- *High beta* or *Beta2* (19-36 Hz): High beta is a hyper-alert band and is associated with tension, anger, anxiety, and agitation; it has a normal amplitude range in adults of 2.5-4 (Demos, 2005).

NFB uses single or multiple electrodes (or channels) placed via the standardized *10-20 International System*, which refers to the distances between adjacent electrodes – either 10% or 20% of the total front-back or left-right distance of the skull (American Electroencephalographic Society, 1994).

Basic underpinnings of NFB include that the brain becomes disregulated for various reasons or combinations of reasons (injury, disease, stress), and this disregulation impedes optimal functioning. Quantitative EEG (QEEG), also referred to as brain mapping, has shown the different parts of the brain and their respective functions. Moreover, previous studies have shown that imbalances for different issues (e.g., depression, anxiety, ADHD, migraine) relate to distinctly different parts of the brain. For some conditions, NFB involves single areas of the brain but more often, multiple areas are affected by disregulation (i.e., comorbid manifestations of the disregulation such as multiple sclerosis and depression or ALS and anxiety). NFB offers an appealing option for treatment because it is non-invasive, medication side effects are avoided, and NFB itself has few if any side effects (Soutar & Longo, 2011; Larsen, 2012).

NFB has proven effective even for very serious conditions. In a poignant example, Bolea (2010) demonstrated the efficacy of NFB in a case study of an inpatient paranoid schizophrenic who had been hospitalized 20 years. After approximately 18 months of NFB and 130 sessions, this patient was released to the community. The author documents the successful treatment of more than 70 inpatient schizophrenics, with long-term follow-up indicating the retention of improvements two years post-treatment. See Appendix A, brain map examples, for illustrations of different areas of the brain responsible for various cognitive, emotional, and sensory functioning.

Problem Statement

Previous studies have shown the multiple areas of life affected by PD, including depression, anxiety, and loss of cognitive function, in addition to the physical symptoms of the disease itself (Den Oudsten, Lucas-Carrasco, Green, & The WHOQOL-DIS Group, 2011; Schipper, Dauwerse, Hendrikx, Leedekerken & Abma, 2014). However, no previous research has addressed how PD patients would prioritize treatment. It stands to reason that tremor, balance and gait would be among the top priorities for patients. However, other issues may interfere more with activities of daily living (ADLs) and QOL than the issues more typically associated with the disease. These other issues may include factors that inhibit social interaction or create embarrassment (facial expression, soft voice, drooling, incontinence) or the ability to fully embrace life (depression, motivation/apathy).

Research has also shown a relationship between gait and cognition in PD patients. Ricciardi, Bloem, & Snijders, Daniele, Quaranta, Bentivoglio & Fasano (2014) conducted clinical and neurological assessments at rest and during walking on a control group (no PD) and three groups of PD patients: (1) without freezing of gait (2) with levodopa-responsive

freezing (3) with levodopa-resistant freezing. Levodopa is a drug used to increase dopamine in PD patients. Compared to PD patients without freezing, those with levodopa-resistant freezing performed worse when tested at rest on tests of phonological verbal fluency ($p = .01$). Walking was associated with a paradoxical improvement of phonological verbal fluency in patients with levodopa-resistant freezing ($p=.04$). This helps demonstrate the link between treatment of different PD symptoms and how an improvement or decline in one symptom may contribute to a similar result in a different symptom, thus underscoring the importance of considering comorbid symptomatology in PD treatment.

In regards to NFB research, most studies focus on a single protocol, attempting to demonstrate effectiveness on a chief area of concern (e.g., Azarpaikan, 2014). While the single protocol methodology may show effectiveness for the concern being addressed, for degenerative diseases, they do not take into account comorbid issues that typically accompany the disease. These issues can include depression, anxiety, and loss of cognitive function, in addition to the physical symptoms of the disease itself. These comorbid issues affect different parts of the brain and are addressed using distinctly different NFB protocols. A comprehensive, holistic approach to NFB with degenerative diseases is required to address comorbid issues that accompany these more serious conditions, and this research has received little attention to-date.

Research Questions

The study is designed in 3 segments to answer the following questions using both qualitative and quantitative analysis methods:

(1) Focus group

- How do Parkinson's Disease (PD) patients prioritize challenges resulting from PD?

(2) Pilot Study

- Can improvements to the QEEG be observed with mid-stage Parkinson patients with relatively few neurofeedback sessions?
- Is there an association between NFB treatment and tremor measures or overall disability scores?
- Can any changes in outcome measures be associated with specific NFB protocols?

(3) Intervention Study

- Do tremor scores improve following NFB treatment? How do tremor scores change 1-month post-treatment?
- Do cognition scores improve following NFB treatment? How do cognition scores change 1-month post-treatment?
- What qualitative changes, if any, do participants report during and 1 month following neurofeedback treatment?
- How does the EEG pattern at sites treating tremor and cognition change following NFB treatment? Are any changes sustained 1 month post-treatment?

Chapter 2. Literature Review

Parkinson's Disease

While common features of PD have been well-documented, the disease is noted for its heterogeneity (Foltynie, 2002), which creates challenges in standardizing treatment protocols at any stage of the disease. The most common initial symptoms of PD are motor symptoms such as tremor and bradykinesis (slowing of movement) (Uitti, Baba, Wszolek & Putzke, 2005). However, the assessment of non-motor symptoms is increasingly recognized as critical in treatment of PD, as they are often as problematic as motor symptoms and therefore, must be addressed as part of holistic treatment of the disease (Bayulkem & Lopez, 2011).

Standard treatment can be generally grouped into two categories, symptomatic and neuroprotective. There are currently no neuroprotective treatment measures for PD, thus all treatment is geared toward alleviating symptoms. PD is thought to occur due to too little dopamine in the brain (Dirkx, den Ouden, Aarts, Timmer, Bloem, Toni, & Helmich, 2017). Therefore, the chief medication intervention, carbidopa-levodopa (brand name Sinemet) is designed to boost dopamine. Levodopa changes to dopamine in the brain and carbidopa prevents the breakdown of levodopa, which allows more of the drug to enter the brain. A key issue is wearing-off while take the drug, i.e., a lack of sustained improvement between doses and a return of symptoms prior to the time for the next dose. Studies have shown that the treatment initiation soon after diagnosis leads to an improved QOL (Grosset, 2006). However, long-term use of levodopa medications is associated with wearing-off and an increase in dyskinesia (involuntary movement). Therefore, the timing of when to begin

medication treatment is debated. Other medications have also demonstrated benefit in early PD (Caslake, Macleod, Ives, Stowe & Counsell, 2009), however they are accompanied by significant side effects including serious impulse control issues in some patients (Antonini & Cilia, 2009). Recent research has linked anticholinergic drugs, which are used to treat movement disorders, including PD, with dementia in older adults (Coupland, Hill, Dening, Morriss, Moore, & Hippisley-Cox, 2019; Gray & Hanlon, 2018).

About half as many women as men are diagnosed with PD, and theories about gender differences include the role of estrogen, which is thought to be neuroprotective and assist in the production and retention of dopamine (Wooten, Currie, & Bovbjerg, Lee & Patrie, 2004). Studies have also shown that levodopa requirements in PD vary substantially and that women use less levodopa than men (Nyholm, Karlsson, Lundberg, & Askmark, 2010). Three types of tremor are distinguished: (1) resting (no movement) (2) postural (e.g., extending an arm or leg), and (3) action (e.g., picking up and holding a cup) (Dai, Zhang & Lueth, 2015).

Exercise has been shown to improve and even delay PD symptoms (Duchesne, 2015). One popular and well-researched exercise program is Big and Loud, in which participants are trained to make bigger motor movements (i.e., steps) and to speak more loudly (Bowers, 2016; Fox, Farley, Ramig, & McFarland, 2005). As the disease progresses from moderate to severe stages, deep brain stimulation implants are an alternative treatment, albeit with significant risks, including improvement in some symptoms but worsening in others (Angeli, Mencacci, Duran, Aviles-Olmos, Kefalopoulou, Candelario … & Foltynie, 2013). Due to the long course and slowly progressive nature of PD, treatment can last 20 years or longer. Parkinson's is typically not fatal and treatment is lifelong from the

time of diagnosis. Studies have shown that people who die with PD have a higher mean number of causes of death (comorbidities) than matched controls (Lethbridge, Johnston, & Turnbull, 2013).

Focus Group

In a qualitative study that included focus groups and interviews with people with PD and close family members, researchers documented the wide-ranging health issues resulting from PD. These issues involved physical health such as gait, balance, and fatigue; mental health, such as depression and anxiety; and cognition, such memory, word-finding, and attention. Group members discussed how these issues combine to affect virtually every aspect of life, including personal relationships (spouse, children, grandchildren); social functioning (extended family, friends); and work (career, volunteering). It becomes difficult for patients and practitioners to delineate comorbidities, including which symptoms take priority and which may be contributing to others (Schipper, Dauwerse, & Hendrikx, et al., 2014; Friedman, Brown, Comella, Garber, Krupp, Lou … & Taylor, 2006). The study concluded that to improve quality of life, multiple factors should be taken into consideration (Dauwerse, Hendrikx, & Schipper, 2014).

Neurofeedback Intervention

Neurofeedback evolved beginning in 1924 when Hans Berger, a Swiss psychiatrist, invented electroencephalography (EEG) and became the first to describe differential rhythms present in normal and abnormal brains (Wiedemann, 1994). Further development is largely credited to Joe Kamiya and Barry Sterman. In 1958, Kamiya, a psychologist teaching at the University of Chicago, showed that subjects could control their brainwaves,

which were previously thought to be involuntary (Kamiya, 1962; Kamiya, 1979). With sensors attached to the head, subjects first guessed whether they were producing alpha waves and received verbal feedback as to whether their guesses were correct or wrong. By the fourth day of training, subjects' guesses were 100% correct. Next, Kamiya showed that subjects could begin or stop producing alpha waves on cue, thus demonstrating the trainability of brainwaves and the behavior they govern.

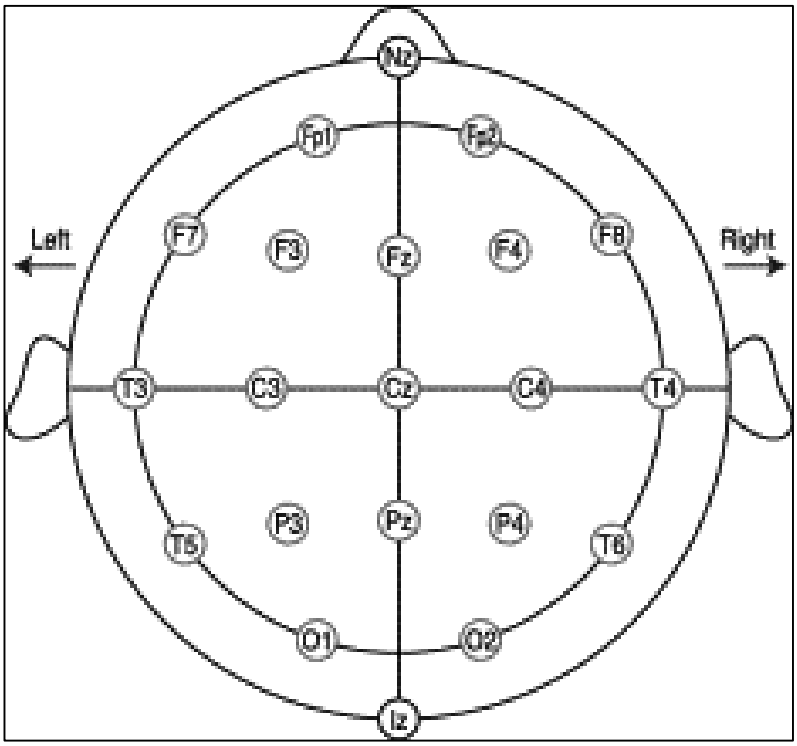
Sterman, now Professor Emeritus, Departments of Neurobiology and Biobehavioral Psychiatry, University of California at Los Angeles (UCLA) began experiments in the mid-1960's involving the operant conditioning of cats to increase their Sensory Motor Rhythm (SMR) across the Sensory Motor Cortex. Later, working with the same cats from his lab to help NASA test the effects of lunar landing fuel, he realized that the cats that received SMR training were more resilient – and even immune – to the effects of the fuel. This was the first demonstration that neurofeedback could positively affect a neurological disorder. As a result, NASA began SMR neurofeedback training for astronauts (Othmer, 2004).

Neurofeedback use and research grew substantially in the following decades. Brain mapping revealed more parts of the brain and their respective functions. Further, studies showed that imbalances for different issues relate to distinctly different parts of the brain, including depression (Cheon, Koo, & Choi, 2016), anxiety (Hammond, 2005), autism spectrum disorders (Thompson, Thompson, & Reid, 2010), and migraine (Walker, 2011). The National Institutes of Health (NIH) has funded 281 neurofeedback studies since 2005, with 45 of those projects currently active (NIH RePORT, 2019). The awards were funded across several different NIH Institutes and Centers, indicating a wide interest in the applications of neurofeedback. Neurofeedback offers an appealing option for treatment

because it is non-invasive and does not involve medication. Therefore, side effects from medication are avoided, and NFB itself has few side effects (Larson, 2012; Luctkar-Flude & Groll, 2015).

The brain map shown in Figure 1 indicates neurofeedback training sites based on the international 10-20 system (Okamoto, Dan, Sakamoto, Takeo, Shimizu, Kohno … & Dan, 2004; American Electroencephalographic Society, 1994). The nose is at the top of the screen. C3 and C4 are on the sensory motor strip and are associated with functions of the arms, hands, and legs, and this is where tremor is treated. FP1, on the left forehead, is associated with attention, focus, getting things done, and planning (Kaller, Rahm, Spreer, Weiller, & Unterrainer, 2011; Reid, Bzdok, Langner, Fox, Laird, Amunts … & Eickhoff 2016).

Figure 1. International 10-20 brain map.



Brain mapping, has shown that people with Parkinson's have excess slower brain waves but insufficient faster waves, a pattern associated with gait imbalance, compared to

controls (Han, Wang, Yi, & Che, 2013). Intervention studies have used NFB to demonstrate improvements in balance with early stage Parkinson's patients. For example, Azarpaikan, Torbati, & Sohrabi (2014) conducted a study with 16 early-stage PD patients, half of whom underwent NFB training to improve balance and gait, while the other half were assigned to a control group. The intervention group (IG) underwent eight 30-minute NFB sessions and controls received sham NFB. The researchers performed NFB at the O1-O2 (bilateral occipital area), hypothesizing that brainwave improvements in this area would increase attention and translate to better focus and improvement in gait and balance. The occipital lobes are "associated with visual processing, sequential memory functions, and arousal … [and] they have connections with the cerebellum … which affects balance and the amygdala" (Soutar & Longo, 2011). The goal of the intervention was to yield a positive effect on static and dynamic balance by increasing low beta waves (beta1, 15-18 Hz), which are associated with focus and "relaxed alertness", and decreasing theta waves (4-7 Hz), which can be associated with daydreaming and slow movement, at O1-O2.

The researchers found improvements in the IG for both static and dynamic balance ($p < .001$), as well as increases in the beta1 mean ($p < .001$) and decreases in theta mean ($p < .001$), leading the authors to conclude that NFB can improve balance for early stage PD patients with relatively few NFB sessions and demonstrating the efficacy of NFB at O1-O2 for PD patients.

In a case study, Ibric (2016) demonstrated the reduction of tremor for an elderly patient with a 24-year history of tremor using the C3-C4 (bilateral central brain) NFB protocol, as will be used in the present study. Erickson-Davis, Anderson, Wielinski, Richter, & Parashos (2012) conducted a study with PD patients to assess whether NFB could have a

positive effect on levodopa-induced dyskinesia (LID). Nine participants were randomized into intervention (NFB) and control (sham NFB) groups and underwent 24 NFB or sham sessions. NFB targeted SMR, similar to Azarpaikan, et al. (2014), but was conducted at C3-C4. Diaries kept by study subjects during the course of the training indicated decreases in motor fluctuations and dyskinesia severity for the intervention group compared to controls, though the improvements were not statistically significant. These differences were accompanied by significant changes in subjects' resting state cortical activity baseline to post-treatment. However, there were no statistically significant differences between the intervention and control groups in primary outcome measures assessing change in dyskinesia severity, nor in secondary outcome measures assessing change in clinical features of PD. It should be noted that this study had statistically significant differences between the intervention and control groups in terms of age and average number of hours per day (a) ON without dyskinesia and (b) with non-troublesome dyskinesia.

Cognitive function (planning, working memory, attention) is treated with NFB in the pre-frontal or frontal lobes of the brain. Research has demonstrated improvements in cognitive functioning with relatively few NFB sessions. For example, Hosseini, Pritchard-Berman, Sosa, Ceja & Kesler (2016) used NFB to train the pre-frontal cortex to test changes in cognitive functions. Ten healthy participants received NFB and 10 received sham NFB. Compared to the sham condition, participants who received NFB showed significantly improved executive function including measures of working memory after just four sessions (100 minutes) of training. Haddadi, Rostami, Moradi & Pouladi (2011) conducted frontal and temporal lobe NFB with children to address issues of learning and memory due to acquired brain injury following surgery for brain tumors. Pre- / post-intervention assessments showed significant

improvements in the Wechsler Intelligence Scale for Children (WISC) and the Child Behavior Checklist (CBCL). Subjects received 40 NFB sessions (45 minutes per session, 3 times per week). NFB targeted decreasing theta activity (4-7 Hz) and increasing beta (15-18 Hz). Wang and Hsieh (2013) conducted a randomized controlled study to test the effect of frontal lobe training, and any impact on cognitive performance, on older (age 61-72) versus younger (age 21-24) subjects. 32 participants were assigned to NFB or sham-NFB groups and underwent 12 training sessions over 4 weeks. Results showed significant improvement in orienting scores in the older neurofeedback training group. In addition, the training was found to improve working memory function in the older participants.

PD treatment typically includes medication protocols that address the physical aspects of the disease (e.g., tremor) but not necessarily other aspects, especially early in the diagnosis (Connolly & Lang, 2014). Few to no long-term side effects have been reported for neurofeedback training (Soutar and Longo, 2011; Niv, 2013). In a survey of NFB practitioners conducted by Cuthbert (2003), 4% reported any adverse reactions, most of which were mild and transient. In fact, a significant factor in the demand for NFB treatment is the avoidance of side effects, including those that are common with medication. Short-term side effects of NFB include fatigue, which typically subsides after a rest period. Treatment is painless.

In conclusion, treatment for PD is life-long from the time of diagnosis, often lasting 20 years or more. Standard treatment is focused on improving or delaying symptoms, and while medication is typically helpful for symptom alleviation, it also requires higher doses and becomes less effective as the disease progresses. Focus groups with PD patients have documented the wide-ranging symptoms of the disease, which are only partially addressed

by standard treatment. NFB has a long history of addressing serious mental and physical health problems, and recent NIH funding demonstrates interest in NFB for addressing a broad spectrum of issues. NFB has shown promise in improving symptoms affecting PD patients, including balance, gait, tremor, and motor fluctuations. Also, NFB to address cognitive function showed improvements in older people compared to younger people. However, no research to-date has examined the impact of using NFB to address comorbid symptom treatment in PD, nor the impact of NFB for cognitive symptoms of PD.

Chapter 3. Methods

Three interrelated studies comprise this research. I conducted a focus group to ascertain how PD patients would prioritize symptom treatment that could be improved with neurofeedback. Key issues identified by the focus group were tremor and planning. Next, I designed and carried out a pilot study to test NFB protocols aimed at improving tremor and planning, as well as broader quality of life outcome measures. Finally, I refined the design and measures and carried out an intervention study.

Focus Group

Participants

Study participants were recruited via flyers at two large, local neurology offices and the local area Parkinson Support Group. A sample script for the support group meeting is provided as Appendix B. Interested persons were instructed to telephone or email the investigator within a given period of time. Persons eligible to participate in the study were those (1) with a diagnosis of PD (2) without significant psychiatric comorbidity and (3) without a significant physical health problem other than PD. "Significant psychiatric comorbidity" was defined as diagnosed dementia, major depressive disorder (MDD), bipolar disorder, or personality disorder. "Significant physical health problem" was defined as any condition that may impede the person's ability to fully participate in the group (e.g., affecting the ability to speak).

Informed Consent (IC) Process. I telephoned each potential participant to inform her/him of the focus group date and to confirm continued interest. Upon arrival at the session, the informed consent document (provided as Appendix C) was provided to each

participant. I reviewed the consent form with each participant, answered questions, and requested a on the consent document.

Measures

A focus group discussion guide, provided as Appendix D, was designed to guide the focus group conversation. The purpose of the discussion was to elicit themes related to PD symptoms that could be improved with neurofeedback in order to help inform the pilot study. Participants were asked to delineate and prioritize issues they face on a regular basis, as well as those that occur less often, and the impact of changes in functioning related to PD. Core questions were as follows:

- My first question has to do with how Parkinson's has affected you lately. When you think about your ability to enjoy life over the past month, in terms of Parkinson's, what has gotten in the way?
- Now, thinking about the last 6 months to a year, when you think about your ability to enjoy life over this longer timeframe, in terms of Parkinson's, what are the issues that have gotten in the way?
- My next question is, how impactful are the changes to functioning that you described in the two first questions in terms of your ability to enjoy life?

Design

The focus group study was designed to elicit responses from PD patients about how they would prioritize symptoms for treatment that would improve quality of life. Discussion was not directed toward specific symptoms but rather allowed to evolve organically based on participants' experiences and responses.

Procedures

This focus group was held at local university with the necessary facilities and technology to hold and record the group, including video- and audio-recording. The building was handicap accessible and had space where people who accompanied focus group participants could wait. Upon arrival for the focus group, each person read and signed the informed consent document.

To mediate the potential for emotional upset due to talking about sensitive topics, a list of support activities for PD in the local area was provided to participants. Also, a break was built-in to the discussion schedule. An additional risk involves informational risk, or the risk of participants sharing information about each other. To help mitigate this, the informed consent document included explicit language about not sharing information learned through participating in the focus group, as well as using relationship references (e.g., "my son") and not names.

Each person was provided a pad of paper and pen. The focus group facilitator paused after asking each major question so that participants could gather their thoughts and write down responses if they wished.

Participants were given a $20 gift card each as a token of appreciation for participating in the group. Participants arranged their own travel to the group. Parking was free. The total time commitment for participating in the group was 3 hours.

Data Analysis

Data analysis consisted of thematic analysis of stories to described the group conversation and determine themes that emerged. Thematic analysis is a "method for identifying, analyzing and interpreting patterns of meaning ("themes") in qualitative data"

(Clarke & Braun, 2017, p. 297). The focus of the analysis was on both evaluating commonalities among participants and preserving the uniqueness of each of their stories and experiences. Data were transcribed and the video and audio recordings were used to verify the speakers and the conversation. The themes that emerged were generally categorized into issues that could be addressed by NFB (e.g., tremor, balance) and those that could not (e.g., relationships with family members). Of the issues that could be addressed by NFB, mentions of each issue were tallied and the conversation regarding the impact of these issues was evaluated (e.g., number of participants who indicated each issue was problematic, severity of impact on daily living). The issues that emerged from the focus group as affecting every group member were tremor and activity planning.

Neurofeedback Pilot Study

A NFB pilot study was designed to test protocols and procedures developed in response to focus group results. The most highly prioritized issues identified were (1) tremor and (2) planning. NFB protocols that address tremor are on the sensory motor strip across the brain midline (ear-to-ear) and specifically, C3 and C4. These sites are associated with function of the arms, hands, feet, and legs.

The frontal and pre-frontal sites of the brain relate to the temporal organization of behavior, speech, and reasoning and critically participate in working (short-term) memory, preparing for action, and control interference (Fuster, 2008). Planning can be addressed in the left hemisphere frontal and pre-frontal areas (FP1, F3, F7). FP1 was selected because it is associated with planning, as well as motivation and apathy, and apathy is common in PD (Pluck & Brown, 2002). Prefrontal sites have been demonstrated to help increase neuroplasticity and improve executive function (Gomes, Ducos, Gadelha, Ortiz, Van Deusen,

Akiba … & Dias, 2018) and a recent study by Aminov, Rogers, Johnstone, Middleton & Wilson (2017) showed that the severity of EEG dysregulation with a single electrode placement at FP1 following a first-ever stroke was moderately to highly correlated with 90-day post-stroke cognitive outcomes.

Participants

Recruitment. Study participants were recruited via flyers at local neurology offices and Parkinson support group meetings.

Eligibility. Eligibility criteria were established to ensure comparability between participants on broad areas of functioning and overall status. Criteria and the reasoning for each was as follows:

(1) With a diagnosis of Parkinson's Disease (a confirmed diagnosis was necessary to create homogeneity within the sample; patients report suspecting PD for some time prior to formal diagnosis);

(2) With mid-stage Parkinson's Disease (previous work has shown NFB benefit with early stage patients but no work has addressed later PD stages; also, mid-stage is the longest stage of the disease);

(3) Without psychiatric comorbidity (e.g., diagnosed dementia; comorbidities such as dementia or serious mental illness would indicate significant brain dysregulation, in addition to dysregulation present that is related to PD alone);

(4) Without previous neurofeedback treatment (previous NFB would create a disparity between participants in that any brain dysregulation present may have already been at least partly addressed by the previous treatment);

(5) Without a deep brain stimulation (DBS) implant (implants may interfere with the EEG signal and therefore, the NFB training).

Mid-stage PD is characterized as follows:

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

Participants were randomly assigned to the intervention groups, while the control person requested assignment based on convenience.

Measures

Participants were given the WHODAS prior to the NFB intervention, at the conclusion of the intervention, and 1-month post-intervention to assess changes pre- and post-intervention, as well as the degree to which any changes were sustained for a month after treatment ended. The WHODAS includes six domains, as follows: cognition (understanding and communicating), mobility (getting around), self-care, getting along with people, life activities, and participation in society. The understanding and communicating domain was used to assess changes in cognition and includes cognitive functions such as: concentrating on doing something for 10 minutes, remembering important things, analyzing and finding solutions to problems in day-to-day life, and learning a new task (e.g., how to get to a new place). The WHODAS is provided as Appendix E. An iPhone application, *Study My Tremor*, was used to assess any changes in tremor. Study My Tremor requires that a person hold the iPhone with an open palm, and the application then records tremor frequency (hertz), power (milliwatts), amplitude (millimeters), and synchronization (steepness of the main peak) (Study My Health, 2018).

QEEGs were done prior to treatment and at the end of treatment. As the intervention progressed, participants noticed changes in functioning (e.g., less freezing of gait) and volunteered these observations, which were documented.

Design

The pilot tested two NFB protocols, as will be described, and compared results of participants in the two protocol groups to each other and to a control (wait-listed) group. The wait-listed group received the intervention that worked best after the 1-month followup. The design is depicted in Table 1. Pilot study design representation.

Table 1. Pilot study design.

	Pretests	Intervention	Posttests	1 Month Followup	Intervention
R (Intervention A)	O	X_a	O	O	--
R (Intervention B)	O	X_b	O	O	--
N (Control)	O	--	O	O	$X_{a\ or\ b}$

R=Random assignment; N=Non-random assignment; O = Observation; X=Intervention

The pilot included C3 and C4 on the sensory motor strip to address tremor and FP1 on the left forehead to address planning, with one person assigned to each of 3 conditions (refer to Figure 1).

The sensory motor (SM) condition included C3 and C4 and 12 sessions of 20 minutes each, for a total of 4 hours of NFB. The second condition included C3 and C4, plus a cognition protocol (SM+Cog) at FP1 for a total of 8 hours of NFB. The length of each NFB session was selected based on previous research (e.g., Azarpaiken, et al., 2014). At C3-C4, the sensory motor rhythm (12-15 hertz) was reinforced and theta (4-7 hertz) and high beta (22-36 hertz) were inhibited. At FP1, beta (15-18 hertz) was reinforced and theta and high beta were inhibited. Participants received 1-2 sessions per day over 2-3 weeks. On days

with two sessions, a 2-hour or longer break was taken between sessions. The treatment groups were blinded to the protocols.

The third condition was a control, with no treatment. Table 2 summarizes the design. Brainmaster Avatar (Brainmaster, 2016) equipment was used to obtain the Quantitative Electroencephalograms (QEEGs). Neurofeedback was conducted using EEGer version 4.3 (EEGer, 2016).

Table 2. Pilot study protocol design.

Group	Description	Placement	Sessions	Minutes per Session	Total Hours Neurofeedback
1	Sensory Motor (SM)	C3-C4	12	20	4
2	SM+Cognition (SM+Cog)	C3-C4 + FP1-A2	12 12	20 20	8
3	--	Control		--	--

Procedures

Major steps in the intervention study included:

(1) Make group assignment;

(2) Conduct pre-test (WHODAS) and QEEG

(3) Carry out intervention

(4) Conduct post-test (WHODAS) and QEEG

(5) Conduct 1-month post-tests

(6) Conduct NFB for waitlisted group

(1) **Group assignment**. At the end of the recruitment period, equal number group assignments were made as follows (1) NFB protocol A (2) NFB protocol B and (3) wait-listed (control).

(2) **Pre-tests**. Upon arrival for the first session, each person was consented (see *Informed Consent Process*), QEEG data were acquired, and pre-tests were conducted using the following assessments:

- World Health Organization Disability Assessment Schedule (WHODAS), version 2.0 (written, self-administered; participant responds to questions on a 5-point scale about quality of life);
- Study My Tremor iPhone Application (assessments of tremor strength and frequency).

The investigator administered the WHODAS and the tremor assessment. The pre-tests were conducted at the clinical office of the investigator.

(3) **Intervention**. The intervention consisted of 12 NFB sessions over 3 weeks. Sessions were held at the clinical office of the investigator. For Intervention group A, the intervention (NFB) lasted 20 minutes per session, with approximately an additional 10 minutes of setup time. For Intervention group B, sessions lasted approximately 40 minutes with approximately an additional 20 minutes of setup time. NFB for the two protocols for group B (SM+Cog) was done sequentially (not simultaneously). Table 3 shows the NFB protocols.

Table 3. Pilot study NFB protocols.

Intervention		Location	Reward	Inhibit		Sessions	Minutes/ Session	Placement
A	B	Central	12-15	4-7	22-36	12	20	C3-C4
		Frontal	15-18	4-7	22-36	12	20	FP1-A2

(4) **Post-test.** Groups A and B completed the intervention within approximately the same (3 week) timeframe. Within one week of completing session 12 (the last NFB session), the physical and mental health assessments were repeated in the same

manner as the pretest (at the clinical office using the same rooms and process) with both intervention groups and controls, and the QEEG was repeated.

(5) **1 Month post-test.** 30 days post-intervention, the physical and mental health assessments were repeated in the same manner as the pretest (at the same office location using the same rooms and process).

(6) **NFB for wait-listed group.** After the 1-month post-test was completed, the wait-listed group was provided Intervention B (both protocols).

Outcome Measures

Outcomes were assessed based on changes to the QEEG and QOL measured by the World Health Organization Disability Assessment Scale (WHODAS) 2.0. The WHODAS 2.0 is a 36-item assessment of physical and mental health and disability that has been validated internationally (Garin, Ayuso-Mateos, & Almansa, et al., 2010; Üstün & World Health Organization, 2010). The assessment items are equally distributed across six domains and provide a standardized disability level (percentage) for each domain and overall. The six component domains are: Cognition (understanding and communicating); Mobility (moving and getting around); Self-care (hygiene, dressing, eating and staying alone); Getting along (interacting with other people); Life activities (domestic responsibilities, leisure, work and school); and participation (joining in community activities) (WHO, 2017).

The WHODAS has been used to describe functioning and disability with chronic conditions (Cieza, Bostan, Ayuso-Mateos, Oberhauser, Bickenbach, Raggi … & Chatterji, 2013), including Parkinson Disease (Chagas, Moriyama, Felício, Sosa, Bressan & Ferri, 2014; Raggi, Leonardi, Ajovalasit, Carella, Soliveri, Albanese & Romito, 2010). The WHODAS is highly correlated with the WHO Quality of Life (WHOQOL, $r = 0.68$), thus it is a

robust measure of QOL as well as specifically designed for those with disability (Ustün, Chatterji, Kostanjsek, Rehm, Kennedy, Epping-Jordan … & WHO/NIH Joint Project, 2010).

I also recorded anecdotal information that participants volunteered. Tremor measures were taken using a phone application; however, the measure proved to be inconsistent (e.g., back-to-back readings that were highly variable, differences in readings based on slight differences in how participants held the phone) and therefore, results are not included.

There were no monetary incentives or cost for participating in the study. Participants arranged their own transportation.

Data Analysis

The independent variable was group assignment, and the key dependent variable was the WHODAS overall disability score. WHODAS sub-scores were also examined. The EEG data acquired for the brain maps were analyzed using Neuroguide software (Applied Neuroscience, Inc., 2016). The resulting brain maps were manually reviewed for pre- and post-treatment differences for each of the 3 conditions. Verbatim statements from the qualitative data were summarized.

Neurofeedback Intervention Study

The intervention study utilized a single subject design (SSD) with multiple subjects, and included two EEG baseline measures prior to the intervention at the treatment sites taken one week apart. An ABA design was used, in which there was a single transition between baseline (A) and the intervention (B), followed by one month with no intervention, or a withdrawal of treatment (A) and a final measurement. Two baseline EEG

measures were done to help substantiate pre-intervention status. All study measures (WHODAS, UPDRS PQ, and EEG measures) were taken at pre-test, post-test and 1-month following post-test.

The SSD is well suited for studying the effect of a clinical intervention by providing flexibility in individual pre-intervention differences and response to the intervention (Zarate, 2015; Denman, Banajee & Hurley, 2015; Lobo, Moeyaert, Baraldi, & Babik, 2017). As established in the pilot study and documented in the literature (e.g., Rana, Siddiqui, & Yousuf, 2012), symptoms can vary significantly in Parkinson's. The SSD allows each participant to serve as her or his own control, thereby helping to eliminate skewing of results due to individual participant differences that are likely to be present in this type of sample. Based on results from earlier studies (e.g., Azarpaikan, et al.), effect can be established with relatively modest sample sizes.

Modifications to the intervention study based on results of the pilot were as follows:

- Use an SSD.
- Drop the mid-stage PD diagnosis requirement for participation.
- Add the patient questionnaire (PQ) from the Movement Disorder Society (MDS) Uniform Parkinson's Disease Rating Scale (UPDRS; International Parkinson and Movement Disorder Society, 2008) as an outcome measure to capture any changes in tremor (replacing the tremor app). The PQ is provided as Appendix F.
- Provide all participants with the same protocol (SM+Cog).
- Use the PQ tremor question to assess tremor changes and use the WHODAS cognition domain to assess cognitive changes (key dependent variables).

Participants

Participants were recruited using Facebook groups (people interested in PD), as well as from local PD support groups and neurologists, similar to the pilot study. Local PD exercise groups were also used for recruitment. Facebook recruitment generated interest and contacts regarding the study. However, most participants were recruited from local PD exercise classes. Unlike the pilot study, the criterion that participants be mid-stage PD was dropped. The pilot study showed variation in QEEG data, even for participants within the same disease stage, indicating that patients in the same disease stage can have substantially different types of brain disregulation. Studies have demonstrated that symptoms can vary widely within the same disease stage, making staging difficult (Rana, et al., 2012) and that currently used scales are skewed toward moderate and severe PD and do not adequately capture non-motor symptoms that impact staging (Getz & Levin, 2017). Further, studies have shown the lack of homogeneity within disease stage, as well as the lack of linearity of the progression of the disease, indicating the impact of risk and protective factors on functioning (Maetzler, Liepelt, & Berg, 2009).

Inclusion criteria for the intervention study were:

(1) With a diagnosis of Parkinson's Disease.

(2) Without psychiatric comorbidity (e.g., diagnosed dementia).

(3) Without previous neurofeedback treatment.

(4) Without a deep brain stimulation (DBS) implant.

Participants were continuously enrolled until a sufficient number of participants was achieved.

Measures

The key outcome measures (dependent variables) were the PQ tremor score and the WHODAS cognition disability percentage. The PQ was used to measure any changes in tremor (replacing the tremor app). Patient report for both motor and non-motor aspects of PD has been shown to be equal to or superior to clinical assessments. For example, in a study of 300 Parkinson's patients designed to assess differences in identification of wearing-off, Stacy, et al. (2005) showed that patients more frequently identified wearing-off using a patient questionnaire than clinicians using clinical assessment tools. Prashanth and Sumantra (2018) used the patient questionnaire portion of the MDS-UPDRS to develop prediction models using machine-learning techniques that could classify early PD from healthy normal patients, which resulted in greater than 95% accuracy.

A qualitative component to outcome measures, anecdotal information that participants reported (e.g., improvements in movement that may not be captured in the self-reported scales) was also added. This information was solicited at the beginning of each NFB session by asking "Have you noticed any changes"? and recording responses in a spreadsheet based on session number (i.e., reports for all participants at session 1 were recorded in the same column), with individual participants identified in rows, so that changes participants noticed at the same or similar point in the intervention could be compared. Session date for each participant was also recorded in order to track days between sessions and total length of the intervention for each participant. Participant reports were recorded verbatim or summarized with minimal editing. Any summaries were repeated back to participants to ensure accuracy.

Design

NFB was carried out for 20 minutes at each training site, as with the pilot study. However, for the intervention study, 20 sessions were conducted (instead of the 12 conducted for the pilot). The additional sessions were done in an attempt to more clearly establish any changes that may be attributable to the intervention. Also, all participants received the same intervention (SM+Cog). Differences in brain disregulation identified in the pilot and previous research (Getz & Levin, 2017) led to the conclusion that it would be difficult to specifically attribute changes in functioning to receiving the SM protocol versus the SM+Cog protocol. The cognition domain on the WHODAS was used to assess specific changes in cognition.

Tables 4 and 5 show the overall study design and intervention protocol design, respectively. Table 6 provides a summary of the specific NFB protocols. Each participant signed a consent form prior to the study (see Appendix G).

Table 4. Intervention study protocol design.

Description	Protocol	Sessions	NFB Minutes per Session	Total Hours of Neurofeedback
Sensory Motor (SM)	C3, C4	20	20	13.3
Cognition (Cog)	FP1	20	20	

Table 5. Intervention study NFB protocols.

Placement	**Reward**	**Inhibit**	
C4	12-15	4-7	22-36
C3, FP1	15-18	4-7	22-36

Procedures

Approval for the study was received from the Western Michigan University Institutional Review Board (IRB). Informed consent was obtained from all participants and extra care was taken to ensure participants understood (a) the overall protocol (b) risks and benefits, including that the protocol may not improve PD or other symptoms and (c) that they may withdraw from the study at any time. The intervention was conducted at my clinical office using the same methods and procedures established in the pilot. Brainmaster (version 1.5.9) neurofeedback equipment was used (Brainmaster, 2016).

Data Analysis

Intervention study data were examined utilizing descriptive and qualitative analysis methods. EEG recordings were taken at the 3 study timepoints (pretest, posttest, and followup), with 2 pretest measures taken 1-week apart. The average amplitude for each waveband included in the intervention for each training site (C3, C4, FP1) was graphed and compared across measurement time points.

Intervention effect based on level, trend, and variability of change to the tremor and cognition dependent variables was assessed, and this was done by comparing participants' individual results across measurement timepoints based on years since diagnosis and participant age. Qualitative information that participants reported while receiving the intervention and at the 1-month followup was examined based on when participants noticed changes (i.e., at what session number). Participant reports are provided verbatim or summarized. Attention was paid to the ABA design and specifically, whether any improvements reported between pre- and post-test were sustained at 1-month followup.

Chapter 4. Results

Focus Group

Five people participated in the focus group, 3 women and 2 men. Two overarching themes regarding PD symptoms were identified: (1) tremor and (2) planning. Discussion regarding tremor had to do with the extent to which tremor affected daily living. Types of tremor, such as Parkinson's tremor, essential tremor, rocking tremor (a form of Parkinson's tremor), and whole body tremors were discussed.

The second theme involved activity planning. For example, participants discussed how much planning was involved in any activity, whether it was getting up from a chair to walk down the hallway, planning to go to dinner with friends, or going to get the mail. Discussion around planning included any movement, such as where to place feet when standing up from a chair, whether to use a cane or a walker, as well as more global activity planning, such as arriving early in order to allow more time for getting into a building and which invitations to accept or decline based on the energy level required to get there and participate in the event. A summary of the narrative follows.

Participant 1 (P1) is retired from university teaching. He describes himself as quiet and reserved, and his wife is active in the local PD family support network. Participant 2 (P2) is a university faculty member and is still working part-time. Her first sign of PD was that her hand began to tremble when she was holding notes in class for her lecture. She is active in the local PD support community. An important goal for her is to decrease the stigma of PD. Participant 3 (P3) is retired from a university staff position. He was diagnosed 4 years earlier, after he noticed he was "walking funny." In hindsight, he realized

that PD symptoms for a few years prior to that. Participant 4 (P4) was diagnosed 2 years earlier and knew only about 8 months prior to her diagnosis that something was wrong. Specifically, she noticed she was in a "permanent brain fog" when she was traveling at Christmastime to visit a family member, and she had begun experiencing tremor. In the year previous to the focus group, she developed gait hesitation (freezing of gait). Participant 5 (P5) was diagnosed 2 years previously, and her diagnosis was a surprise to her. She had a family history of benign tremor, and she thought that her own tremor was like that of her relatives and nothing more. She was treating at a local pain clinic following back surgery, and one of the staff members asked if she had ever been evaluated for PD and referred her to a neurologist, where she was diagnosed. She is a retired computer systems specialist. A key issue for her has to do with anxiety that she feels anytime she is out of her home or away from her husband, who is her main support.

The key objective of the focus group was framed "to gain insight about how PD patients would prioritize symptoms of the disease in terms of how much they interfere with quality of life". Questions were designed to elicit responses about how PD might interfere with (1) day-to-day function on a regular basis (2) activities that occur routinely but not daily (e.g., church, social activities, holidays).

In response to the first question about symptoms that get in the way on a regular basis, P3 indicated "walking is the biggest problem". He used a cane until the previous summer but then his physical therapist told him he should be using a walker. While he feels "a whole lot better with a walker" and that he can go more places with it, it gets in the way when he has to turn around or do anything with his hands. He felt that he was "always turning around" and figuring out how to maneuver with his walker.

P4 indicated that “weather is a problem” for her because she still drives, lives in an apartment building, and parks her car in an uncovered parking area (lot). It is not a long walk for her to get to her car but brushing the snow off, with the risk of freezing of gait or gait hesitation at any point, “makes me think twice about how I have to want to get out and whether I can get a ride or whether there is enough time to clear off my car and things like that; I always have to plan ahead.”

P2 said that her biggest issue “has been an increase in anxiety” stemming from “the fact that I know I have to plan ahead; I have to plan how I dress because when its really cold, my whole body goes into tremors.” She indicated that the whole body tremors were the only issue that upsets her family, especially her husband and grandchildren. This anxiety has been the cause of her “almost slowing down” to the point of giving up teaching. However, student evaluations are still positive, and she feels she is still cognitively very able, so she has kept going. She contributed that she has never before encountered anything like the anxiety that “can take over your life” and be so “overpowering”. She stated that she has an anti-anxiety prescription and is learning “how to deal with it”. Another participant asked if it was like an anxiety attack, to which P2 said that it is not an attack but that she gets “real anxious” and then it triggers an issue she has with her stomach, similar to Crohn’s disease; she said that the issues with anxiety “go to her stomach”, which she has had problems with her whole life. She attempts to calm down by breathing and “concentrating on how to get it under control”. P2 also indicated that she has tremor predominantly with her right hand.

P1 said “at the moment, my biggest problem is the side effects from the medicine I took to help with what had been my biggest problem before I started taking the medicine”.

The current issue this participant was referring to had to do with the drowsiness side effect from a medication for tremor that was recently added to his protocol. He reported that he has Parkinson's tremor, which manifests for him as a rocking motion when he grasps anything. This makes it difficult, if not impossible, for example, to drink from a water bottle or coffee cup. In response, P2 said that she had the same issue with increased tremor when grasping but less predominantly than P1. P1 added that symptoms and side effects are varied and whichever one is causing the most difficulty at the time is the one on which you are focused. P5 added that this is something "you fight everyday".

P2 underscored the importance of the support of her husband, saying "knowing that I'm not alone with this and that I live with someone who is so understanding and helpful" is vital.

Participants noted how each person in the group had a different set of symptoms, some of which are common among them and some of which are not. P1 commented that it was "an advanced al la carte menu" and that whatever is "your worst symptom at this moment" gets all of your attention. All agreed that it was difficult to sort out symptoms that are related Parkinson's, medication side effects, and normal aging. Everything gets attributed to PD, when some symptoms are likely just normal aging. For example, P2 commented, "Does anyone else feel that it's sometimes confusing to know that it is Parkinson's or if its aging because at 75 I know that aging is setting in." P2 also commented that PD adds uncertainty to normal aging and planning, and planning becomes more complicated. For example, she had cataract surgery recently, and being without the use of one eye for a period of time was especially frightening for her. Therefore, she had to do extra thinking ahead about how she would manage. P3 added that he compares himself to

his brother who is 13 years older but does not have PD as a type of reality check regarding what might be normal aging and what could be contributed to PD. P5 underscored her anxiety anytime she is away from her husband: "we have been married 24 years; if something happens to him, I don't know what happens to me … the fear of being left alone here without him … you never know from one day to the next …".

Regarding fear, participants discussed the importance of self-talk and "talking your way through" whatever is of concern at the moment. Participants also noted that "Parkinson's is the good disease to get" because you "die *with* Parkinson's, not *from* it". P3 noted that "there is not a sonic boom when we walk by" but "we are still around" and that you have got to keep your sense of humor. P2 felt that her involvement in the PD support group and Delay the Disease meetings helps her maintain a sense of humor and counteract any depression that she begins to feel. P3 added that he and his wife will accomplish something that should have been quick (but was not) and say to each other "look how easy that was!" P4 noted that when she goes to the grocery store and gets back home, she feels that was a great accomplishment for one day because she got what she needed, did not fall, and interacted with people; she added that "you have to pat yourself on the back for the small things". P3 agreed that with PD, you can easily lose track of what you want to do each day but even if you did one thing, such as pay a bill, you can "look back and say I did something and the day wasn't a waste; I accomplished something no matter how small it is."

When thinking about less routine activities over the longer-term, and PD issues that get in the way of enjoying life, P2 indicated that she need to constantly remind herself that her balance was off. Prior to her diagnosis, she would get a step stool and climb onto the

counter to reach dishes on higher shelves. Her balance has improved significantly as a result of exercise; however, she reported, “the biggest hurdle [in the longer timeframe] was to understand that I had a balance problem”. P4 commented that getting caught in social situations, and the anxiety this can provoke, has been difficult for her. The onset of her anxiety can be sudden, making her “weepy and confused”. Two examples she cited were when she drove with her sister to visit friends and when they arrived, the friends ran out “screeching and yelling hello” and the dog started barking, and it was all overwhelming to her. Her second example involved attending live events at a local auditorium, which has led her to figure out that she needed to arrive early and avoid intermission in order to circumvent the crowd, but then she needs to use the restroom after intermission and when the event has resumed. She has a thought process that she has developed in order to calm herself. Both participants 2 and 4 had determined their preferred seating at this venue so that they can make a quick exit if needed. P4 added that anytime she travels where there might be an escalator or door that opens and closes quickly or that revolves, she has to think ahead and pad her time in order to get from point A to B on time. She said “you have to think about the layout of their living room and how you get from point A to point B and, I know a friend who is 95, and I can't go and see her anymore because I would have to park in the street and then go up the driveway and her driveway is so narrow that the grass grows right to the edge, and if were to get out, I would get out on grass and lumpy stuff and her railing is very wobbly. So there are a lot of things like that I have to think about so I have to plan to see her elsewhere.” She also said “it takes a lot of planning and preparation”. P2 added that “it slows you down socially” and “takes away some of the social freedoms we felt before”. She commented that before her diagnosis, she would not think

twice about flying but now she has to plan a great deal more than before her diagnosis before any type of travel. P1 commented that he always gets an aisle seat on a plane to make getting in and out of the seat easier.

In response to being asking to think about the impact of PD in the longer-term, P3 commented that there are "little things that I used to be able to do that I can't anymore; I used to roll the garbage can out to the street … but now I have got to get back and I have my walker [whereas before], I had my cane". He further noted that winter seems worse because of the weather. Prior to his diagnosis, he did all the grocery shopping, but he cannot do that anymore, and even to "run out and get milk" creates issues of figuring out how to manage picking up items while using his walker; therefore, he feels able to do less and less. P4 noted that she chooses grocery stores that are quiet and will carry groceries to the car for her. She also uses a backpack, which frees her hands to use her walking pole.

P4 noted that overtime, it is taxing to think about things like visiting a friend "because you have to think about the layout of their living room and how you get from one point to the next." She has a friend she can no longer visit at her home because the walk up to the house is uneven and the railing is not secure; therefore, she said "I have to plan to see her elsewhere". P5 added that she cannot even think about going out very much anymore. She and her husband used to be square dancers but they had to give that up; she commented, "you do lose a lot, you lose a life, you really do; I feel like I've lost my life ... its gone". P2 responded that the Delay the Disease class has helped her a lot, including that she has not had to increase her medication in 3.5 years.

P3 noted the paradoxical functioning with PD; for example, he needs a walker yet he can drive just fine. One way he has adapted is that he volunteers to do anything that

involves driving and picking up without needing to get out of the car, such as prescriptions and carryout.

P2 underscored the importance of exercise and Delay the Disease classes to her, to which P3 responded that it is hard for him to get out in the winter because of his walker and there is limited ability to exercise in his house. He has 3 walkers that he has "stationed" in different places so they are where he needs them for different activities. He added that it takes "pre-planning" to figure out which device one needs for different situations. He also commented that he has reading glasses in several locations so he does not have to walk to find a pair. Participants exchanged information about the car cane, which inserts into a car's door latch and provides a handle for assisting with exiting a car. P2 replied, "see how creative we have become with planning!"

P1 responded, "Figuring anything out is more challenging. Just feel like my brain has slowed down. It is hard to even put together a sentence. When you are trying to uh, like now when I am trying to think of the right words I want to say, just takes an effort. But on the other hand, another symptom that is common is apathy. It is almost like a saving grace because if it is impossible for you to do stuff that you know you are used to doing, it kind of helps to not care. You get depressed, you know. I have a train lying around too [P3 had commented that he did as well] and I was sure that I was going to spend my old age working and getting the cars working just right and getting the tracks .... you can't work with your hands and so.... it is a separate syndrome, a symptom, that you do not care, and it helps that you get to think of apathy as being beneficial. But the reality is that it is not all bad." P3 responded: "You get to the point where you say, 'good enough' … "I used to be able to do this really better but today I got it done and that is good enough."

Participants had varying levels of comfort in talking to family members and others about their PD. P5 commented that very few people, including family members know she has PD, while P2 discussed having a feeling of obligation to talk about her PD in order to decrease the stigma. P3 at times feels he needs to let people know, for example, while waiting in line, because he moves more slowly than others. He added that even strangers had been "very, very nice" and that he had met a lot of wonderful people through talking about his PD. This discussion led P3 to share that a big fear of his is getting halfway to where he is going and not being able to continue, or go to a performance or activity where he is seated and not being able to get back up. P4 indicated that PD makes her feel self-conscious, for example, if she holds up an elevator. P2 responded "I was given this disease and now I have to do something positive from it. I have to say it proudly, I'm not ashamed of it, I did not do anything to hurt anyone for it to happen to me, it just happened for a reason and that's the only way I can survive …" P5 responded that she felt she had lost part of her uniqueness and part of herself. P2 underscored the importance of helping people "combat … feeling less about themselves …". The focus group ended with P2 reiterating the importance of helping people "conquer those fears", to which P3 responded "you have to keep yourself going and [not let] the bad side take over."

Focus Group Summary

While participants touched on many aspects of PD, analysis revealed that, of all the issues discussed, the only 2 issues that all participants indicated were troublesome were tremor and the need to plan activity regardless of the simplicity or complexity involved, and this differed significantly than before the PD diagnosis. While everyone needs to plan (e.g., for travel), participants indicated the consciousness related to planning now required due to the PD diagnosis, as well as how essential contingency planning had become. The need to plan was not discussed as a symptom per se but rather as an added burden to every activity. Also, tremor and planning were among the top mentions of any topic, with tremor having 32 mentions and planning having 35 mentions. Tremor was important because it directly affected each participant, though it manifested differently for each person. In contrast, only 3 participants mentioned balance and gait, which are also highly associated with PD. Discussion about planning was woven throughout the focus group as a type of added burden to the disease, rather than a direct symptom of PD. Based on the results of the focus group, a pilot study was designed that included 2 protocols, one to attempt to address tremor and one to address planning. Table 6 summarizes issue mentions.

Table 6. Focus group issues and mentions by number of participants.

Themes	Number of mentions	Number of participants
COGNITION		
Plan, planning, figure, figure out, think ahead, think about, learn	32	5
PHYSICAL		
Tremor, shake, shaking	35	5
Walking, walk, mobility, balance, balance, gait, walker, cane, stand	41	3
Constipation	3	3
Pain	8	3
Sexual dysfunction	3	2
MENTAL HEALTH		
Depression, alone, feeling alone	12	3
Anxiety, fear, afraid, loss of control	46	3
OTHER		
Side effects	2	1
Changing symptoms	11	3
Family, social impact, social freedom	4	2

Neurofeedback Pilot Study

Participant characteristics are provided as Table 7. All participants were mid-stage Parkinson's, characterized by bilateral disease, and mild to moderate disability but physical independence (Goetz, Poewe, & Rascol, et al., 2004). People with previous NFB or deep brain stimulation implants were excluded, and participants had to have a confirmed PD diagnosis. Participants were 66-75, 2 female, and 1 male, and they had key issues of tremor, anxiety, and freezing, and they were 2-5 years since diagnosis. Participants were randomly assigned to the intervention groups, while the control person requested assignment based on convenience.

Table 7. Pilot study participant characteristics.

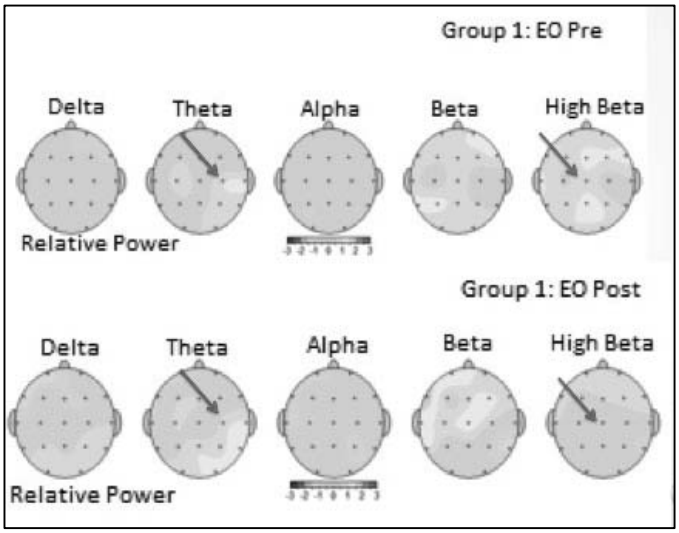
Group		Age	Gender	Key Issues	Employment	Years from Diagnosis
1	SM	75	F	Essential tremor, Anxiety	Part-time	3
2	SM+Cog	66	F	Freezing of Gait	No	2
3	Control	73	M	Rocking tremor	No	5

QEEG Results

SM Condition. Figure 2 shows the brain map results for the person who received the SM condition. The map shows Z scores to indicate the number of standard deviations between the mean amplitude of each band (delta, theta, and so on) compared to normative databases. Normal is shown as green, deficiency as shades of blue, and excess is shown progressively as yellow, orange and red. The color legend is provided below each set of maps. The top row shows the pre-test, while the bottom shows the post-test.

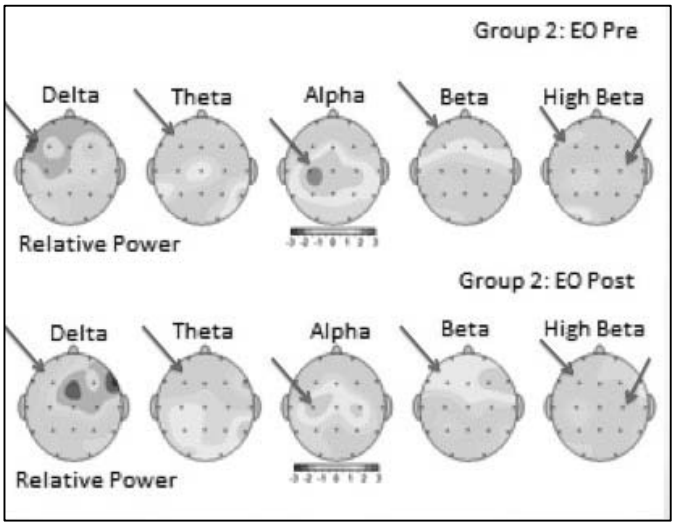
Theta and high beta were decreased (i.e., were more normalized) at post-test. Importantly, Z scores fell two standard deviations, from four to two**.**

Figure 2. SM condition pre/post QEEG results.



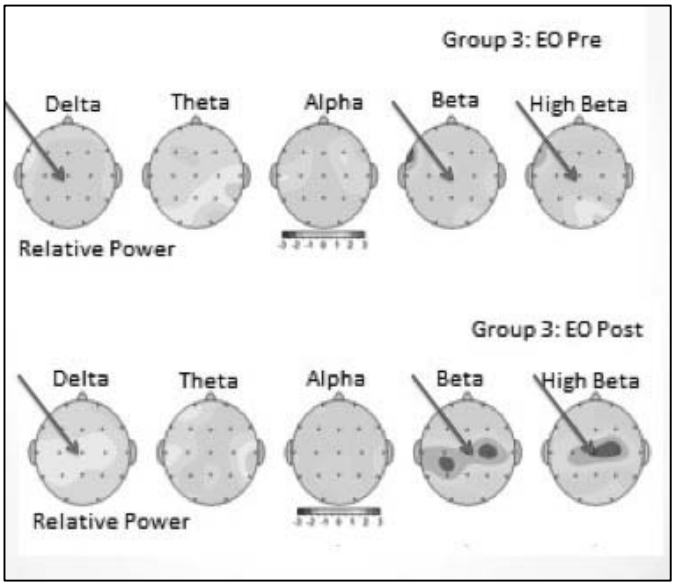
SM+Cog Condition. For the SM+Cog protocol, changes can be noted across the bands, with improvements in frontal delta and theta, central alpha, frontal beta, and frontal and central high beta, as shown in Figure 3.

Figure 3. SM+Cog condition pre/post QEEG results.



Control Condition. Results for the person in the control condition are provided as Figure 4. Here, we see some apparent declines at posttest in delta, beta, and high beta.

Figure 4. Control condition pre/post QEEG results.



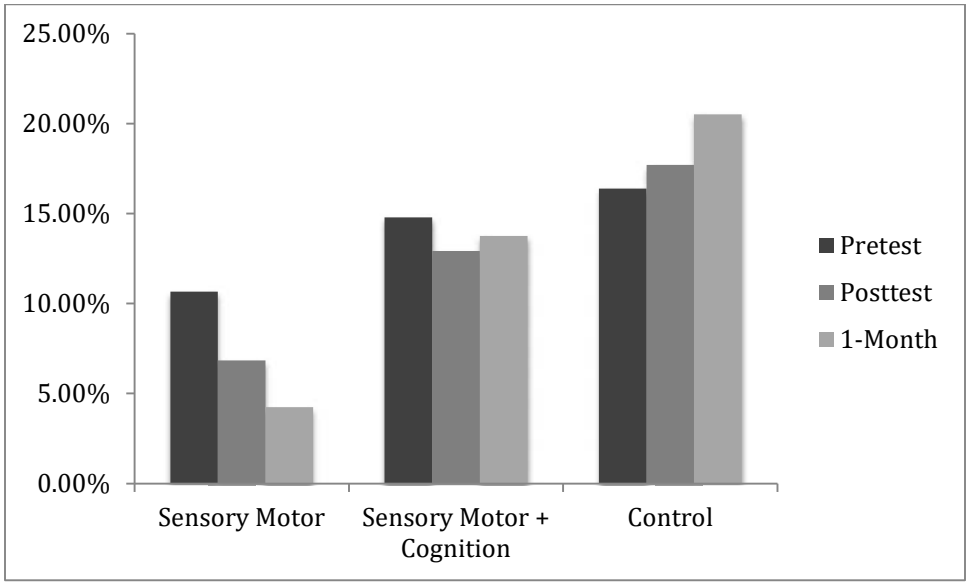
Disability Percentage and QOL Results

Between pre- and post-test, the overall percent disability decreased 36% (from 10.6% to 6.8%) for the person in the SM condition, which was the most for any group. This person also reported the least pre-intervention disability. This participant reported a further disability decrease of 38% at the 1-month followup (from 6.8 to 4.2%), for a total disability decrease of 60% between the pre-test and the 1-month followup.

The person in the SM+Cog condition reported a 12% disability decline (from 14.8 to 12.9%) between pre- and post-test, while at the 1-month followup, this participant reported a slight increase in disability to 13.7%, for an overall decrease of 7% between pre-test and followup.

The person who served as the control reported a slight disability increases between pre- and posttests and again between posttest and followup, for an overall increase of 25% (from 16.3% to 20.5%). These results are provided in Figure 5.

Figure 5. WHODAS overall disability percentages by treatment condition.



In terms of the 6 component WHODAS domains, participants reported the following results:

Cognition: The person in the SM condition reported a 50% disability decrease (from 8 to 4%), the person in the SM+Cog condition reported no problems at either time point, and the control person reported a 25% disability decrease (from 33 to 25%).

Mobility: The person in the SM+Cog group, who had freezing, showed a 10% decreased disability (from 45 to 40%). There were no changes in the other two groups.

Self care: There was no change in any group.

Getting along: The control person reported a 100% worsening (from 10 to 20%).

Life activities: The person in the SM condition reported a 33% decrease in disability (from 9 to 6%), while the SM+Cog person reported no change and the control group person reported a 33% worsening (from 9 to 12%).

Participation: People in both treatment conditions reported improvements on this domain, while the control person's score was unchanged. The person in the SM condition reported a 59% decreased disability (from 22 to 9%), while the person in the SM+Cog group reported a 12% decrease (from 25 to 22%).

Anecdotal Reports

In terms of anecdotal information: In sessions 1-4, the person in the SM condition reported improvement in tremor, even when she was hungry and tired. In sessions 5-8, she reported that her tremor, usually visible by evening was less at that time now, and in sessions 9-12, she reported that during a workout, she was better able to stand on 1 foot, and she noted a possible improvement in anxiety, and that her "neck pain has decreased, perhaps related to anxiety reduction".

For the person in the SM+Cog condition, reports in sessions 1-4 included improvements in freezing. During sessions 5-8, she reported improved sleep, further improvements in freezing, and an "overwhelming sense of calm" and "well-being". By the final sessions, she had walked from her car to front door twice without freezing, and she could not remember the last time she was able to do that. Also, when grocery shopping, she noted being extra focused, without extraneous thinking, and she returned home within 1 hour, which was a short time for her.

Table 8 provides a summary of findings. Note that decreases indicate improvement (less disability) and conversely, increases indicate declines (more disability).

Table 8. Pilot study summary by group assignment.

Group		Key Complaint	Map	Improvements (Anecdotal)	Specific Domains % Disability	Overall % Disability
1	SM	Tremor Anxiety	Improved central theta, high beta, SD	Tremor Balance Anxiety Neck pain	-50% cognition -33% life activities -59% participation	-53.8%
2	SM+Cog	Freezing	Improved frontal & central all bands, theta SD	Freezing Focus "Calm" Sleep	-10% mobility -12% participation	-7.6%
3	Control	Rocking tremor	Declines delta, beta, high beta (unclear)	--	-25% cognition +50% getting along +33% life activities	+28.4%

Research Questions

To answer the first research question, 12 NFB sessions appear to successfully demonstrate improvements with mid-stage Parkinson Disease. Positive changes were observed in QEEG maps, QOL measures, and anecdotal information. Based on anecdotal information, participants began to notice changes as early as session 4 of the intervention. For the second question, changes appear to be enough to improve QOL indicators, in general. The people receiving either intervention showed an improvement in overall QOL scores.

Related to the third question, the people in both intervention groups reported improvements both on the WHODAS and anecdotally. The greatest decrease in disability for either intervention group was participation in society, which includes issues such as "problems with barriers, living with dignity, and being emotionally affected by your health

condition." The person in the SM condition additionally reported improvements in cognition and life activities, and the person in the SM+Cog condition additionally reported an improvement in mobility, as well as improvement in cognition – the extra focus – though this was anecdotal.

In summary, results of the pilot study showed the following:

Brain Mapping

- Some consistency in type of brain disregulation across participants was noted; however, variations were also noted, though all participants were within the same disease stage (mid-stage).

Pilot Results Summary

- 12 sessions of NFB was sufficient to demonstrate changes in QOL using the WHODAS (main outcome measure).
- The tremor measure tested did not produce reliable results.
- The person who reported the least disability pre-intervention showed the most post-intervention improvement.
- People in both treatment groups indicated a notable improvement on the WHODAS participation in society domain.
- Participant observations were important in understanding the results.
- Sham NFB for the control group or additional baseline measures for all participants should be used to strengthen the validity of conclusions.

Neurofeedback Intervention Study

Final design modification based on the pilot study included the following:

- **Measures**: Use WHODAS cognition sub-measure to assess changes related to NFB training at FP1; use the Unified Parkinson's Disease Rating Scale (UPDRS) patient questionnaire item for tremor to assess any changes related to NFB training at C3 and C4; drop the tremor app measure. Add formal component for participants to report any changes they note that may not be captured in the written surveys.
- **Participants**: Based on brain map results and differences noted for participants within the same disease stage, drop the attempt to include only mid-stage Parkinson patients.
- **Design**: Use a single subject design and compare participants' post-intervention and followup scores to their own pretest scores. Improve comparability between pre-test and post-test results by adding two baseline EEG measures prior to the intervention. Simplify design and interpretation by including one protocol that includes both C3/C4 and FP1 in the intervention. Inclusion criteria were (1) Confirmed PD diagnosis (2) No DBS implant (3) No significant comorbidity and (4) no previous NFB treatment.

Participants

Participants completing the intervention were 6 males and 1 female and an average of 4.9 years since diagnosis (range 1.5 – 6.5). Their mean age was 67.8 (range 59-80), and they had key issues of unilateral tremor, soft voice, word-finding, brain fog, balance, sleep problems, drooling, dystonia, weakness, fatigue and short-term memory loss. One person worked full-time, 2 had regular volunteer or part-time work (< 5 hours per week), and all others did not work or regularly volunteer. Table 9 provides characteristics of the

intervention participants ordered according to years since diagnosis and then age. Participants A-G completed the intervention. Participant H began the study but dropped out after session 3 due to the time commitment required and conflicts with a number of other appointments he needed to schedule. The average number of days for completing the 20 NFB sessions was 33.4 (range 19-48).

Table 9. Intervention participant characteristics.

							Issue Report	
ID	Years since dx	Age	Sex	Surgical, other history	Work, volunteer hours per week	Walk aid	Tremor	Cognition
A	1.5	59	F	--	0	No	X	--
B	1.5	66	M	Ruptured colon, concussion	< 5	No	X	--
C	3.5	67	M	--	0	No	X	X
D	4.5	66	M	Knee replacement (1), face reconstruction due to injury, plate inserted, concussion	40	No	X	X
E	6.5	68	M	Pacemaker, ACL repair, diabetes	0	No	X	X
F	6.5	69	M	Knee replacement (2), prostate, Achilles tendon (2)	< 5	Yes	X	X
G	6.5	80	M	Parent had non-PD tremor	< 5	No	X	--
H	10	78	M	Heart attack, stints (twice), back surgery, adult-onset asthma	No	No	X	X

Qualitative Reports

Qualitative reports for each of the 7 participants are provided to document changes participants noticed during the intervention and demonstrate the variation in individual response.

Participant A had chief PD symptoms of fatigue and mild left-side tremor. She reported no significant personal or family history related to PD, and she is no longer working.

At Session (S) 11, this participant said that over the previous weekend her husband commented that she seemed to be doing better. She reported that she felt good over the weekend but it was hard to pinpoint anything specific. At S17 she reported that she had some better days regarding tremor since beginning the study but also some days that seemed worse.

Participant B reported key symptoms of communication problems and "coming across the wrong way" and right-side issues of leg tremor, arm stiffness, and hand tremor.

At S2 he reported that he felt more calm and had a slight headache after the previous session. At S3 he reported that he felt even more calm and that his tremor may be a little better. At S5 he said that he continues to feel increasingly calm. At S7 he said that he has noticed subtle changes that are hard to precisely identify; he feels better and continues to feel calm. At S10, he felt that his right-leg tremor was improved. At S15, he reported continued improvement in tremor and indicated that hand tremor has not been noticeable and that leg tremor is also improved. At S16, he said that he seems to be "thinking more clearly, the cobb webs are clearing out", and that he was "remembering things better". He had a slight headache after the previous session that went away without medication. At

S17, he indicated that at times, the hand and leg tremor are gone and that the remaining tremor is in his right foot. He had a very mild headache after the previous session that went away without medication. At S18 he said that he continues to "just feel better" and that he reduced his dose of Sinemet yesterday from 3 to 2 pills per day. At the 1-month followup session, he indicated that the tremor improvement and overall "feeling better" has continued to improve since the posttest, and that his wife has noticed the changes and agrees. His right leg and foot tremor have improved and at times, he has no tremor at all. He has noticed that if he gets anxious, his right leg tremor increases. He also indicated that he continues to remember things better.

Participant C reported symptoms of left-side hand tremor, drooling, short-term memory issues, and mild balance problems. At S2 and S6, he reported that he was mildly fatigued after his sessions. At S12 he said that his balance and light-headedness on standing may be improving. At the posttest session, he reported that he can now tap both hands without his left hand beginning to tremor. Previously when he did this, his left hand would start to tremor. He can also move his hands per an exercise class movement (waving his hands in the air in front of him) without his left hand beginning to tremor. At the 1-month followup he reported that his sense of smell has been better, though not consistently. His sense of taste may also have improved, but again it is not consistent. His tremor seems about the same, and mild right-side tremor has begun. His back pain has been worse, and he noted that exercise makes it worse but it is recommended that he continue his current exercise routine.

Participant D had chief PD symptoms that included bilateral tremor, soft voice and word-finding. He was hit in the face with a baseball in his 40's, which resulted in a serious

concussion and the need to have reconstructive surgery and an implant on one side of his face. He has also had knee replacement. His chief improvement involved improved cognitive ability, including word-finding, memory, and the ability to continue talking and holding his thoughts in spite of tremor.

At session 3 (S3), he noted that he was "possibly thinking more clearly." At S4, he said that he was "grasping words better" and at an earlier doctor's appointment that day, he could remember all of the questions he wanted to ask, which he could not previously do with confidence. At S8 he felt that word-finding continued to improve. At S10 he reported that a colleague told him he was "mentally sharper and remembering things better". At S12, his tremor seemed a little worse to him (bilateral instead of unilateral) the last couple of days but he was still able to hold a train of thought and keep talking in spite of tremor. Previously, increased tremor led to increased issues of word-finding, soft voice, and speech fluency.

At S13, he reported continued improvements in his "brain working better" and better ability to think and speak in spite of tremor. He had stopped taking propranolol, a drug used for tremor, prior to beginning the intervention due to having surgery, and at S15, he reported that he began taking the drug again.

At the followup session, he reported that he had some regression since finishing the intervention, including the improvements he had gained in the ability to continue speaking and holding his train of thought in spite of tremor. Also, he had fallen at the gym 2 weeks earlier when doing an exercise involving running backwards.

Participant E had chief symptoms of tremor, predominantly in his left hand, problems getting to sleep due to tremor, and mild balance issues. Sinemet and other

medications for tremor have been ineffective for him; therefore, he does not take them. He had ACL repair several years ago, and he is diabetic. He also received a pacemaker a few months prior to the intervention.

At S2, he reported that he was fatigued after the previous session. At S5, he reported that he had a particularly good day the previous day. At S7, he had gotten his driver's license back; he had not driven since he had the pacemaker because prior to the pacemaker, he had fainted a few times. At S18 he reported that his wife noted he seems more alert. At the followup appointment, he had not noticed further changes.

Participant F had chief PD symptoms of right-side tremor, especially in his hand, balance, and bilateral palsy. Significant medical history includes double knee replacement, Achilles tendon surgery (both sides) and prostate surgery.

At S2, he reported that the evening following S1 he noticed more details at home, had "better ability to focus" and that he had not realized what he was missing [in conversation at home]. At S3, he reported that he was "better able to think about how to get back on track" when he loses focus. At S4, he indicated that his brain fog was improving, and that it was normally like "looking through a mirror or window with soapy film on it and the film is beginning to clear away." At S6 he noted that he has felt fatigued following sessions. At S7, he said he has continued to feel fatigued following sessions but that he feels his focus is improved. At S8, he said he feels his balance may be a little worse but that he had forgotten to take his mid-day medication dose today and that he missed 2 doses the previous day, or took them late.

This participant continued to report fatigue at S9 and that he was going to bed about 2 hours earlier than usual. He takes 10 mg melatonin and a prescription sleep aid. He is

sleeping 9-10 hours instead of his previous 7-8. At S10, he reported that tremor seems stable. At S11 and S12, he noted that he has not attended his exercise class the last 2 weeks due to the weather and feels his balance is off due to this and that the extremely cold weather may be affecting his knee replacements and therefore, his balance.

He reported more fatigue than usual S13, as well as that he napped the previous day late in the day and still went to bed at 9:30 pm, and that the earlier improvements he noted in focus have held. At S17, he reported that he had gotten up in the middle of the night and when trying to get up, slid down the bed and onto the floor; his wife was able to help him get back up. At S18, pain had increased, making it more difficult to rise from a seated position. At S19, he was fatigued at the beginning of the session, which was later in the day than usual. At S20, he reported that he went to a concert at church the previous Sunday and a friend noted that he did not shake during the entire concert, which was significantly different than before the intervention. He is also feeling better today and slept from about 11-7; he feels that his stability and walking are better.

At the followup session, he reported that he feels his tremor is about the same as when he ended the intervention and that his "focus does seems better", though he is still forgetful, and he noted that it is hard to tell the difference between PD symptoms and normal aging.

Participant G had chief PD symptoms of bilateral hand tremor and occasional balance issues, with no significant personal or family history related to PD. He is diagnosed with restless leg syndrome (RLS). Notable improvements he mentioned during the intervention were less tremor and better sleep quality. At S2, he indicated that his tremor has been worse the last couple of weeks, including increased tremor at rest. After S1 (the

previous day), his tremor was notably better and he had no tremor at rest. At S3, he indicated that he usually wakes one or more times per night for an hour or more each time, and that the previous night (following S2), he "had a great night's sleep." In addition to continued improvements in sleep, at S4, he reported improvements in tremor, including while brushing his teeth, and that during the C3, C4 protocol that day (S4), his tremor at rest improved. At S6 he noted he had gained 3-4 pounds since beginning the intervention, which he indicated that he wanted to do. Over sessions 8-9, he noted continued improved sleep and that he was trying to take medications at the same time every day, which had been a challenge for him (e.g., leaving the house in the morning and forgetting to take his afternoon medications with him). He also noted at S8 that he no longer needed an afternoon nap.

At S10, he said that his wife noticed 2-3 days previously that he was not moving around as much at night due to restless leg syndrome (RLS). On the way to the session that day he began to get nervous due to the slippery roads but was quickly able to calm down. At S11, he felt that his tremor was improved at times but at other times, he felt it may be worse. However, at S12, he noted that on Sunday he was better able to hold a hymnal with one hand and with either hand, and that his sleep and RLS remain improved. At S13 he noted that he had an easier time drinking coffee that morning but a harder time brushing his teeth. At S14, he noted that he was up later than usual the night before so he thought he would be fatigued this morning, but he was not.

At S15, he reported that while doing a home project last night involving using an electric drill to do a ceiling repair, he could hold the drill over his head with one hand, and he was able to use a screwdriver with one hand and could get it into the screw head easily.

Previously, he would have needed to use both hands for either task. He could hold his coffee cup better this morning, his hand would tremble then stop, whereas previously, it would begin to tremble and not stop. He was up once the previous night for 1.5 hours. At S17, he reported some regression in tremor over the previous weekend and that he had not slept well the past 2 nights.

At S18, he reported overall improvements in tremor, with some regression, and that at the beginning of the intervention he had tremor "100% of the time" when brushing his teeth or drinking from a cup. He now has "at least 50% improvement". He can brush his teeth 50% of the time without tremor and can grasp the handle of a cup normally, whereas before he had learned a specific way to grasp a cup handle that helped with tremor, and he had to use 2 hands. Recently, he has been able to "grasp a cup normally" and use one hand. At S19, he reported that he combines a thought process with the new improvements in tremor in which he thinks "stop shaking" or "hold", which seems to help. At S20 he noted that he had one-third success for brushing his teeth the last few days, that holding a cup remains improved, and that his sleep the last few nights was "excellent".

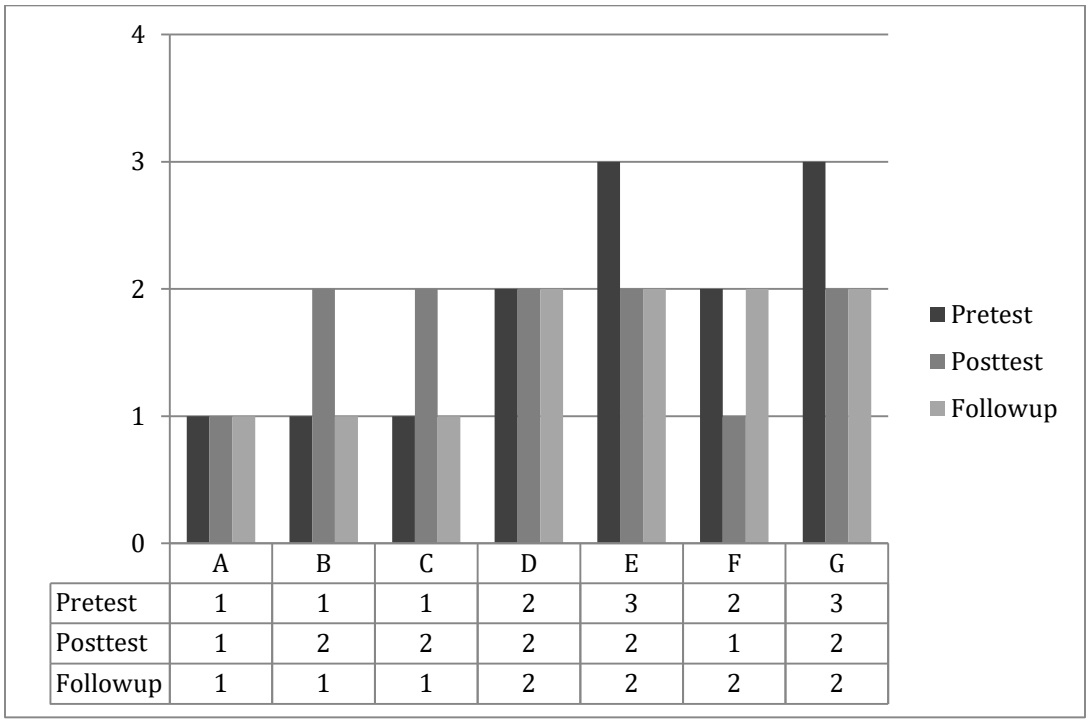
At the followup session, he said that tremor had remained improved until the previous week. He has been anxious due to an upcoming 3-week trip and believes the anxiety made tremor worse. Sleep and RLS remained improved. He is sleeping 7 – 7.5 hours per night without waking. He feels he no longer has RLS; he has leg pain but he no longer feels the need to move his legs, as he did prior to the intervention. He has noticed that toothbrushing is better at night than in the morning and holding a coffee cup has remained improved.

Tremor Scores

Tremor scores for each participant at pretest, posttest, and followup are shown in Figure 6. From the graph we see that all participants reported at least a minimum level of tremor at pretest, and that pretest tremor scores are generally worse as the years since diagnosis increase across participants A-G. We also observe that reported tremor scores worsened at posttest for participants B and C before returning to pretest levels at followup. Scores for participants A and D were unchanged across measurement timepoints. Improvement was noted at posttest for participants E, F, and G, all of whom were diagnosed 6.5 years prior to the intervention. This improvement held at followup for participants E and G but returned to pretest levels for participant F.

Magnitude of change. Any reported change in either direction was one point between measurement periods.

Figure 6. Tremor scores by participant.



	A	B	C	D	E	F	G
Pretest	1	1	1	2	3	2	3
Posttest	1	2	2	2	2	1	2
Followup	1	1	1	2	2	2	2

The EEG bands that were included in the protocols are provided in Table 10, along with their normalized (expected) amplitudes for adults and a brief description.

Table 10. Training bands, normalized amplitudes, and descriptions.

Band	Normalized amplitude	Description
Theta	8.0 - 12.0	Drowsy, state between awake and asleep, meditative
SMR	4.0 - 6.0	Relaxed but alert
Beta	3.5 - 4.5	Active attention
High beta	2.5 - 4.0	Hyper-alert, anxious, tense angry, agitated

EEG Results at C3 and C4

The following bands were down-trained at the training sites C3 and C4, which were treated to attempt to improve tremor: theta (4-7 hertz) and high beta (22-36 hertz). SMR (12-15 hertz) was up-trained at C4, while Beta (15-18 hertz) was up-trained at C3.

The EEG results show different patterns for participants based on reported quantitative scores, as shown in the graphs below. Amplitudes are on the Y axis and each measurement period is on the X axis. Because theta and high beta were down-trained, we expect those lines to decline at posttest, and because SMR/beta were uptrained, we expect that line to increase at posttest.

Figure 7 shows the C3 EEG for those who reported an improved quantitative tremor score at posttest, which includes participants E, F, and G, all of whom were diagnosed 6.5 years prior to the intervention. The data show desirable declines in theta and high beta amplitudes at posttest, but also a modest undesirable decrease in beta. We also observe that high beta and beta lines are in reverse order, with a larger amplitude of high beta than beta, and we see a trend in theta toward baseline at the followup.

Figure 7. C3 EEG amplitude, tremor score improved at posttest.

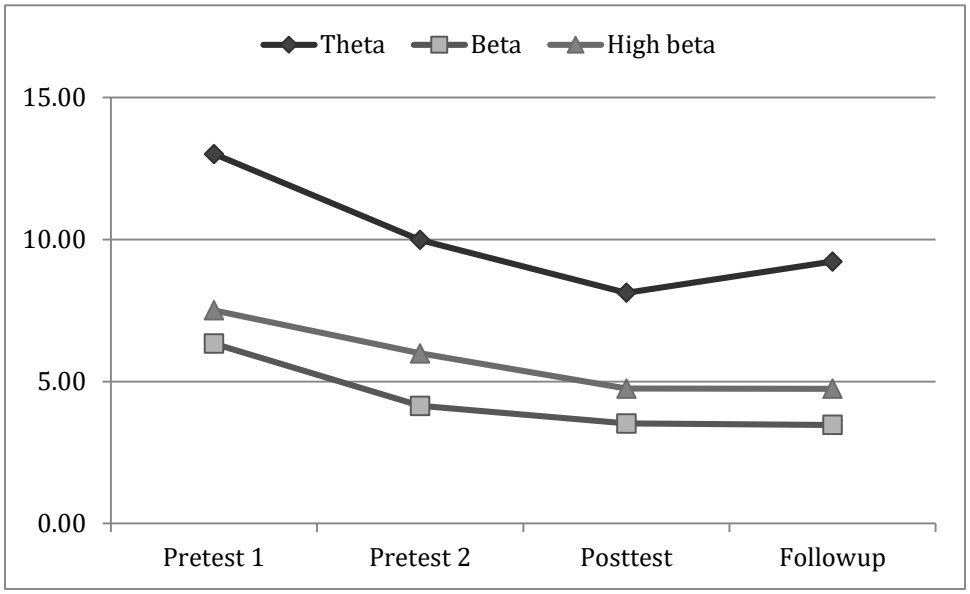


Figure 8 shows results for the 2 participants (B and C) who had verbal reports of tremor improvement but not an improved quantitative score, Here, we see that high beta is especially elevated and has the largest amplitude of any band but that high beta declines at followup.

Figure 8. C3 EEG amplitude, tremor improved per verbal report.

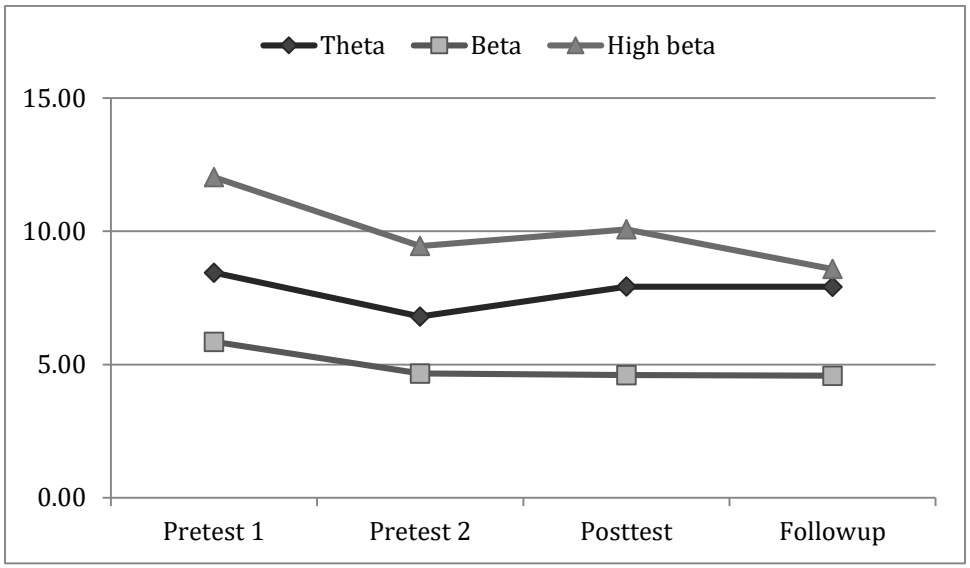
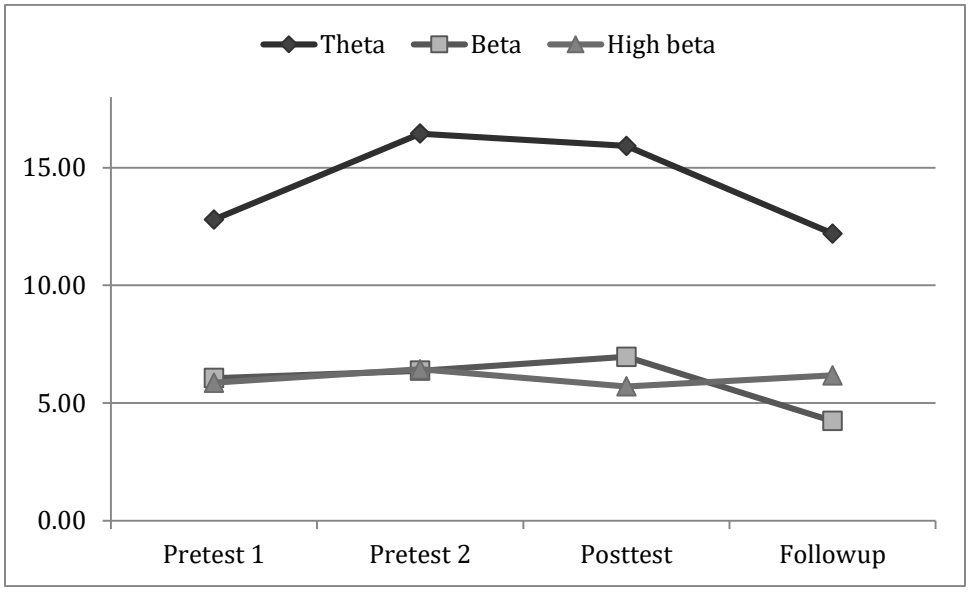


Figure 9 shows participants A and D, who reported no tremor change across measurements and had no verbal report of change. We see from this graph that these participants showed elevated theta compared to other groups and that bands were generally stable across measurements, except for the decline in theta at followup.

Figure 9. C3 EEG amplitude, no tremor change.



A similar pattern was observed with the EEG results for C4, shown in graphs 10-12. Graph 10 includes participants E, F and G; Graph 11 includes participants B and C, and Graph 12 includes participants A and D.

Figure 10. C4 EEG amplitude, tremor score improved at posttest.

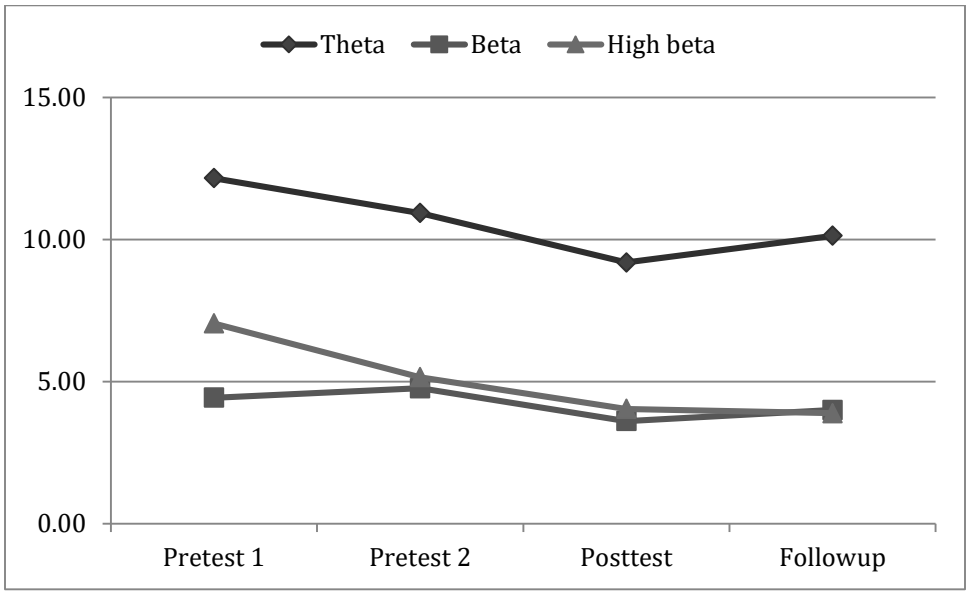


Figure 11. C4 EEG amplitude, tremor improved per verbal report.

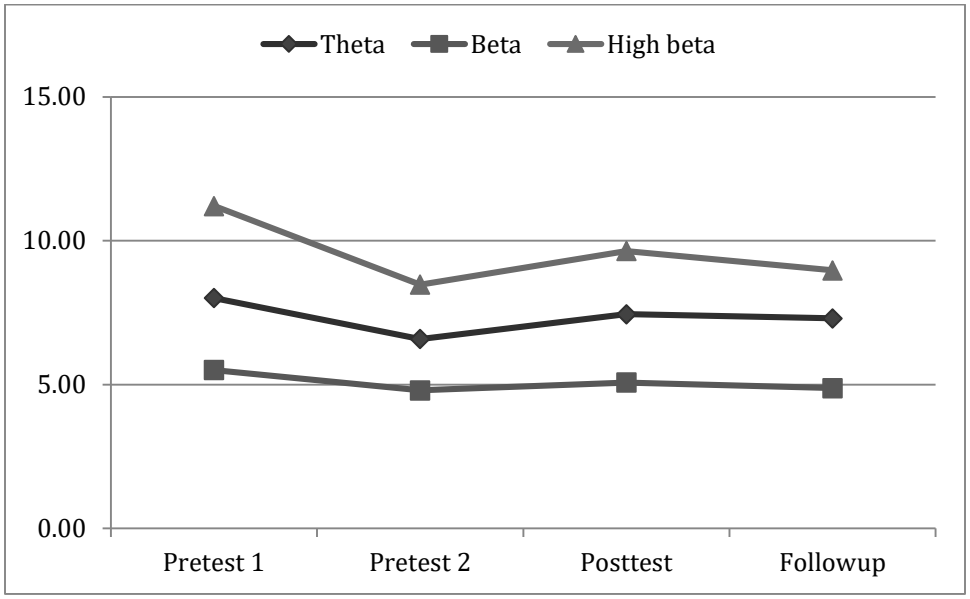
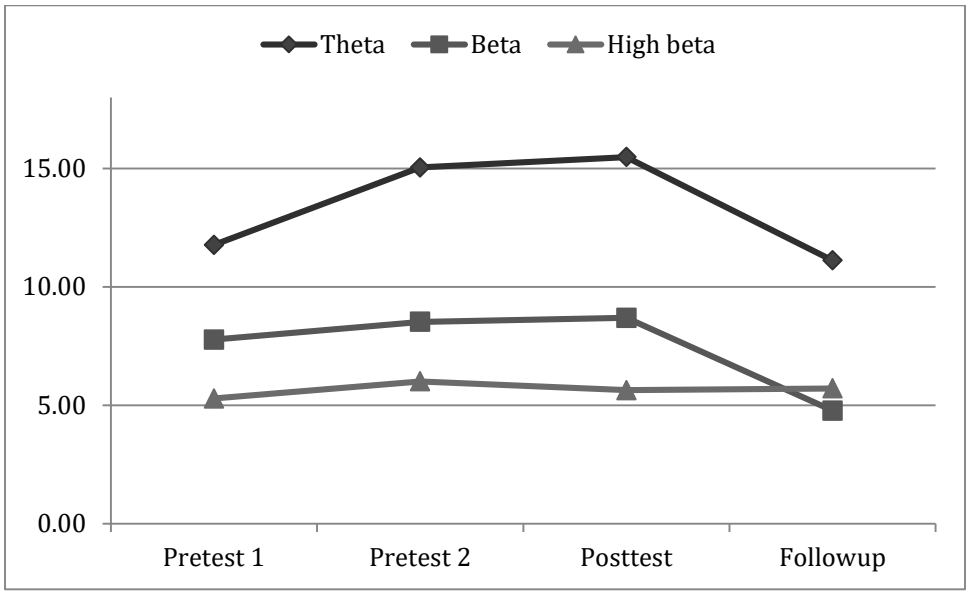


Figure 12. C4 EEG amplitudes, no tremor change.

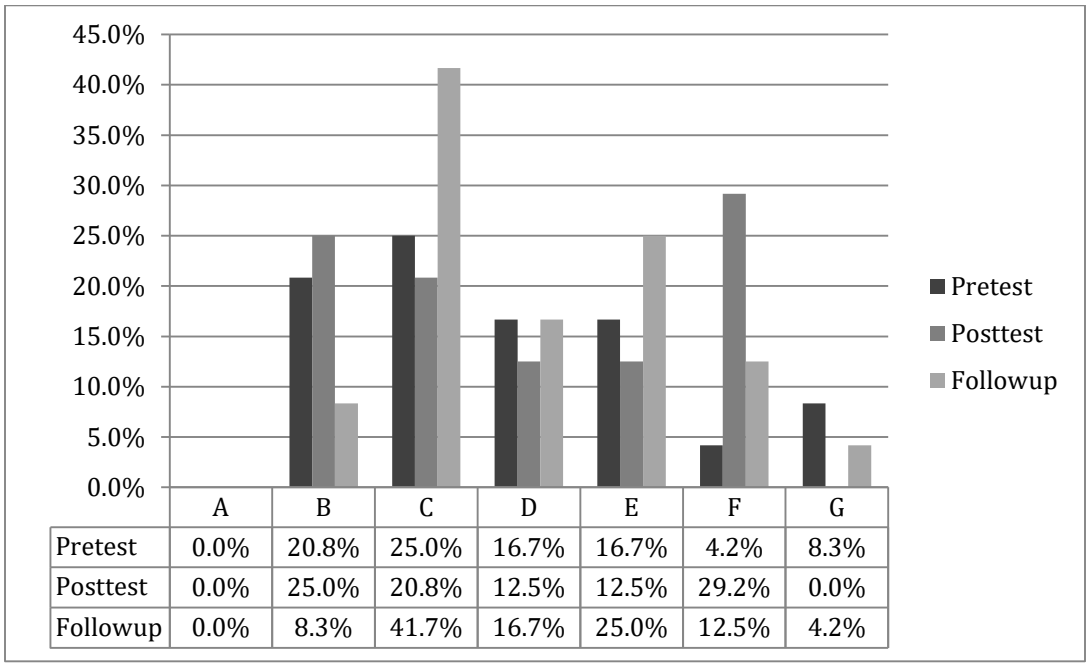


Cognition Scores

Figure 13 shows cognition scores (percent disability) at pretest, posttest, and followup by participant. The range of disability percentage was 0-25% at pretest. Participants C, D, E, and G reported improvements at posttest, with decreased effect (i.e., increased disability) reported at followup. Participant A reported zero disability at all 3 timepoints, participant B reported an initial increase at posttest, with a decrease (improvement) between the pretest and followup scores, and participant F reported increases from pretest at both posttest and followup.

Magnitude of change. Score decreases for the group reporting improvement at posttest were 4.2-8.3%, while the improvement for participant B between pretest and followup was 12.5% and the decline between pretest and followup for participant F was 8.3%.

Figure 13. Cognition scores by participant.

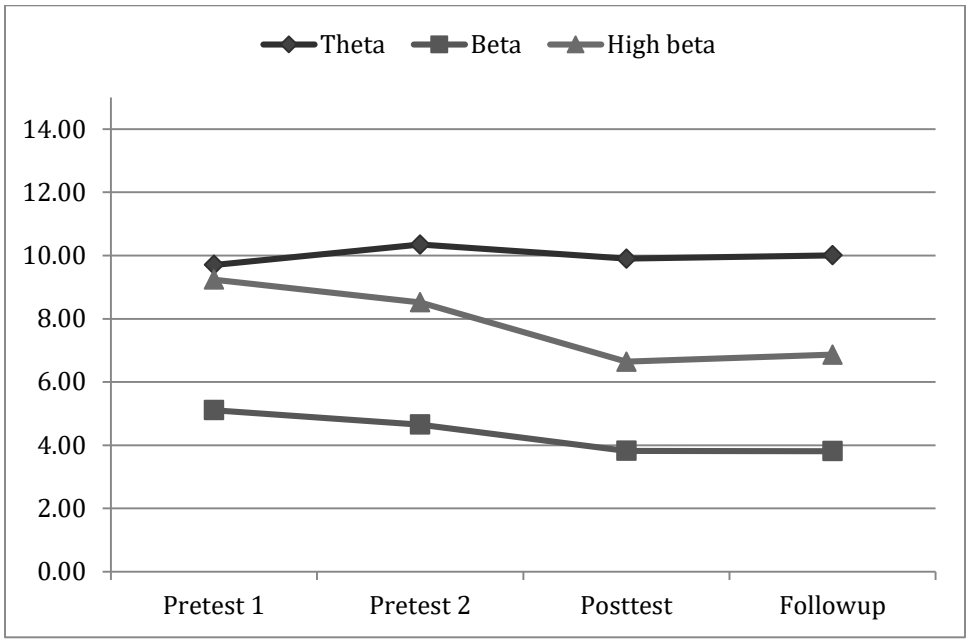


	A	B	C	D	E	F	G
Pretest	0.0%	20.8%	25.0%	16.7%	16.7%	4.2%	8.3%
Posttest	0.0%	25.0%	20.8%	12.5%	12.5%	29.2%	0.0%
Followup	0.0%	8.3%	41.7%	16.7%	25.0%	12.5%	4.2%

EEG Results at FP1

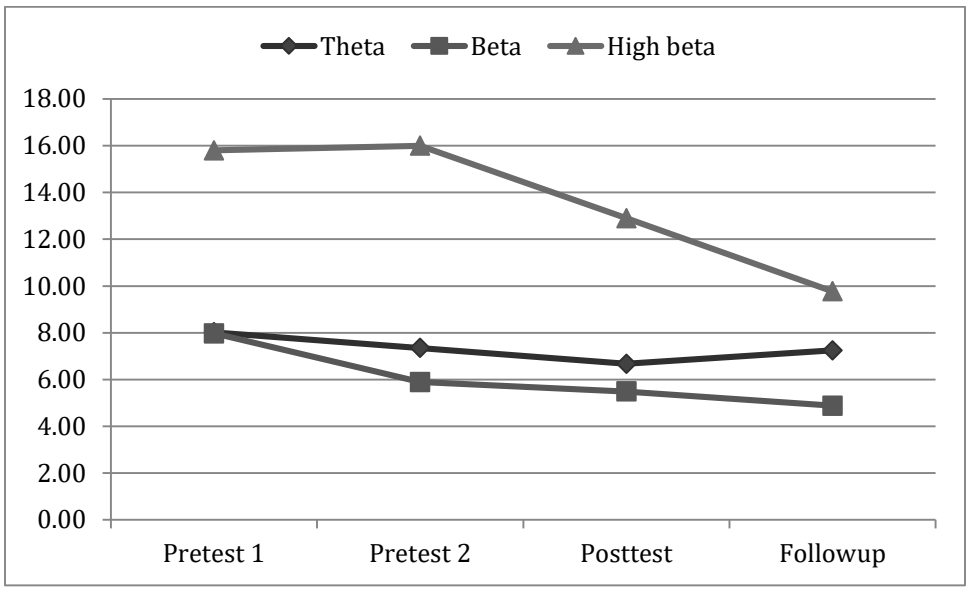
EEG results at FP1, which was treated to improve cognition, showed desirable decreases in high beta at posttest for the group reporting improvement at posttest, with a modest increase in high beta at followup. Beta was modestly decreased at posttest (undesirable), which was unchanged at followup. Theta was unchanged across measurement periods. These results applied to participants C, D, E, and G and are represented in Figure 14.

Figure 14. FP1 EEG amplitude, cognitive score improved at posttest.



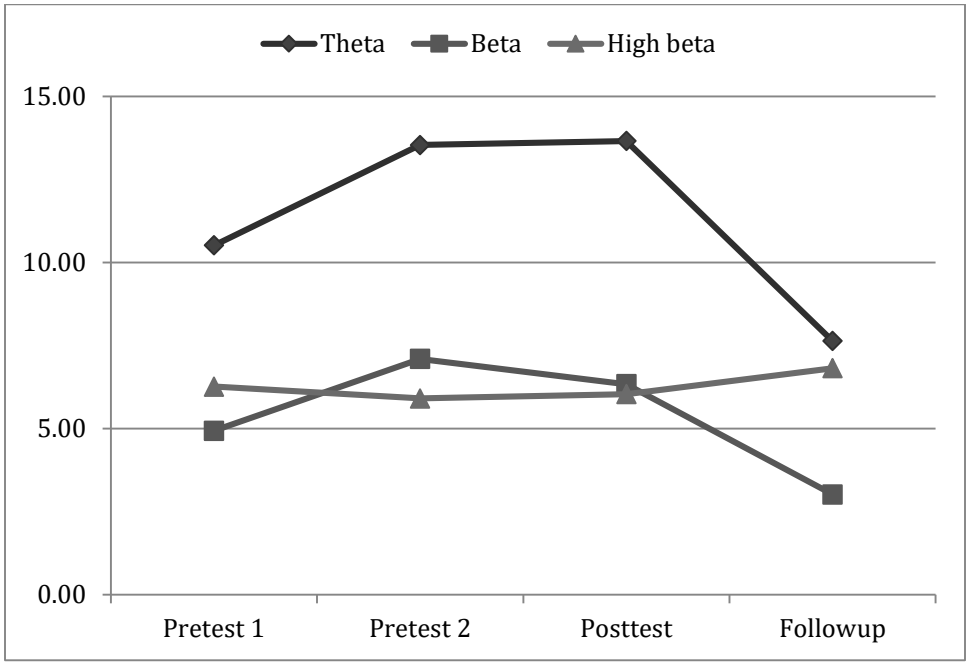
As shown in Figure 15, Participant B, who reported improvement at followup, had decreases in high beta at posttest and again at followup, with a comparatively elevated high beta at pretest; he also had a modest decrease in theta at posttest followed by a small increase at followup, and small decreases in beta at posttest and again at followup.

Figure 15. FP1 EEG amplitude, cognitive score improved at followup.



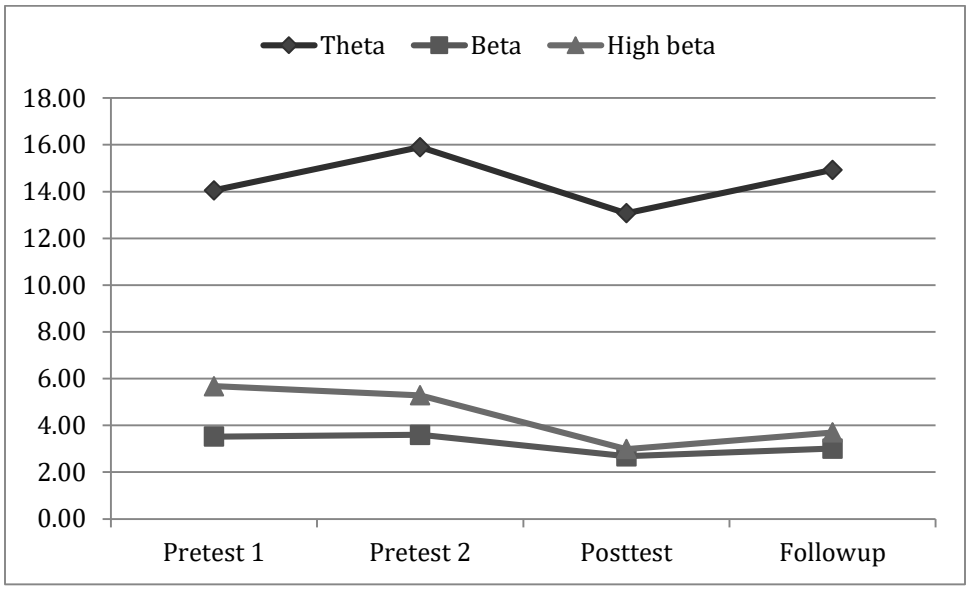
Participant A, who reported no change across measurements showed stable EEG results between pretest and posttest, with declines in theta (desirable) and beta (undesirable) at followup, as shown in Figure 16.

Figure 16. FP1 EEG amplitude, no change in cognitive score or verbal report.



Participant F, who reported a worsened cognitive score at posttest but improvement based on verbal report, had declines across bands at posttest with increases at followup, as shown in Figure 17.

Figure 17. FP1 EEG amplitude, worsened cognitive score, improved per verbal report.



Combined results for tremor and cognition scores and qualitative reports are summarized in Table 11. Only participant G, who was 6.5 years post-diagnosis and the oldest participant, had improvements in both the tremor and cognition quantitative measures that were sustained at followup; the cognition score (i.e., disability) increased at followup but not to the baseline level.

From the qualitative reports summarized in the final column of Table 11, we see that only participant A, who was the youngest and 1 of 2 most recently diagnosed participants, did not notice a great deal of change during or following the intervention. She was also the only female participant.

Table 11. Combined results by years since diagnosis and age.

			Score Change						
ID	Dx Years	Age	Tremor			Cognition			Qualitative Report
			Pre	Post	1-Mo	Pre	Post	1-Mo	
A	1.5	59	1	1	1	0	0	0	--
B	1.5	66	1	2	1	21%	25%	8%	Calm, tremor, thinking, memory
C	3.5	67	1	2	1	25%	21%	42%	Tremor, sense of smell
D	4.5	66	2	2	2	17%	12.5%	17%	Word-finding, memory, speaking in spite of tremor
E	6.5	68	3	2	2	17%	12.5%	25%	More alert
F	6.5	69	2	1	2	4%	26%	12.5%	Focus, tremor, walking
G	6.5	80	3	2	2	8%	0%	4%	Tremor, calm, energy, sleep

Chapter 5. Discussion and Conclusions

This was a multi-stage study designed to ascertain symptoms that patients identity as most significant that can be addressed using NFB, to pilot test NFB protocols to address those symptoms, and to then conduct a larger intervention study.

Focus Group

The chief research question for the focus group was "How do Parkinson's Disease patients prioritize challenges resulting from PD?" The only issues identified by all focus group participants were tremor and planning. Similar to previous studies, participants discussed a wide range of issues. However, unlike other studies, participants explicitly discussed the challenge of planning, and this was woven throughout the discussion. Strengths of the focus group were beginning the overall study with a component to ask PD patients their priorities in order to tailor the intervention to the identified priorities. Limitations include conducting just a single focus group. Recommendations include using a qualitative component in research design to develop intervention protocols with practical significance to patients and conducting similar focus groups with a broader population of PD patients, such as groups for those in the different stages of disease.

Neurofeedback Pilot Study

The pilot study was designed to determine the feasibility of the full study and to answer the following research questions:

- Can improvements to the QEEG be observed with mid-stage Parkinson patients with relatively few neurofeedback sessions?

- Is there an association between NFB treatment and QOL scores?
- Can changes in QOL scores be associated with specific NFB protocols?

The results were similar to previous work that showed specific types of disregulation in Parkinson patients, specifically high theta and too little beta. Findings were consistent with research showing positive results in few sessions. Unlike other studies, multiple symptom treatment and QOL measures were included. The pilot was useful in testing QOL and tremor measures.

Anecdotal information was important in understanding the results, and the study showed that selectively targeting motor and cognitive issues may result in specific, differential outcomes. Adding multiple baseline measures or a sham condition to blind all participants to the treatment they receive would strengthen findings.

Participants in both treatment conditions improved, while the control person did not. However, the person who reported the most improvement also reported the least disability at pretest. This indicates that the extent of change may depend on level and perhaps type of pre-treatment impairment, even within a given disease stage. This participant was also the oldest of the pretest cohort.

Strengths of the pilot study include a multi-dimensional treatment approach for treating PD with neurofeedback and inclusion of QOL measures to assess changes in various domains of functioning. Limitations include challenges in obtaining a truly homogeneous sample, pilot data with just three participants, and lack of random assignment for the control condition. Also, obtaining brain maps at just two points in time (pre- and post-intervention) does not provide interim results that might show a trend, or that might help explain changes observed. A final limitation is the placebo effect; that is,

participants knew they were receiving treatment, and therefore, may have over-reported improvements (the anecdotal information), and they may have guessed that treatment would target motor symptoms.

Recommendations resulting from the pilot include using only the cognition domain of the WHODAS and the PQ tremor question as the outcome variables and incorporating a diary or qualitative component to capture what study participants noticed during and following the intervention.

Neurofeedback Intervention Study

The NFB intervention component of the study was designed to determine whether self-reported tremor and cognition scores improve following 20 NFB sessions, whether any changes are noted 1-month post-treatment, what changes participants notice during and following treatment in addition to quantitative measurements, and how the EEG is changed following treatment. Research questions and a summary of results were as follows:

- *Do tremor scores improve following NFB treatment? How do tremor scores change 1-month post-treatment?* Tremor scores improved at posttest for the 3 participants who were 6.5 years away from diagnosis. This improvement held at the 1-month followup for 2 participants but not for the other participant. The change in any direction for any participant was a one point (on a 5-point scale).
- *Do cognition scores improve following NFB treatment? How do cognition scores change 1-month post-treatment?* Cognition scores improved at posttest for 4 of the 7 participants and for an additional participant at followup. Of the 4 participants who reported improvement at posttest, cognition scores returned to pretest levels or

worsened at the 1-month followup for 3 participants and also worsened for the 4th participant, but not back to pretest levels. Overall, changes were modest except for one participant (B), whose pretest EEG indicated particularly elevated high beta.

- *What qualitative changes, if any, do participants report during and 1 month following neurofeedback treatment?* Verbal reports by 4 of the 7 participants indicated improvements in tremor. In all, 5 participants reported tremor improvements in quantitative or qualitative reports. 5 participants noted cognitive improvements and a 6th participant provided verbal report of improved cognition but did not have an improved quantitative score. Qualitative reports documented improvement during and following the intervention in motor symptoms that included tremor and balance, cognitive symptoms that included memory, focus, word-finding, and holding a train of thought in spite of tremor, and other symptoms that included sleep, RLS, anxiety/agitation, fatigue, and light-headedness upon standing.
- *How does the EEG pattern at sites treated for tremor and cognition change following NFB treatment? Are any changes sustained 1 month post-treatment?* At C3 and C4, participants reporting improvement were successful at reducing theta and high beta but not at increasing beta. At FP1, participants were especially effective at reducing high beta. The EEG at the 1-month followup was generally improved from pretest but not to the extent observed at posttest.

Similar to a study by Erickson, et al. (2012), qualitative reports from participants indicated positive change. However, changes in the Erickson study did not reach statistical significance and in the current study, results were inconsistent and any changes were generally modest. Unlike Azarpaikan, et al. (2014), this study attempted to change self-

reported measures, rather than objective measures and included PD patients with varying levels of affectedness from PD.

Strengths and Limitations

Strengths of the study include an attempt to treat multiple PD symptoms simultaneously and to assess results using quantitative and qualitative measures. The 1-month followup provided a glimpse of the impact of neurofeedback after sessions ended. Limitations include a relatively small sample size and the lack of more precise measures of tremor and cognition.

Research Recommendations

Future research should focus on a larger intervention study. Due to the time required to conduct NFB (about 30 hours per participant for the current study), this would likely require a multi-site intervention with practitioners using the same equipment.

Prevention is difficult to measure (Galea, 2015). For all study participants but especially those who reported less impact by PD at pretest, and therefore had little room for improvement at subsequent measurement time points, it is unknown whether any benefit from NFB will be realized in terms of delayed symptoms and need for medication. Future studies should include longer followup to help determine this. Case review could be utilized in order to ascertain the need for medication for those receiving NFB compared to a match set of controls. Several additional recommendations related to design resulted from the study, as follows.

- *Measures*. Objective and more precise tremor and cognition measures may result in stronger documentation of changes. It is possible that objective

measures of symptoms (e.g., time required to complete dexterity tests, neuropsychology tests), rather than subjective self-report, would produce an improved understanding of results. As noted in the literature (e.g., Dauwerse, et al., 2014), as well as the focus group for the current study, symptom comorbidity in PD is extensive. As demonstrated in the pilot study, EEG dysregulation can manifest quite differently, even for PD patients in the same disease stage. Azarpaikan et al. (2014) showed statistically significant results with early stage PD participants using eight 30-minute NFB sessions and objective measures of balance and gait. It is possible that more general measures of symptoms and disability, such as were used in the current study, are not precise enough to capture changes. Also, the confluence of symptoms may make it difficult for participants to notice improvements in one symptom when other symptoms worsen, injury occurs, or life events cause stress. Changes unrelated or co-related to PD make interpretation of results challenging.

Objective and more precise tremor and cognition measures may result in stronger documentation of changes. Self-report has been shown to be correlated to clinical assessment, therefore, the development of a more detailed quantitative tremor measure that includes the different tremor types (at rest, postural, and action) and a more refined scale (e.g., 10 point) may more accurately capture changes and lead to better correlation between qualitative and quantitative measures. It would also be useful to conduct the

self-reported questionnaires at the mid-way point in the intervention to attempt to show trends.

- *Recruitment*. Extensive recruitment efforts were carried out and included contacting local neurologists and PD support groups, as well as using Facebook ads targeted to groups related to PD. The most fruitful recruitment arena, however was the local PD exercise groups. It stands to reason that if someone is motivated to attend exercise groups, they may also be motivated to participate in a research study. Exercise is related to improved PD symptomology. Therefore, another area for future research is the impact of combined NFB and exercise, comparing groups who exercise with those who do not.
- *Research design and practical considerations*. Due to the number of sessions and the time commitment required by participants, the single subject design is more practical than an experimental design using a control group. Asking people with a significant health condition such as PD to attend 20 or more NFB sessions, knowing half would receive placebo treatment, is requesting a great deal of research participants. For the pilot study, there was no sham condition, and the control person was offered and accepted the same number of NFB sessions the treatment groups received after data collection was completed. For a placebo (sham) condition, however, this means those in the control group have to attend twice as many sessions as the experimental group (sham sessions and then the actual NFB sessions following the end of

the study). This is a challenge for anyone with a chronic condition, and other factors, such as bad weather, add to the respondent burden this creates.

- *PD staging and sample selection*. The single subject design may minimize the effect of the sample including participants at different stages of PD. That is, each participant serves as her or his own control; therefore, results are based on differences between pre- and post-response for each person. However, as PD advances, the number, variability, and interactions of symptoms also progress, and this may affect results. With mid-stage and later stages of PD, it becomes increasingly difficult to isolate the effects of the intervention. One way to determine sample comparison would be to stratify the sample based on the pretest cognition (WHODAS) or tremor (PQ) pretest scores. In this way, people with similar levels of disability or affectedness from PD at pre-test could be compared.
- *Under- and over-reporting*. Because PD is slowly progressive, patients and families are able to adapt to changes in activity levels over time, as well as make adaptations that may be required at home, which means they may not be acutely aware of the impact of these changes. This gradual accommodation may result in an under-reporting of symptoms at pretest. For example, at pre-test, one participant began to write "none" in response to the WHODAS item "How much difficulty do you have moving around inside your home?" His wife observed his answer and pointed out that he could no longer go up or down stairs at home and that they had made many personal and structural accommodations for PD. In fact, they were selling their current

home and building a new one because of his PD. It was accurate that he could move around his current home without difficulty but this was due to the accommodations they had made. Conversely, during the intervention, participants are perhaps more focused on their symptoms (and whether or not they are improving) and therefore, may be more likely to over-report symptoms at post-test and followup. Measures that eliminate this type of ambiguity would more accurately capture any changes resulting from the intervention. Though the WHODAS has been well-tested and validated internationally, it may not always capture the impact of disease for this population. Another way to offset any under- or over-reporting would be to include reporting by family members (e.g., spouse, adult child) in order to document differences noted by more than one person.

- *Number of NFB sessions*. In order to demonstrate significant changes on broad measures of disability, more than 20 sessions, or in other words, a higher dosing of neurofeedback, is likely required. It may also take more sessions to up-train SMR and beta, which were the only EEG bands that did not show improvement. SMR and beta are associated with active attention and being alert yet relaxed. ADHD is one condition that has been well-researched using NFB, and 40 sessions are often used in protocols for ADHD (e.g., Lofthouse, et al., 2011). While comorbidity may exist with any condition, ADHD is non-degenerative and therefore, any comorbidity may be less impactful on outcome measures than with a degenerative condition, such as PD. Also, ADHD research typically involves children and youth, and with

degenerative conditions, the study populations are typically older and more likely to have comorbid conditions and life events that impact symptoms that are unrelated to the intervention. Resting tremor may also have interfered with training for some participants, and in these cases, more sessions may also be required to demonstrate change.

Clinical Recommendations

Specific clinical recommendations include the following:

- *Protocols*. Based on the qualitative reports, most participants noticed improvement in the cognitive and motor issues addressed by the protocols, and these issues showed improvement on quantitative measures for some participants, especially those diagnosed longer ago. Based on the reported importance of planning in the focus group, and the nearly universal impact of tremor in PD, retaining a multiple symptom focus on these conditions seems advised.
- *Session length*. Three of the 7 participants (C, E, and F) reported short-lived fatigue following sessions, and one participant noted mild headache. A more gradual approach to session length may have the advantage of creating less fatigue in the early sessions by allowing participants to slowly become accustomed to the training. For example, for a 20 session protocol, the first 5 sessions could be 12 minutes in length for each protocol, the next 10 sessions, 20 minutes each, and the final 5 sessions, 30 minutes. This would result in a comparable total hours of training as the current study (13.6 hours, compared to 13.3 for the current study). Also, if fatigue is less of a

problem at posttest, this may allow for the capture of a more accurate result based on the training, without the influence of transient fatigue due to NFB training. Another possibility is home-training, in which the subject (or family member) is trained to use NFB equipment at home for a given number of sessions. This would create issues of fidelity to procedures for a research study but may work well for clinical use.

More generally, in terms of clinical practice, this study adds to the evidence that NFB can be a useful therapy in alleviating motor symptoms of PD, particularly for those who are further away from diagnosis and as symptoms progress. NFB may be especially useful for symptoms not typically addressed by medication, such as cognitive problems. The high cost and long course of the disease, high prevalence of significant comorbidities, and importance of symptom delay, including delaying medication initiation and increases, make NFB an important therapy in defending against disease progression.

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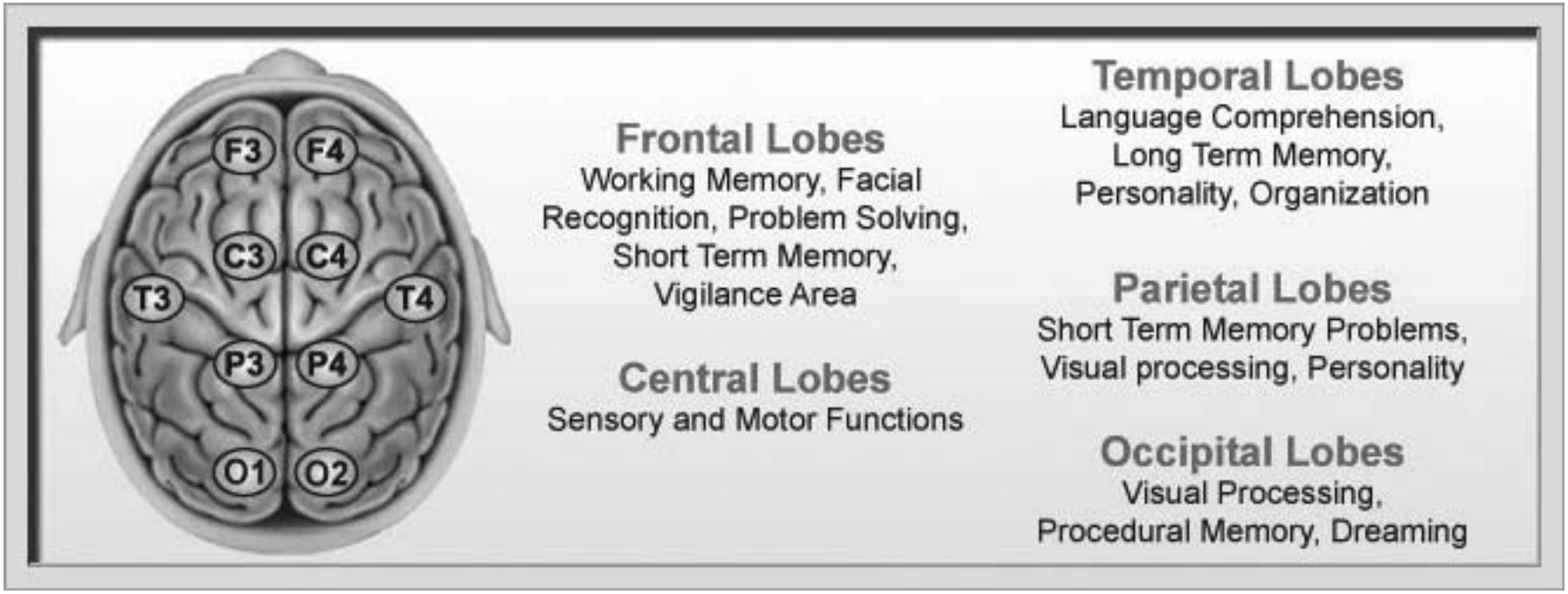
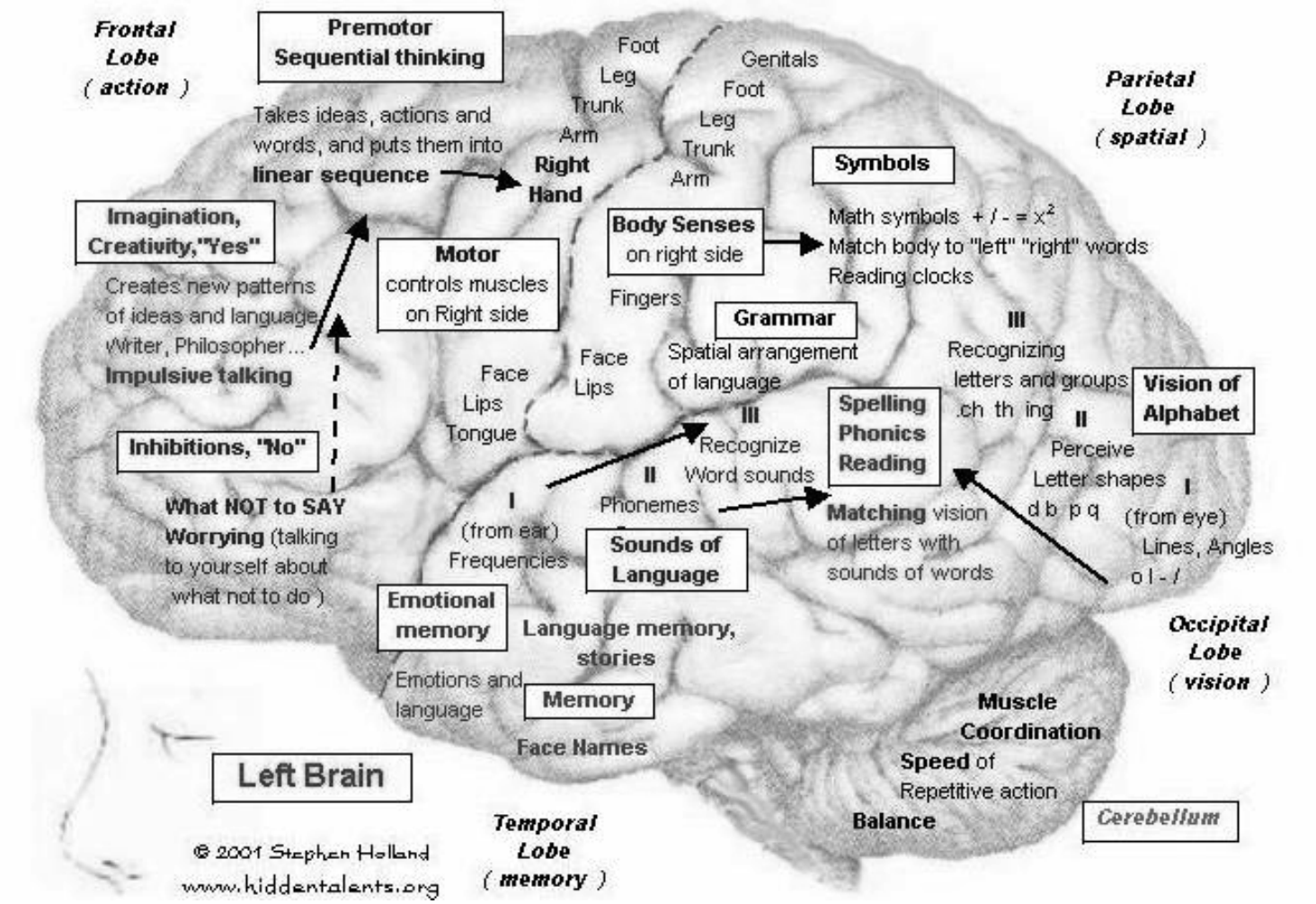
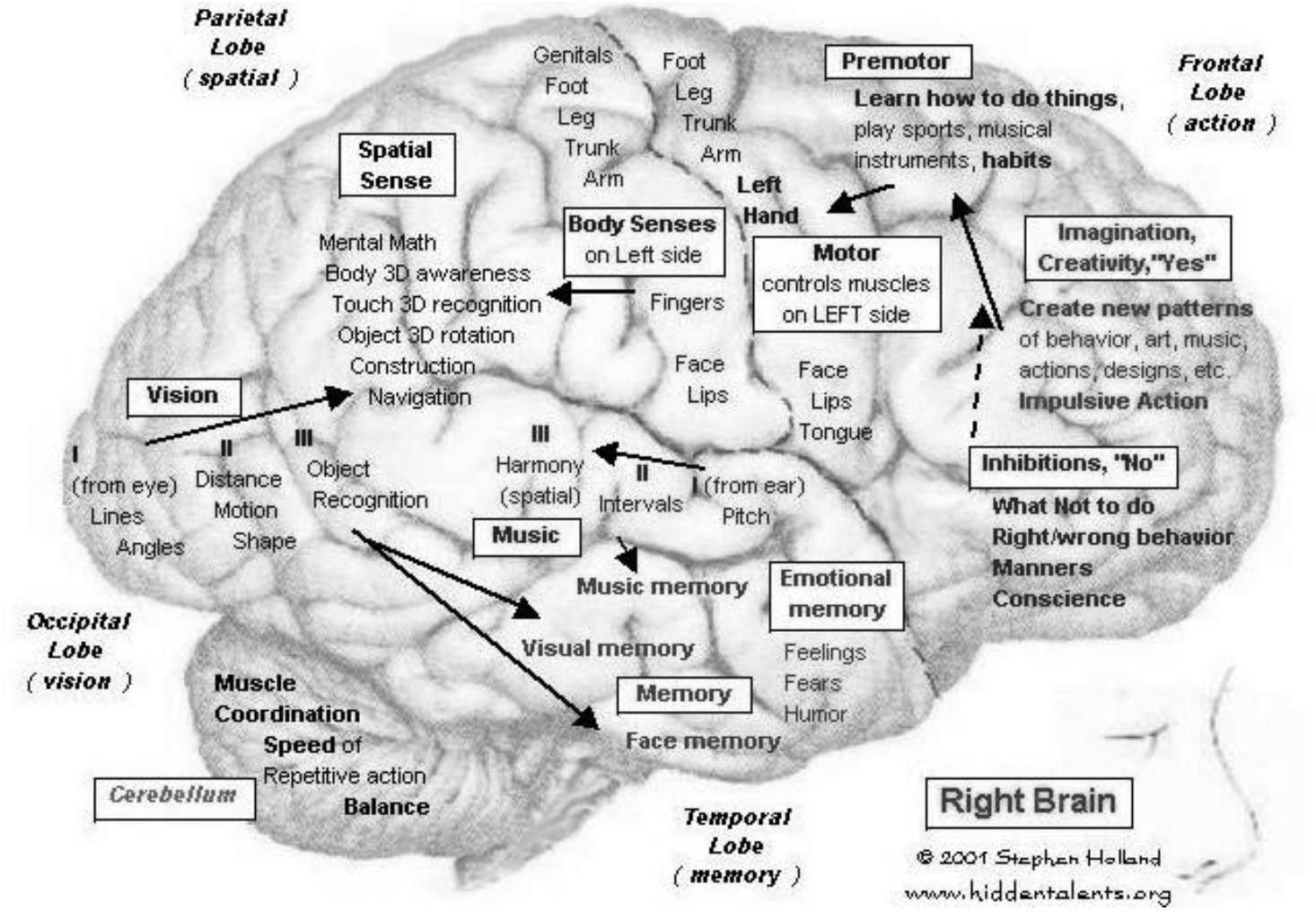
Appendix A. Brain Map Examples



Retrieved from http://downes.asamdev.com/services/neuro-map-reports, 12/20/14.



Retrieved from http://hiddentalents.org/brain/113-maps.html, 12/20/14.



Retrieved from http://hiddentalents.org/brain/113-maps.html, 12/20/14

Appendix B. Focus Group Recruitment Script

My name is JoAnne McFarland O'Rourke, and I am leading a study examining the effect of neurofeedback on the symptoms of Parkinson's Disease. I am the Director of Research in the College of Health and Human Services at WMU and I have a neurofeedback and counseling private practice. I am also a PhD student at WMU and plan to use the data that I collect for this study for my dissertation.

I am recruiting between 6-12 people to be part of a focus group discussion about the symptoms people experience as a result of Parkinson's Disease. If you agree to be part of the focus group, you will be asked to participate in a single meeting. The discussion topics will include the aspects of Parkinson's that you find particularly challenging and those that may be present but less challenging to you.

You will need to arrive an hour early and the discussion will last about 2 hours. Therefore, your time commitment will be 3 hours. The meeting will be held during business hours, Monday to Friday starting between 9-11 AM and concluding between 12-2 PM. The meeting will be held on the WMU East Campus (Oakland Drive).

We will videotape the discussion to ensure that responses are accurately captured. Therefore, you must agree to be videotaped to participate in the focus group.

I would like to hold the group in the next month and will try to arrange a time that is most convenient for the participants. If you are interested in learning more, please let me know. I will stay after the meeting to talk with you or you may call me at (269) 387-8445. I can also provide you with my business card.

Appendix C. Focus Group Informed Consent Document

CONSENT TO PARTICIPATE IN A RESEARCH STUDY
PRIORITIZING PARKINSON'S DISEASE SYMPTOMS
FOCUS GROUP

Introduction and Purpose

You are invited to be part of a research project. The purpose of the project is finding ways to decrease symptoms of Parkinson Disease (PD).

There are two parts to the project:

1. A focus group with Parkinson Disease patients about the symptoms that patients find problematic and

2. An intervention study that will test two different neurofeedback protocols.

This consent is for the focus group study (1) only.

The Michigan Parkinson Foundation (MPF) is funding the study. JoAnne McFarland O'Rourke, LMSW, Director of Research, College of Health and Human Services (CHHS), Western Michigan University (WMU), is the student investigator who is conducting the study.

What participation involves

If you agree to be part of the focus group, you will be asked to participate in one meeting. The meeting will be held at the College of Health and Human Services building on the WMU East Campus (Oakland Drive).

Between 6-12 people will meet for about 2 hours to discuss the symptoms they experience. You will need to arrive one hour early to turn in or sign this informed consent document and to have any questions you have answered.

The discussion topics will include the aspects of PD that you find particularly challenging and those that may be present but less challenging to you. You will need to arrive an hour early; therefore, your time commitment will be 3 hours.

Ms. McFarland O'Rourke will help guide the discussion. Her role includes managing the discussion and making sure everyone has a chance to respond. We will videotape the discussion to ensure that responses are accurately captured. You must agree to be videotaped to participate in the focus group.

Subject Recruitment and Participant Selection

Persons eligible to participate in the study are those:

With a diagnosis of Parkinson's Disease
Without significant psychiatric illness
Without a significant physical health problem other than PD

Study participants were recruited via flyers from the Bronson Neuroscience Center, Bronson Healthcare Midwest Neurology, and the Kalamazoo Area Parkinson Support Group, which meets at the Bronson Athletic Club.

People were invited to the group on a first-come basis, and you were among this group.

Voluntary nature of the study

Participating in this study is completely voluntary. Even if you decide to participate now, you may change your mind and stop at any time. You may choose not to answer a focus group question for any reason. Also, you may stop participating in the study at anytime for any reason. There are no adverse consequences for deciding to stop participating.

Participating in the focus group will not affect the likelihood that you will be invited to participate in the next part of the study.

Location

The focus group will take place in a conference room on the third floor of the WMU College of Health and Human Services (Room 3267). The building is located at 1101 Cass Street, Kalamazoo MI 49008, at the intersection of Oakland Drive and Oliver Street. The building is fully handicap accessible (elevators, restrooms, flooring).

Free parking will be provided and directions will be sent.

Risks and discomforts

Answering questions or talking with others about illness can be difficult. You may choose not to answer any discussion question. Also, you can stop your participation in the focus group at any time. You will be provided with a list of local agencies that can provide you with additional information or support if you are interested.

All focus group members will be asked to respect the privacy of other group members. You may tell others that you were in a focus group and the general topic of the discussion. However, actual names, stories, and any other identifying information of other participants should not be shared. While unlikely, there is a chance that another member of the focus group could reveal something about you or your family that they learned in the discussion.

Benefits

There are no direct benefits from participating in this research. However, some people find sharing their stories to be a valuable experience. Also, the ultimate goal of the study is to find ways to address symptoms associated with PD. Therefore, your participation may help in this effort.

Compensation and Cost

You will receive a $20 gift card for participating in the focus group session. Parking will be free-of-charge but you will need to arrange and pay for your own travel to the College of Health and Human Services. If someone drives you to the focus group, they will be asked to wait in the building atrium.

Confidentiality and data use

The data from the study are planned for publication but will not include any information that would identify you. To keep your information safe, the videotape of the focus group will be stored on a secure computer at CHHS. Later, a transcript of the discussion will be created. Study data will be entered on a computer that is password-protected and accessible only to Ms. O'Rourke. To further protect confidentiality, your real name will not be used in the written copy of the discussion. The videotape will be destroyed after 3 years.

There are some reasons why people other than the researchers may need to see information you provided as part of the study. This includes organizations responsible for making sure the research is done safely and properly. These organizations may include Western Michigan University or government research offices. If you reveal something that makes us believe that you or others have been or may be physically harmed, we are obligated to report that information to the appropriate agencies.

When referring to family members, friends, or others, please use the person's relationship to you (e.g., "my son") and not the person's name (e.g., "Chris").

Contact information

If you have questions about this research, including questions about the scheduling of the focus group or your payment for participating, you may contact:

JoAnne McFarland O'Rourke, Director of Research
College of Health and Human Services
1903 W. Michigan Avenue
Kalamazoo MI 49008-5243
(269) 387-8445 Phone
(269) 387-7435 Fax
joanne.orourke@wmich.edu

If you have questions about your rights as a research participant, or wish to obtain information, ask questions or discuss any concerns about this study with someone other than the researcher, please contact:

Health Sciences Institutional Review Board, Chair
Western Michigan University
251 W. Walwood Hall
Kalamazoo, MI 49008-5456 USA
(269) 387-8293 Phone
(269) 387-8276 Fax
research-compliance@wmich.edu

Consent

The WMU Human Subjects Institutional Review Board (HSIRB) has approved this consent document. The approval is valid for one year. The approval period is indicated by the stamped date and signature of the board chair in the upper right corner. Do not participate in this study if the stamped date is older than one year.

By signing this document, you are agreeing to be in the focus group. You will be given a copy of this document upon request and one copy will be kept with the study records. Be sure that your questions about the study have been answered and that you understand what you are being asked to do. Please contact Ms. O'Rourke if you think of a question later.

I have read this document. I have had the opportunity to ask questions about it. Any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate in this research. As part of my consent, I agree to be videotaped and not to share names, stories, or any other identifying information about others in the group.

_____

Name (printed)

_____ _____

Signature Date

Appendix D. Focus Group Protocol

Overview and Guidelines

Thank you very much for agreeing to participate in today's focus group. My name is JoAnne McFarland O'Rourke, and I am leading a study examining the effect of neurofeedback on the symptoms of Parkinson's Disease. I am the Director of Research in the College of Health and Human Services at WMU and I have a neurofeedback and counseling private practice. I am also a PhD student at WMU and plan to use the data that I collect for this study for my dissertation.

I would like to outline a few ground rules. First, we are video recording today's group, and as a backup, we are also audio recording. It will be very helpful if you can speak up, as well as speak one at a time to help ensure that your comments come through on the recording.

Second, a few words about confidentiality: Please use only first names when addressing each other, and when speaking about a family member or friend, please refer to that person's relationship to you and not her or his name. I ask that you respect the group's privacy by not repeating what others say here today.

In terms of the data I am collecting through this group, the information that each of you has to share regarding your experience with Parkinson's Disease is very important. However, individual identities are not important. Therefore, no reports will ever link your name to what you say or identify you in any way.

This group is intended to be a discussion among you, the participants, so please address your responses to the entire group and feel free to respond to each other's comments. My role is to ask questions, listen, and when needed, clarify responses and ensure that everyone has a chance to speak. I would like to hear from everyone and to hear your response to questions, even if they are different than everyone else's. The group may form a agreement on some questions, and on other questions, there may be a difference of opinion – both of these are OK.

I will ask each question and then we will pause for about a minute or two to allow you to gather your thoughts before we start the discussion. The notepads and pencils in front of you are for writing down ideas during the pause before each question or at other times, as you wish.

At about the halfway point we will stop for a 10-15 minute break and then pick up where we left off. If anyone needs to take a break before the halfway point, just let me know and we will take a break then. [POINT OUT WHERE RESTROOMS ARE LOCATED]. If you have not done so already, please silence your cell phones.

Let's begin by having each of you introduce yourself, including your first name and anything else that you would like to add.

[INTRODUCTIONS]

Thank you. Do you have any questions before we begin with the focus group?

[RESPOND TO QUESTIONS]

INTRODUCTION

The key objective of this focus group is to gain insight about how Parkinson's Disease patients would prioritize symptoms of the disease in terms of how much they interfere with quality of life.

Question 1

My first question has to do with how Parkinson's has affected you lately. When you think about your ability to enjoy life **over the past month**, in terms of Parkinson's, what has gotten in the way?

[PAUSE FOR A MINUTE AND THEN INVITE RESPONSES]

PROBES:

- WHAT ARE THE FIRST THINGS YOU THINK OF?
- WHAT SEEMS MOST SIGNIFICANT?
- SOME THINGS MIGHT HAVE TO DO WITH GETTING AROUND, INTERACTING WITH OTHER PEOPLE, HOW YOU FEEL PHYSICALLY, HOW YOU FEEL EMOTIONALLY, OR YOUR ENERGY LEVEL.
- SEE SYMPTOM LIST IF NEEDED.

Question 2

Thank you. Now, thinking about the last 6 months to a year, when you think about your ability to enjoy life over this longer timeframe, in terms of Parkinson's, what are the issues that have gotten in the way?

PROBES:

- ARE THERE THINGS YOU WOULD ADD TO THE LIST FROM QUESTION 1?
- WHAT HAVE BEEN SOME OTHER AREAS OF CONCERN?
- ARE THERE ACTIVITIES THAT ONLY HAPPEN 1-2 TIMES A YEAR, SUCH AS CHRISTMAS OR BIRTHDAY PARTIES, THAT HAVE CREATED SPECIAL CHALLENGES FOR YOU?
- SEE SYMPTOM LIST IF NEEDED

BREAK FOR 10-15 MINUTES

Question 3

Thank you very much. Some changes to functioning may impact you daily but you find that they are manageable, either through medication or ways that you have learned to adapt. Other changes may not affect you daily but overall, they impact you a lot in terms of affecting your ability to enjoy things that are important to you.

My next question is, how impactful are the changes to functioning that you described in the two first questions in terms of your ability to enjoy life?

PROBES:
HOW HAS YOUR DIAGNOSIS AFFECTED YOU THE MOST?
ENSURE ALL ISSUES MENTIONED IN QUESTION 1 AND 2 ARE DISCUSSED

Closing

Thank you. This concludes the questions for the group. Please accept my thanks for participating in today's group. I appreciate your time and candor, and want to assure you that your responses will be very helpful.

[Distribute gift cards and wrap-up]

Definitions

QOL:

Both positive and negative aspects of life.

Physical and mental health perceptions and their correlates—including health risks and conditions, functional status, social support, and socioeconomic status.

Symptoms / changes list

Moving
Balance
Tripping, falling
Walking, getting around, walking speed

Executive function and cognition
Driving
Balancing checkbook
Making decisions
Thought process
Multi-tasking

Communication
Talking
Clarity
Expression
Word-finding
Sound, softness
Maintaining thought process

Other physical symptoms
Swallowing
Tremors/shaking

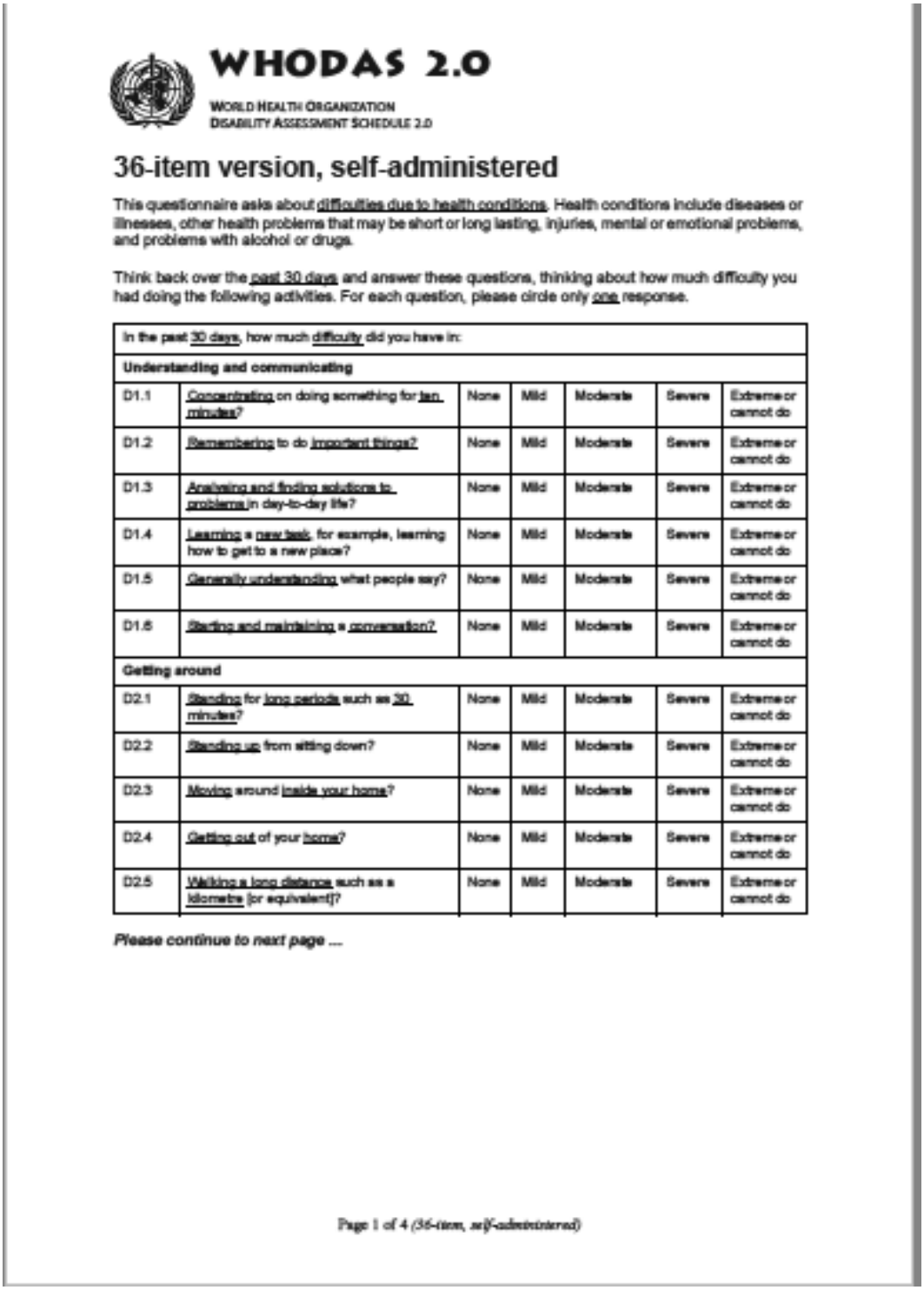
Mood
Low mood
Depression
Motivation
Enthusiasm
Apathy

Anxiety
Worry
Fear
Concern
Apprehension

Life changes
Relationships, impact
Job, volunteering

Medication
Interactions/side effects
Medication ineffective

Appendix E. World Health Organization Disability Assessment Scale



WHODAS 2.0

WORLD HEALTH ORGANIZATION
DISABILITY ASSESSMENT SCHEDULE 2.0

36-item version, self-administered

This questionnaire asks about difficulties due to health conditions. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the past 30 days and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please circle only one response.

In the past 30 days, how much difficulty did you have in:						
Understanding and communicating						
D1.1	Concentrating on doing something for ten minutes?	None	Mild	Moderate	Severe	Extreme or cannot do
D1.2	Remembering to do important things?	None	Mild	Moderate	Severe	Extreme or cannot do
D1.3	Analysing and finding solutions to problems in day-to-day life?	None	Mild	Moderate	Severe	Extreme or cannot do
D1.4	Learning a new task, for example, learning how to get to a new place?	None	Mild	Moderate	Severe	Extreme or cannot do
D1.5	Generally understanding what people say?	None	Mild	Moderate	Severe	Extreme or cannot do
D1.6	Starting and maintaining a conversation?	None	Mild	Moderate	Severe	Extreme or cannot do
Getting around						
D2.1	Standing for long periods such as 30 minutes?	None	Mild	Moderate	Severe	Extreme or cannot do
D2.2	Standing up from sitting down?	None	Mild	Moderate	Severe	Extreme or cannot do
D2.3	Moving around inside your home?	None	Mild	Moderate	Severe	Extreme or cannot do
D2.4	Getting out of your home?	None	Mild	Moderate	Severe	Extreme or cannot do
D2.5	Walking a long distance such as a kilometre [or equivalent]?	None	Mild	Moderate	Severe	Extreme or cannot do

Please continue to next page ...

Page 1 of 4 *(36-item, self-administered)*

WHODAS 2.0

WORLD HEALTH ORGANIZATION
DISABILITY ASSESSMENT SCHEDULE 2.0

36
Self

In the past 30 days, how much difficulty did you have in:						
Self-care						
D3.1	Washing your whole body?	None	Mild	Moderate	Severe	Extreme or cannot do
D3.2	Getting dressed?	None	Mild	Moderate	Severe	Extreme or cannot do
D3.3	Eating?	None	Mild	Moderate	Severe	Extreme or cannot do
D3.4	Staying by yourself for a few days?	None	Mild	Moderate	Severe	Extreme or cannot do
Getting along with people						
D4.1	Dealing with people you do not know?	None	Mild	Moderate	Severe	Extreme or cannot do
D4.2	Maintaining a friendship?	None	Mild	Moderate	Severe	Extreme or cannot do
D4.3	Getting along with people who are close to you?	None	Mild	Moderate	Severe	Extreme or cannot do
D4.4	Making new friends?	None	Mild	Moderate	Severe	Extreme or cannot do
D4.5	Sexual activities?	None	Mild	Moderate	Severe	Extreme or cannot do
Life activities						
D5.1	Taking care of your household responsibilities?	None	Mild	Moderate	Severe	Extreme or cannot do
D5.2	Doing most important household tasks well?	None	Mild	Moderate	Severe	Extreme or cannot do
D5.3	Getting all the household work done that you needed to do?	None	Mild	Moderate	Severe	Extreme or cannot do
D5.4	Getting your household work done as quickly as needed?	None	Mild	Moderate	Severe	Extreme or cannot do

Please continue to next page ...

If you work (paid, non-paid, self-employed) or go to school, complete questions D5.5–D5.8, below. Otherwise, skip to D6.1.

Because of your health condition, in the past 30 days, how much difficulty did you have in:						
D5.5	Your day-to-day work/school?	None	Mild	Moderate	Severe	Extreme or cannot do
D5.6	Doing your most important work/school tasks well?	None	Mild	Moderate	Severe	Extreme or cannot do
D5.7	Getting all the work done that you need to do?	None	Mild	Moderate	Severe	Extreme or cannot do
D5.8	Getting your work done as quickly as needed?	None	Mild	Moderate	Severe	Extreme or cannot do

Participation in society						
In the past 30 days:						
D6.1	How much of a problem did you have in joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	None	Mild	Moderate	Severe	Extreme or cannot do
D6.2	How much of a problem did you have because of barriers or hindrances in the world around you?	None	Mild	Moderate	Severe	Extreme or cannot do
D6.3	How much of a problem did you have living with dignity because of the attitudes and actions of others?	None	Mild	Moderate	Severe	Extreme or cannot do
D6.4	How much time did you spend on your health condition, or its consequences?	None	Mild	Moderate	Severe	Extreme or cannot do
D6.5	How much have you been emotionally affected by your health condition?	None	Mild	Moderate	Severe	Extreme or cannot do
D6.6	How much has your health been a drain on the financial resources of you or your family?	None	Mild	Moderate	Severe	Extreme or cannot do
D6.7	How much of a problem did your family have because of your health problems?	None	Mild	Moderate	Severe	Extreme or cannot do
D6.8	How much of a problem did you have in doing things by yourself for relaxation or pleasure?	None	Mild	Moderate	Severe	Extreme or cannot do

Please continue to next page ...

H1	Overall, in the past 30 days, how many days were these difficulties present?	*Record number of days* _____
H2	In the past 30 days, for how many days were you totally unable to carry out your usual activities or work because of any health condition?	*Record number of days* _____
H3	In the past 30 days, not counting the days that you were totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?	*Record number of days* _____

This completes the questionnaire. Thank you.

Appendix F. UPDRS Patient Questionnaire

Patient Questionnaire:

Instructions:

This questionnaire will ask you about your experiences of daily living.

There are 20 questions. We are trying to be thorough, and some of these questions may therefore not apply to you now or ever. If you do not have the problem, simply mark 0 for NO.

Please read each one carefully and read all answers before selecting the one that best applies to you.

We are interested in your average or usual function over the past week including today. Some patients can do things better at one time of the day than at others. However, only one answer is allowed for each question, so please mark the answer that best describes what you can do most of the time.

You may have other medical conditions besides Parkinson's disease. Do not worry about separating Parkinson's disease from other conditions. Just answer the question with your best response.

Use only 0, 1, 2, 3, 4 for answers, nothing else. Do not leave any blanks.

Your doctor or nurse can review the questions with you, but this questionnaire is for patients to complete, either alone or with their caregivers.

Who is filling out this questionnaire (check the best answer):

☐ Patient ☐ Caregiver ☐ Patient and Caregiver in Equal Proportion

Part I: Non-Motor Aspects of Experiences of Daily Living (nM-EDL)	
1.7 SLEEP PROBLEMS Over the past week, have you had trouble going to sleep at night or staying asleep through the night? Consider how rested you felt after waking up in the morning. 0: Normal: No problems. 1: Slight: Sleep problems are present but usually do not cause trouble getting a full night of sleep. 2: Mild: Sleep problems usually cause some difficulties getting a full night of sleep. 3: Moderate: Sleep problems cause a lot of difficulties getting a full night of sleep, but I still usually sleep for more than half the night. 4: Severe: I usually do not sleep for most of the night.	**SCORE** ☐
1.8 DAYTIME SLEEPINESS Over the past week, have you had trouble staying awake during the daytime? 0: Normal: No daytime sleepiness. 1: Slight: Daytime sleepiness occurs but I can resist and I stay awake. 2: Mild: Sometimes I fall asleep when alone and relaxing. For example, while reading or watching TV. 3: Moderate: I sometimes fall asleep when I should not. For example, while eating or talking with other people. 4: Severe: I often fall asleep when I should not. For example, while eating or talking with other people.	☐

	SCORE
1.9 PAIN AND OTHER SENSATIONS Over the past week, have you had uncomfortable feelings in your body like pain, aches tingling or cramps? 0: Normal: No uncomfortable feelings. 1: Slight: I have these feelings. However, I can do things and be with other people without difficulty. 2: Mild: These feelings cause some problems when I do things or am with other people. 3: Moderate: These feelings cause a lot of problems, but they do not stop me from doing things or being with other people. 4: Severe: These feelings stop me from doing things or being with other people.	☐
1.10 URINARY PROBLEMS Over the past week, have you had trouble with urine control? For example, an urgent need to urinate, a need to urinate too often, or urine accidents? 0: Normal: No urine control problems. 1: Slight: I need to urinate often or urgently. However, these problems do not cause difficulties with my daily activities. 2: Mild: Urine problems cause some difficulties with my daily activities. However, I do not have urine accidents. 3: Moderate: Urine problems cause a lot of difficulties with my daily activities, including urine accidents. 4: Severe: I cannot control my urine and use a protective garment or have a bladder tube.	☐

	SCORE
1.11 CONSTIPATION PROBLEMS Over the past week have you had constipation troubles that cause you difficulty moving your bowels? 0: Normal: No constipation. 1: Slight: I have been constipated. I use extra effort to move my bowels. However, this problem does not disturb my activities or my being comfortable. 2: Mild: Constipation causes me to have some troubles doing things or being comfortable. 3: Moderate: Constipation causes me to have a lot of trouble doing things or being comfortable. However, it does not stop me from doing anything. 4: Severe: I usually need physical help from someone else to empty my bowels.	☐
1.12 LIGHT HEADEDNESS ON STANDING Over the past week, have you felt faint, dizzy or foggy when you stand up after sitting or lying down? 0: Normal: No dizzy or foggy feelings. 1: Slight: Dizzy or foggy feelings occur. However, they do not cause me troubles doing things. 2: Mild: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down. 3: Moderate: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling. 4: Severe: Dizzy or foggy feelings cause me to fall or faint.	☐

	SCORE
1.13 FATIGUE Over the past week, have you usually felt fatigued? This feeling is <u>not</u> part of being sleepy or sad. 0: Normal: No fatigue. 1: Slight: Fatigue occurs. However it does not cause me troubles doing things or being with people. 2: Mild: Fatigue causes me some troubles doing things or being with people. 3: Moderate: Fatigue causes me a lot of troubles doing things or being with people. However, it does not stop me from doing anything. 4: Severe: Fatigue stops me from doing things or being with people.	☐
Part II: Motor Aspects of Experiences of Daily Living (M-EDL)	
2.1 SPEECH Over the past week, have you had problems with your speech? 0: Normal: Not at all (no problems). 1: Slight: My speech is soft, slurred or uneven, but it does not cause others to ask me to repeat myself. 2: Mild: My speech causes people to ask me to occasionally repeat myself, but not everyday. 3: Moderate: My speech is unclear enough that others ask me to repeat myself every day even though most of my speech is understood. 4: Severe: Most or all of my speech cannot be understood.	☐

	SCORE
2.2 SALIVA AND DROOLING Over the past week, have you usually had too much saliva during when you are awake or when you sleep? 0: Normal: Not at all (no problems). 1: Slight: I have too much saliva, but do not drool. 2: Mild: I have some drooling during sleep, but none when I am awake. 3: Moderate: I have some drooling when I am awake, but I usually do not need tissues or a handkerchief. 4: Severe: I have so much drooling that I regularly need to use tissues or a handkerchief to protect my clothes.	☐
2.3 CHEWING AND SWALLOWING Over the past week, have you usually had problems swallowing pills or eating meals? Do you need your pills cut or crushed or your meals to be made soft, chopped or blended to avoid choking? 0: Normal: No problems. 1: Slight: I am aware of slowness in my chewing or increased effort at swallowing, but I do not choke or need to have my food specially prepared. 2: Mild: I need to have my pills cut or my food specially prepared because of chewing or swallowing problems, but I have not choked over the past week. 3: Moderate. I choked at least once in the past week. 4: Severe: Because of chewing and swallowing problems, I need a feeding tube.	☐

	SCORE
2.4 EATING TASKS Over the past week, have you usually had troubles handling your food and using eating utensils? For example, do you have trouble handling finger foods or using forks, knives, spoons, chopsticks? 0: Normal: Not at all (no problems). 1: Slight: I am slow, but I do not need any help handling my food and have not had food spills while eating. 2: Mild: I am slow with my eating and have occasional food spills. I may need help with a few tasks such as cutting meat. 3: Moderate: I need help with many eating tasks but can manage some alone. 4: Severe: I need help for most or all eating tasks.	☐
2.5 DRESSING Over the past week, have you usually had problems dressing? For example, are you slow or do you need help with buttoning, using zippers, putting on or taking off your clothes or jewelry? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need help. 2: Mild: I am slow and need help for a few dressing tasks (buttons, bracelets). 3: Moderate: I need help for many dressing tasks. 4: Severe: I need help for most or all dressing tasks.	☐

	SCORE
2.6 HYGIENE Over the past week, have you usually been slow or do you need help with washing, bathing, shaving, brushing teeth, combing your hair or with other personal hygiene? 0: Normal: Not at all (no problems). 1: Slight: I am slow but I do not need any help. 2: Mild: I need someone else to help me with some hygiene tasks. 3: Moderate: I need help for many hygiene tasks. 4: Severe: I need help for most or all of my hygiene tasks.	☐
2.7 HANDWRITING Over the past week, have people usually had trouble reading your handwriting? 0: Normal: Not at all (no problems). 1: Slight: My writing is slow, clumsy or uneven, but all words are clear. 2: Mild: Some words are unclear and difficult to read. 3: Moderate: Many words are unclear and difficult to read. 4: Severe: Most or all words cannot be read.	☐
2.8 DOING HOBBIES AND OTHER ACTIVITIES Over the past week, have you usually had trouble doing your hobbies or other things that you like to do? 0: Normal: Not at all (no problems). 1: Slight: I am a bit slow but do these activities easily. 2: Mild: I have some difficulty doing these activities. 3: Moderate: I have major problems doing these activities, but still do most. 4: Severe: I am unable to do most or all of these activities.	☐

	SCORE
2.9 TURNING IN BED Over the past week, do you usually have trouble turning over in bed? 0: Normal: Not at all (no problems). 1: Slight: I have a bit of trouble turning, but I do not need any help. 2: Mild I have a lot of trouble turning and need occasional help from someone else. 3: Moderate: To turn over I often need help from someone else. 4: Severe: I am unable to turn over without help from someone else.	☐
2.10 TREMOR Over the past week, have you usually had shaking or tremor? 0: Normal: Not at all. I have no shaking or tremor. 1: Slight: Shaking or tremor occurs but does not cause problems with any activities. 2: Mild: Shaking or tremor causes problems with only a few activities. 3: Moderate: Shaking or tremor causes problems with many of my daily activities. 4: Severe: Shaking or tremor causes problems with most or all activities.	☐
2.11 GETTING OUT OF BED, A CAR, OR A DEEP CHAIR Over the past week, have you usually had trouble getting out of bed, a car seat, or a deep chair? 0: Normal: Not at all (no problems). 1: Slight: I am slow or awkward, but I usually can do it on my first try. 2: Mild: I need more than one try to get up or need occasional help. 3: Moderate: I sometimes need help to get up, but most times I can still do it on my own. 4: Severe: I need help most or all of the time.	☐

2.12 WALKING AND BALANCE	SCORE
Over the past week, have you usually had problems with balance and walking? 0: Normal: Not at all (no problems). 1: Slight: I am slightly slow or may drag a leg. I never use a walking aid. 2: Mild: I occasionally use a walking aid, but I do not need any help from another person. 3: Moderate: I usually use a walking aid (cane, walker) to walk safely without falling. However, I do not usually need the support of another person. 4: Severe: I usually use the support of another person to walk safely without falling.	☐
2.13 FREEZING Over the past week, on your usual day when walking, do you suddenly stop or freeze as if your feet are stuck to the floor. 0: Normal: Not at all (no problems). 1: Slight: I briefly freeze but I can easily start walking again. I do not need help from someone else or a walking aid (cane or walker) because of freezing. 2: Mild: I freeze and have trouble starting to walk again, but I do not need someone's help or a walking aid (cane or walker) because of freezing. 3: Moderate: When I freeze I have a lot of trouble starting to walk again and, because of freezing, I sometimes need to use a walking aid or need someone else's help. 4: Severe: Because of freezing, most or all of the time, I need to use a walking aid or someone's help.	☐

This completes the questionnaire. We may have asked about problems you do not even have, and may have mentioned problems that you may never develop at all. Not all patients develop all these problems, but because they can occur, it is important to ask all the questions to every patient. Thank you for your time and attention in completing this questionnaire.

Appendix G. Intervention Study Informed Consent Document

Western Michigan University
College of Human and Health Sciences

Principal Investigator:	JoAnne McFarland O'Rourke
Faculty Advisor:	Kieran Fogarty
Title of Study:	Evaluation of Two Neurofeedback Protocols with Parkinson's Disease Patients

You have been invited to participate in a research project titled "*Evaluation of Two Neurofeedback Protocols with Parkinson's Disease Patients*". This project will serve as Ms. O'Rourke's dissertation for the requirements of the Doctor of Philosophy. This consent document will explain the purpose of this research project and will go over the time commitments, the procedures used in the study, and the risks and benefits of participating in this research project. Please read this consent form carefully and completely. Also, please ask any questions if you need more clarification.

What are we trying to find out in this study?
The overall purpose of the study is to examine ways to decrease symptoms of Parkinson's disease (PD). The study will test the effectiveness of addressing symptoms of Parkinson's Disease using neurofeedback (NFB).

Who can participate in this study?
Study participants are recruited via flyers from the Bronson Neuroscience Center, Bronson Healthcare Midwest Neurology, the Kalamazoo and Battle Creek Area Parkinson Support Groups, and through Facebook.

Eligibility requirements are reviewed with people who contacted the PI about participating in the study. Persons eligible to participate in the study are those:

(1) With a diagnosis of Parkinson's Disease
(2) Without previous neurofeedback treatment
(3) Without a deep brain stimulation (DBS) implant
(4) Without diagnosed psychiatric illness, such as bipolar disorder or major depression

There are expected to be 8 participants in the study.

Where will this study take place?
Study activities will take place at the Kalamazoo Neurofeedback and Counseling Center, 5786 Blue Jay Drive, Kalamazoo, Michigan 49009.

What is the time commitment for participating in this study?
The time commitment for the study is 2 months and a total of 29 hours. Each participant will receive 13.3 hours of neurofeedback.

See Table 1 for project phases, timeframes, and time commitments.

Table 1. Timeframes, project phases, and time commitment for each group.

TIMEFRAME	PROJECT PHASE	HOURS
MONTH 1	Pre-tests	3
	Intervention	20
	Post-tests	3
MONTH 2	1-Month Follow-up	3
TOTAL TIME COMMITMENT IN HOURS		29

What will you be asked to do if you choose to participate in this study?
The intervention consists of 20 NFB sessions over 2-4 weeks (up to 10 per week). Sessions will be held at the clinical office of the PI. The intervention (NFB) will last approximately 40 minutes per session, with 20 minutes of setup time.

During a neurofeedback session, you will be seated and electrodes (leads) will be placed on your head. You will then attempt to maintain a state of "relaxed focus" while watching a display on a computer monitor. The feedback you receive will be both auditory and visual. For example, you will hear more beeps from the computer when you are responding well to the stimuli (computer game).

What information is being measured during the study?
This section will describe the measurements that we are going to take during your participation in the study. Quality of life measures will be self-reported through a written survey. Issues you may have with movement disorders will be self-reported, also through a written survey. If you prefer, the surveys can be read to you and your answers recorded for you. Measurements of your brainwave activity will be recorded and anecdotal information you provide about any changes in may notice during treatment will be recorded.

What are the risks of participating in this study and how will these risks be minimized?
Few to no long-term side effects have been reported for neurofeedback training. In a survey of NFB practitioners, 4% reported any adverse reactions in patients, most of which were mild and transient. Short-term side effects of NFB include fatigue, which typically subsides after a rest period. Treatment is painless.

It is possible that the study findings show no improvement from the NFB interventions being tested. A 2014 study demonstrated positive effect of NFB with early-stage PD patients. Therefore, while it is reasonable to expect that some positive effect will be demonstrated, there is no guarantee.

As in all research, there may be unforeseen risks to study participants. If an accidental injury occurs, appropriate emergency measures will be taken. However, no compensation or additional treatment will be made available to you except as otherwise stated in this consent document. Any new significant findings regarding risk will be immediately reported to you.

What are the benefits of participating in this study?
Direct benefits of participating in this study include that your PD symptoms may improve. It is unknown how long any improvements will last. Indirect benefits include that the study will inform treatment approaches for PD patients and aid in our understanding of the impact of treating multiple symptoms of PD at the same time. This has implications for PD, as well as other serious chronic conditions.

Are there any costs associated with participating in this study?
The only cost to you is travel time to and from sessions, in addition to the value of your time and that of someone who may drive you to and from appointments

Is there any compensation for participating in this study?
You will not receive compensation for participating in the study. Parking will be free-of-charge. If someone drives you to your sessions, they will be asked to wait in the waiting area, which is near to where the study is taking place.

Who will have access to the information collected during this study?
The data collected from this study are planned for publication but will not include any information that would identify you. Your name and contact information will be kept confidential and will not be listed on the data forms. Your name will be replaced with an assigned code.

The principal investigator will maintain a file of identifying participant information with non-identifying record numbers. Hardcopy documents will be kept in a locked file cabinet in the PI's office and destroyed (shredded) after 3 years.

Western Michigan University
H.S.I.R.B.
Approved for use for one year from this date:

JUN 07 2018

HSIRB Office

What are the risks of participating in this study and how will these risks be minimized?
Few to no long-term side effects have been reported for neurofeedback training. In a survey of NFB practitioners, 4% reported any adverse reactions in patients, most of which were mild and transient. Short-term side effects of NFB include fatigue, which typically subsides after a rest period. Treatment is painless.

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As in all research, there may be unforeseen risks to study participants. If an accidental injury occurs, appropriate emergency measures will be taken. However, no compensation or additional treatment will be made available to you except as otherwise stated in this consent document. Any new significant findings regarding risk will be immediately reported to you.

What are the benefits of participating in this study?
Direct benefits of participating in this study include that your PD symptoms may improve. It is unknown how long any improvements will last. Indirect benefits include that the study will inform treatment approaches for PD patients and aid in our understanding of the impact of treating multiple symptoms of PD at the same time. This has implications for PD, as well as other serious chronic conditions.

Are there any costs associated with participating in this study?
The only cost to you is travel time to and from sessions, in addition to the value of your time and that of someone who may drive you to and from appointments

Is there any compensation for participating in this study?
You will not receive compensation for participating in the study. Parking will be free-of-charge. If someone drives you to your sessions, they will be asked to wait in the waiting area, which is near to where the study is taking place.

Who will have access to the information collected during this study?
The data collected from this study are planned for publication but will not include any information that would identify you. Your name and contact information will be kept confidential and will not be listed on the data forms. Your name will be replaced with an assigned code.

The principal investigator will maintain a file of identifying participant information with non-identifying record numbers. Hardcopy documents will be kept in a locked file cabinet in the PI's office and destroyed (shredded) after 3 years.

Western Michigan University
H.S.I.R.B.
Approved for use for one year from this date:

JUN 07 2018

HSIRB Office

There are some reasons why people other than the PI may need to see information you provide. This includes organizations responsible for making sure the research is done safely and properly, including Western Michigan University or government research offices. We are obligated to report any information to the appropriate agencies that you reveal if it makes us believe that you or others have been or may be physically harmed.

What if you want to stop participating in this study?
Participating in this study is completely voluntary. Even if you decide to participate now, you can change your mind and stop at any time. There are no consequences or adverse effects for withdrawing from the study.

In order for the study to be completed on time, it is very important that you attend your scheduled sessions. If you miss more than 3 sessions without effort to re-schedule, the PI may terminate your participation.

Consent
Should you have any questions prior to or during the study, you can contact the principal investigator, JoAnne McFarland O'Rourke at (269) 330-7030 or joanne.orourke@wmich.edu. You may also contact the Chair, Human Subjects Institutional Review Board at 269-387-8293 or the Vice President for Research at 269-387-8298 if questions arise during the course of the study.

This consent document has been approved for use for one year by the Human Subjects Institutional Review Board (HSIRB) as indicated by the stamped date and signature of the board chair in the upper right corner. Do not participate in this study if the stamped date is older than one year.

I have read this informed consent document. The risks and benefits have been explained to me. I agree to take part in this study.

_____
Please Print Your Name

_____ _____
Participant's signature Date

WESTERN MICHIGAN UNIVERSITY

Human Subjects Institutional Review Board

Date: August 13, 2015

To: Amy Curtis, Principal Investigator
B. Joanne O'Rourke, Student Investigator for dissertation

From: Amy Naugle, Ph.D., Chair Amy Naugle

Re: HSIRB Project Number 15-08-01

This letter will serve as confirmation that your research project titled "Prioritizing Parkinson Disease Symptoms Focus Group" has been **approved** under the **expedited** category of review by the Human Subjects Institutional Review Board. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

Please note: This research may **only** be conducted exactly in the form it was approved. You must seek specific board approval for any changes in this project (e.g., ***you must request a post approval change to enroll subjects beyond the number stated in your application under "Number of subjects you want to complete the study***)." Failure to obtain approval for changes will result in a protocol deviation. In addition, if there are any unanticipated adverse reactions or unanticipated events associated with the conduct of this research, you should immediately suspend the project and contact the Chair of the HSIRB for consultation.

Reapproval of the project is required if it extends beyond the termination date stated below.

The Board wishes you success in the pursuit of your research goals.

Approval Termination: August 12, 2016

1903 W. Michigan Ave., Kalamazoo, MI 49008-5456
PHONE: (269) 387-8293 FAX: (269) 387-8276
CAMPUS SITE: 251 W. Walwood Hall