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Anxiety in Parkinson's disease: relation to cognition and potential of non-pharmacological interventions

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ANXIETY IN PARKINSON'S DISEASE: RELATION TO COGNITION AND POTENTIAL OF NON-PHARMACOLOGICAL INTERVENTIONS

by

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ABSTRACT

In addition to the classic motor symptoms, Parkinson's disease (PD) causes a variety of non-motor symptoms that compromise quality of life and daily functioning. Anxiety, in particular, is prevalent and debilitating, but under-studied and under-treated. There is urgent need to understand the relation of anxiety to other non-motor symptoms, and to develop evidence-based treatments. Cognitive-behavioral therapy (CBT) and aerobic and resistance exercise are promising non-pharmacological treatment strategies for anxiety in PD, with potential to simultaneously reduce additional PD symptoms.

Study 1 assessed a large sample of non-demented individuals with mild to moderate PD (N=77) and examined the relation between self-reported anxiety (Beck Anxiety Inventory [BAI]) and cognition with a focus on executive function and attention (Trail Making, Verbal Fluency, Digit Span). The majority of participants reported subclinical symptoms of anxiety (BAI ≤18). Higher anxiety correlated with poorer set-shifting, as well as with more advanced disease stage and severity.

Study 2 implemented a single-case experimental design to evaluate the utility and feasibility of a 12-week cognitive-behavioral intervention for individuals with PD who

also met criteria for a DSM-5 anxiety disorder (N=9). Weekly therapy sessions were conducted in-person (N=5) or via secure videoconferencing (N=4). At post-treatment, five participants reported significant reductions in anxiety and two additional participants reported significant reductions in comorbid depression. Most improvements were maintained at 6-week follow-up. Effects of CBT on secondary outcome measures (e.g., cognition, motor symptoms, sleep) varied widely across participants. Adherence and retention were high, as was satisfaction with treatment.

Study 3 reviewed the effects of aerobic and resistance exercise on disturbances of mood, cognition, and sleep in PD and healthy adults. The literature supports aerobic and resistance exercise as feasible and promising adjunct treatments for mood, cognition, and sleep in PD, contingent upon additional exercise research that systematically targets non-motor symptom outcomes.

Together these studies show that even subclinical anxiety is associated with cognitive disturbance in mild-moderate PD, and provide preliminary evidence for the effectiveness of CBT (in-person and internet-delivered), as well as aerobic and resistance exercise, as encouraging and viable treatments for anxiety in this disorder.

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LIST OF ABBREVIATIONS

ADIS-5	Anxiety Disorders Interview Schedule for DSM-5
ADL	Activities of Daily Living
AD	Alzheimer's Disease
AS	Apathy Scale
ASI	Anxiety Sensitivity Index
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory – Version II
BDNF	Brain-Derived Neurotrophic Factor
CARD	Center for Anxiety and Related Disorders
CBT	Cognitive Behavioral Therapy
CI	Confidence Interval
CSQ-8	Client Satisfaction Questionnaire
CSR	Clinical Severity Rating
DAT	Dopamine Transporter
DBS	Deep Brain Stimulation
DSM	Diagnostic and Statistical Manual of Mental Disorders
DX	Diagnosis
DYS	Dysthymia
FAS	Phonemic Fluency
FES	Falls Self-Efficacy Scale
FOG	Freezing of Gait
GAD	Generalized Anxiety Disorder
GDS	Geriatric Depression Scale
GOR	Gretchen O. Reynolds
HADS (-A)	Hospital Anxiety and Depression Scale (-Anxiety Scale)
H&Y	Hoehn & Yahr motor stage
IE	Independent Evaluator
LC	Locus Coeruleus
LED	Levodopa Equivalent Dosage
LPD	Left-side Motor Symptom Onset
LSA	Limited-symptom Panic Attack
McGill-SF	Short-Form McGill Pain Questionnaire
MCI	Mild Cognitive Impairment
MDD	Major Depressive Disorder
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
NMS	Non-motor Symptoms
NOS	Not Otherwise Specified
NSRI	Noradrenaline Selective Reuptake Inhibitors
OASIS	Overall Anxiety Severity and Impairment Scale
ODSIS	Overall Depression Severity and Impairment Scale
PAS	Parkinson Anxiety Scale

PCS	Pain Catastrophizing Scale
PD	Parkinson's Disease
PDQ-39	Parkinson's Disease Quality of Life Questionnaire
PDSS	Panic Disorder Severity Scale
PDSS-2	Parkinson's Disease Sleep Scale – Version 2
PSQI	Pittsburgh Sleep Quality Index
PSWQ	Penn State Worry Questionnaire
QoL	Quality of Life
RC	Reliable Change
RCT	Randomized Controlled Trial
RPD	Right-side Motor Symptom Onset
SAD	Social Anxiety Disorder
SCED	Single-Case Experimental Design
SD	Standard Deviation
S_{diff}	Standard Error of the Difference
SIAS	Social Interaction Anxiety Scale
SOC	Social Anxiety Disorder
SPIN	Social Phobia Inventory
SSRI	Selective Serotonin Reuptake Inhibitors
STAI (-S/T)	State-Trait Anxiety Inventory (-State/Trait)
TMT	Trail Making Test
UP	Unified Protocol for Transdiagnostic Treatment of Emotional Disorders
UPDRS	Unified Parkinson's Disease Rating Scale

CHAPTER 1: GENERAL INTRODUCTION

Parkinson's disease (PD) affects approximately 1.8% of the population over age 65, as well as younger individuals, with the prevalence projected to double by 2040 (Kowal, Dall, Chakrabarti, Storm, & Jain, 2013; Mayeux, 2003; Prediger, Matheus, Schwarzbold, Lima, & Vital, 2012). The national economic burden of PD in 2010 was estimated to be over $20.7 billion in the United States alone (Kowal et al., 2013). In light of the substantial human, economic, and societal costs, it is imperative to better characterize and understand the many symptoms of PD that emerge throughout the course of the disorder, in order to develop treatments to alleviate current symptoms or to potentially delay disease progression.

Traditionally conceptualized as a classic movement disorder, PD is characterized by dopaminergic neuronal death in the substantia nigra and subsequent basal ganglia dysfunction. The disease is diagnosed upon observation of the cardinal motor signs: reduced movement and/or speed of movement (akinesia or bradykinesia), rigidity, tremor, and disorders of gait, balance, and posture (Grimbergen, Langston, Roos, & Bloem, 2009; Jankovic, 2008; Kim, Allen, Canning, & Fung, 2013; Rodriguez-Oroz et al., 2009). In addition to the motor symptoms, various non-motor symptoms (NMS) also appear during the course of the disease, but they remain poorly understood and grossly undertreated. Prevalent NMS include neuropsychiatric symptoms (e.g., anxiety, depression, apathy, and hallucinations), sleep disruption, cognitive impairments, sensory symptoms (e.g., hyposmia, vision difficulties, and pain), and autonomic and

gastrointestinal dysfunction, as well as fatigue (Chaudhuri, Healy, & Schapira, 2006; Rodriguez-Oroz et al., 2009). The NMS often emerge in the early stages of PD or in the prodromal period before the emergence of motor symptoms, and significantly contribute to a reduced quality of life, often to an even greater extent than the motor symptoms (Chaudhuri et al., 2006; Hanna & Cronin-Golomb, 2012; Martinez-Martin, Rodriguez-Blazquez, Kurtis, Chaudhuri, & Group, 2011; Prakash, Nadkarni, Lye, Yong, & Tan, 2016). Although research is increasingly beginning to examine the NMS (Cronin-Golomb, 2013), they continue to be under-diagnosed and inadequately treated in this population (Chaudhuri & Odin, 2010; Seppi et al., 2011; Shulman, Taback, Rabinstein, & Weiner, 2002). Accordingly, there is a critical need to better characterize and treat these symptoms, particularly those for which there are efficacious, evidence-based treatments within the general (non-PD) population. With better recognition and diagnosis of NMS, we can hope to adapt extant interventions for use in PD and also to develop novel treatments to improve NMS in this population, with the goal of optimizing quality of life and daily functioning across all stages of the disease.

Anxiety in PD: Prevalence and Manifestation

Of the NMS, anxiety is especially common and disabling. Anxiety disorders occur at higher rates in PD than in age- and sex-matched control adults (Nuti et al., 2004) as well as control adults matched for having a chronic disorder affecting movement (osteoarthritis) (M. A. Menza, Robertson-Hoffman, & Bonapace, 1993). In a sample of 127 adults with idiopathic PD, current and lifetime prevalence rates of at least one

anxiety disorder diagnosis were 43% and 49%, respectively (Pontone et al., 2009), although prevalence estimates for anxiety in PD vary widely across studies. In considering persons with PD and clinically significant anxiety disorders or those who score above clinical cutoffs on anxiety rating scales, current prevalence rates range from 12.8% to 43.0% (Broen, Narayen, Kuijf, Dissanayaka, & Leentjens, 2016; N. N. Dissanayaka et al., 2010; N. N. Dissanayaka et al., 2014; Pontone et al., 2011; Richard, Schiffer, & Kurlan, 1996; Walsh & Bennett, 2001), with anxiety symptoms occurring in 20% to over 50% of individuals with PD (Chen & Marsh, 2014; Marinus, Leentjens, Visser, Stiggelbout, & van Hilten, 2002; Shulman et al., 2002).

With regard to types of anxiety, the most common anxiety disorders reported in PD are panic disorder, generalized anxiety disorder (GAD), social phobia, and anxiety disorder, not otherwise specified (NOS) (N. N. Dissanayaka et al., 2010; N. N. Dissanayaka et al., 2014). At the same time, additional clinical subtypes of anxiety have been described in PD, e.g., anxious-depression (R. G. Brown et al., 2011). To further complicate the classification and diagnosis of anxiety in PD, some individuals with PD report situational anxiety related to motor symptoms, such as fear of falling or avoidance of crowded areas due to freezing of gait (Pontone et al., 2009). There is a need to better elucidate the unique characteristics and subtypes of anxiety in PD in order to improve symptom recognition and diagnostic accuracy and also to inform treatment development.

In addition to its high prevalence, anxiety is particularly problematic in PD because of its co-occurrence with various other NMS. Anxiety is frequently comorbid with additional psychiatric symptoms, especially depression, as well as with fatigue,

sleep disruption, and sensory symptoms. Comorbidity of these NMS is associated with increased disease severity as indexed by the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn & Yahr motor stage (H&Y), and the Schwab & England ADL scale (Jiang et al., 2015; M. A. Menza et al., 1993; Shulman, Taback, Bean, & Weiner, 2001). Moreover, NMS may reduce quality of life to a greater degree than the motor symptoms (Qin et al., 2009) and also increase caregiver burden (Schrag, Hovris, Morley, Quinn, & Jahanshahi, 2006). Anxiety, in particular, correlates with greater disability (Witjas et al., 2002) and uniquely contributes to a poorer quality of life in PD, independent of depression (Havlikova et al., 2011), and more so than depression, cognitive status, or motor stage (Hanna & Cronin-Golomb, 2012). Unfortunately, despite such adverse effects, anxiety in PD continues to be understudied, under-diagnosed, and under-treated, with many trials continuing to focus on depression and only including anxiety as a secondary outcome, if at all (Leentjens, Dujardin, Marsh, Martinez-Martin, et al., 2011; Shulman et al., 2002; Weintraub & Burn, 2011). Better recognizing and describing anxiety across all stages of the disease may lead to the development of novel interventions to directly target anxiety in PD and improve quality of life.

Brain Bases of Anxiety in PD

Although the increased prevalence of anxiety in PD may be related, in part, to the psychosocial stress and/or stigma that may occur in response to diagnosis, it is also clear that it is endemic to the disease. A variety of neurobiological mechanisms may contribute to the development and maintenance of anxiety in this population. Since the

1960s, PD has been well-characterized by dopaminergic loss in the striatum and associated disruption of the basal ganglia and motor circuits (Rodriguez-Oroz et al., 2009). Distinctive inclusion aggregates, either globular Lewy bodies and/or spindle-like Lewy neurites, develop in vulnerable neurons as the disease progresses (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004; Obeso, Rodriguez-Oroz, Rodriguez, Arbizu, & Gimenez-Amaya, 2002). Braak and colleagues divided the neuropathological progression in PD into six stages, with pathology first emerging in the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus (stages 1-2), then progressing to the substantia nigra and midbrain (stages 3-4), and ultimately compromising the neocortex (stages 5-6) (Braak et al., 2004). Across these stages, neuronal deterioration significantly affects both somatomotor and limbic systems (Braak et al., 2003), including the amygdala and its nuclei, which may contribute to changes in emotional, cognitive, and autonomic functioning in PD, given the amygdala's projections to limbic areas (e.g. hippocampus and entorhinal region), prefrontal cortex, and centers that regulate endocrine functions (Braak et al., 1994).

Both animal and human studies suggest an association between dopaminergic depletion and anxiety in PD. Tadaiesky and colleagues (Tadaiesky et al., 2008) reported an increase in anxiety among rats following induced degeneration of dopaminergic neurons in the striatum and subsequent dopaminergic loss in prefrontal regions. In humans, striatal dopamine transporter (DAT) imaging has revealed an inverse association between anxiety in PD and DAT availability in the left anterior putamen (Weintraub et al., 2005), although the study only included individuals with relatively mild affective

symptoms. A second DAT study reported a positive correlation between social anxiety symptoms and DAT density in the bilateral putamen and left caudate (Moriyama et al., 2011). This second study was limited by the relatively small sample size (11 PD adults with social anxiety disorder (SAD) vs. 21 PD adults without SAD), as well as the relatively young mean age of the sample (51.2 years) and the failure to measure or control for depressive symptoms. A study of 34 newly diagnosed, untreated adults with PD revealed significantly lower DAT availability in the bilateral caudate and left putamen when comparing PD participants with (n=9) and without (n=25) anxiety, using a cut-off score of 7 on the anxiety subscale of the Hospital Anxiety Depression Scale (Erro et al., 2012). In the overall PD group, increased anxiety correlated with reduced DAT availability in the right caudate. Taken together, these studies implicate dopaminergic dysfunction in the striatum in the development of anxiety in PD, and suggest the need for research to clarify the potential lateralization of this association across all stages of PD.

In addition to dopaminergic systems, non-dopaminergic dysfunction has also been implicated as a potential neurobiological mechanism of anxiety in PD, specifically within noradrenergic and serotonergic systems. First, postmortem studies of individuals with PD have revealed the most extensive neuronal loss in the noradrenergic locus coeruleus (LC), even in comparison to the substantia nigra (Zarow, Lyness, Mortimer, & Chui, 2003). The basal ganglia's extensive connections with brainstem nuclei, including the LC and raphe nuclei, suggest disruption to noradrenergic and serotonergic functioning, respectively (Obeso et al., 2002), starting in early disease stages with PD neuropathology now thought to begin in the lower brainstem before progressing to the substantia nigra

(Braak et al., 2004). This disruption may contribute to the development of anxiety in PD, given that noradrenergic and serotonergic systems and their projections to corticolimbic regions are heavily involved in the modulation of anxiety in the general population (Millan, 2003; Ressler & Nemeroff, 2000). Indeed, anxiety was reported to negatively correlate with dopamine and noradrenaline transporter binding in the left LC, as well as the left ventral striatum, left caudate, and bilateral amygdala and thalamus in a sample of 20 adults with PD, eight of whom had a history of major depression (Remy, Doder, Lees, Turjanski, & Brooks, 2005). Although the study focused on depression in PD and only examined anxiety as a secondary outcome, the authors noted that the inverse association between anxiety and LC binding, in particular, implicates noradrenergic dysfunction in the neurobiology of anxiety in PD. Of note, the noradrenergic LC has been associated with panic disorder in PD and the general population (Gorman, Kent, Sullivan, & Coplan, 2000; Walsh & Bennett, 2001), and panic disorder in PD has been correlated with an earlier age of motor symptom onset (Pontone et al., 2009), underscoring the need to consider non-dopaminergic dysfunction in the brainstem as a potential mechanism of anxiety in the early stages of PD.

In addition to disruption to multiple neurotransmitter systems, PD pathology affects various brain regions involved in the modulation of anxiety, namely limbic structures, as well as ventral prefrontal and parietal regions. The olfactory bulb is one of the first affected structures, with neuropathology emerging in the presymptomatic stages of the disease (Braak et al., 2004). This finding is important because anxiety, in turn, has been associated with olfactory impairment in a study of 96 non-demented adults with PD

with a short disease duration on average, suggesting that NMS, including olfactory and mood disturbances, may develop early in the disease as a result of brainstem neuropathology (Berendse, Roos, Raijmakers, & Doty, 2011). In addition to early involvement of the brainstem and limbic structures, there is evidence of focal cortical thinning in orbitofrontal cortex, ventrolateral prefrontal cortex, and occipito-parietal regions, as well as subcortical volume loss in the striatum, among non-demented adults with early-stage PD, who also reported high levels of state anxiety relative to that seen in healthy control participants (Tinaz, Courtney, & Stern, 2011). Although anxiety did not correlate with imaging data, Tinaz and colleagues (2011) posited that the higher anxiety levels in the PD group may relate to cortical thinning and subsequent disruption of information flow between limbic and neocortical areas involved in emotional processing.

In sum, abnormalities in many neurotransmitter systems and brains regions may contribute to the development and maintenance of anxiety in PD, suggesting that anxiety is not solely a reaction to the motor symptoms of the disease, but rather a symptom arising from the pathophysiology of the disease. For further review of potential neurobiological mechanisms of anxiety in PD, refer to (Prediger et al., 2012).

Current Treatment of Anxiety in PD: Pharmacological Strategies

Despite the high prevalence and detrimental impact of anxiety in PD, there are very few relevant treatment studies (Chen & Marsh, 2014; Djamshidian & Friedman, 2014; Seppi et al., 2011; Weintraub & Burn, 2011). In regard to pharmacological interventions for anxiety in PD, there is a concerning lack of recommended treatments or

consistent prescribing patterns by neurologists (Palanci, Marsh, & Pontone, 2011; Pontone et al., 2013; Prediger et al., 2012). Among 250 adults with PD, over half of the patients with anxiety disorders without comorbid depression were untreated with medications (Pontone et al., 2013), highlighting its under-recognition and under-treatment.

Anxiolytic medications with potential application in PD include benzodiazepines, buspirone, selective serotonin reuptake inhibitors (SSRIs), noradrenaline selective reuptake inhibitors (NSRIs), tricyclic antidepressants, and adjustment in dopaminergic dose, although the potential of these agents is mitigated in part by concerns about variable efficacy and unfavorable side-effect profiles in this population. For example, many of these drugs have the potential for adverse side effects, including sedation, cognitive impairment, falls, insomnia, and nausea (Chen & Marsh, 2014; Pena et al., 2016; Prediger et al., 2012). It is important to note that there is also the potential for harmful drug-drug interactions among older adults who frequently use both prescription and nonprescription medications (Qato et al., 2008), and persons with PD, many of whom are older, may wish to avoid adding another medication to their regimen if alternative treatments for anxiety are available. Finally, pharmacological treatments designed to treat anxiety in the general population are not PD-specific and therefore may not consider the underlying neurobiology of the disorder (B. S. Connolly & Fox, 2012). Antidepressants, commonly prescribed for the treatment of both depression and anxiety in the general population, are generally well-tolerated in PD (Pena et al., 2016), and across two studies, have yielded large, but non-significant, secondary effects on anxiety

(Troeung, Egan, & Gasson, 2013); the authors noted that the effects likely did not reach statistical significance due to the limited sample size and the potential for Type II error. Antidepressants, do not, however, work for many individuals with PD (Weintraub & Hoops, 2011). These findings together highlight the need for controlled treatment trials with a focus on anxiety in PD, in order to clarify the effects of antidepressants on this prevalent, but often under-studied, symptom.

Potential of Cognitive-Behavioral Treatment for Anxiety in PD

Given the counter-indications of pharmacologic treatments for anxiety in PD, psychosocial and behavioral treatments may present a viable alternative treatment strategy for anxiety in PD, with emerging evidence to support the use of cognitive-behavioral therapy (CBT), in particular. As in pharmacological studies, anxiety has also been largely neglected in psychosocial treatment research in PD, typically appearing as only a secondary outcome measure in depression studies (S. Yang, Sajatovic, & Walter, 2012). A review of psychosocial interventions in PD found only eight studies published between 1997 and 2011 that included depression or anxiety as outcomes, including studies of CBT, psychodrama, education, behavior therapy, and multidisciplinary rehabilitation (S. Yang et al., 2012). In this review, CBT was the most frequently studied intervention and showed promising effects for depression and anxiety in PD, although the studies were generally limited by small sample sizes, and none included individuals with PD who met diagnostic criteria for an anxiety disorder (e.g., per DSM-5).

The evidence that does exist so far suggests that CBT may be effective for treatment of depression and/or anxiety in PD and warrants significant clinical and research attention (Armento et al., 2012; Egan, Laidlaw, & Starkstein, 2015; Pachana et al., 2013). In a pilot study (Dobkin, Allen, & Menza, 2007) followed by a randomized controlled trial (Dobkin, Menza, Allen, Gara, et al., 2011), individual CBT improved depression in a sample of 80 depressed adults with PD relative to clinical monitoring, and also improved anxiety, quality of life, coping, and PD symptoms (motor and non-motor) as indexed by the Unified Parkinson's Disease Rating Scale (total score). In exploratory analyses of UPDRS subscales, significant improvements were observed in mood and motor function in the CBT group (Dobkin, Menza, Allen, Gara, et al., 2011). There is also preliminary evidence that telephone-administered or internet-based CBT may be feasible and effective treatments for depression and anxiety in PD (Calleo et al., 2015; Kraepelien, Svenningsson, Lindefors, & Kaldo, 2015; Veazey, Cook, Stanley, Lai, & Kunik, 2009). Group CBT has also yielded promising reductions in depression and anxiety in PD with follow-up periods of one to six months, though samples were small (Feeney, Egan, & Gasson, 2005; Troeung, Egan, & Gasson, 2014). Specific to anxiety, a single case report of a 60-year-old man with PD reported significant improvement in his social anxiety after 12 weeks of group CBT, both at post-treatment and at a 6-month follow-up (Heinrichs, Hoffman, & Hofmann, 2001). In light of these promising findings, it would be of value to systematically examine the utility and feasibility of CBT for anxiety among adults with PD, particularly in larger samples, with longer follow-up periods, and with diagnostic information as an inclusion criterion, as many studies

continue to rely on self-report cutoffs to determine anxiety levels. In addition to improvements in anxiety and depression, CBT may also yield benefits for other NMS, such as cognition or sleep (Dobkin et al., 2014; H. Yang & Petrini, 2012). Accordingly, CBT for anxiety in PD represents an attractive treatment approach and a viable alternative to pharmacological treatment with minimal side effects and with the potential to teach lasting skills to individuals to manage anxiety and improve overall quality of life.

Potential of Exercise Interventions for Anxiety and Non-Motor Symptoms in PD

In addition to CBT, exercise interventions represent another treatment strategy that may improve anxiety and other NMS in PD, particularly for those who do not respond to CBT or who do not have access to CBT. To date, exercise research in PD has largely focused on the physical benefits, with evidence that aerobic and resistance exercise improve motor symptoms, strength, balance, and gait in PD, as well as quality of life (da Silva et al., 2016; Goodwin, Richards, Taylor, Taylor, & Campbell, 2008; Lamotte et al., 2015; Lamotte G., 2015; Monteiro et al., 2016).

Besides the promising effects on physical functioning, aerobic and resistance exercise may also improve specific NMS in PD, including mood, cognition, and sleep (Lamotte et al., 2015; Murray, Sacheli, Eng, & Stoessl, 2014; Nascimento et al., 2014; Reynolds, Otto, Ellis, & Cronin-Golomb, 2016), as will be discussed in detail in Study 3. To illustrate, in a small study of 20 participants (10 per group), twelve weeks of twice weekly Nordic walking significantly reduced fatigue, depression, and apathy among PD participants, relative to a usual-care control group (Cugusi et al., 2015). With regard to

potential cognitive benefits, a recent RCT revealed that two years of structured exercise, either progressive resistance training or a program of stretching, balance and strengthening yielded improvements in attention and working memory in non-demented adults with mild to moderate PD (David et al., 2015). Aerobic and resistance training may also improve sleep in PD (Nascimento et al., 2014; Rodrigues de Paula, Teixeira-Salmela, Coelho de Morais Faria, Rocha de Brito, & Cardoso, 2006). Additional research with larger sample sizes, objective sleep measures, and more rigorous control groups are needed to better understand the potential effects of exercise on sleep, as well as cognition and mood, in this population.

As well as aerobic and resistance training, there is a growing body of evidence on the utility of alternative forms of exercise, such as dance, tai chi, and qigong as potential treatments for motor and non-motor symptoms in PD. Dance, especially tango, may yield benefits for quality of life, mood, cognition, and sleep in PD, besides motor improvements (Hackney & Earhart, 2009; Hashimoto, Takabatake, Miyaguchi, Nakanishi, & Naitou, 2015; Lewis, Annett, Davenport, Hall, & Lovatt, 2016; McNeely, Duncan, & Earhart, 2015; Rios Romenets, Anang, Fereshtehnejad, Pelletier, & Postuma, 2015; Sharp & Hewitt, 2014; Sumec, Filip, Sheardova, & Bares, 2015). Likewise, individuals with PD who engaged in 16 weeks of tai chi (three times per week), relative to a non-contact control group, showed significant improvement on overall quality of life and emotional well-being, as well as a trend toward improvement in working memory (Nocera, Amano, Vallabhajosula, & Hass, 2013). Similarly, in a small pilot study of 7 participants with PD, six weeks of qigong improved gait and sleep (Wassom, Lyons,

Pahwa, & Liu, 2015). Given these encouraging results, further studies with larger sample sizes are warranted to determine the most effective type of alternative exercise in PD and to more systematically examine questions of exercise dose and longevity of effects with regard to both motor and non-motor symptoms.

The potential mechanisms of exercise-induced effects in PD are discussed in greater detail in Study 3, but broadly speaking, exercise in humans is thought to increase levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (Szuhany, Bugatti, & Otto, 2015), which has significant implications for the potential mechanisms of action of exercise in neurodegenerative diseases, such as PD, and any associated improvements in cognition (Campos et al., 2016). It has been suggested that exercise may exert neuroprotective effects and also improve cognition in PD via neurotrophic factors and neuroplasticity (Ahlskog, 2011b). More specifically, the combination of aerobic exercise and goal-based motor skill training in PD may support neuroplasticity in critical motor circuits known to be affected in the disease, such as the striatopallidal (indirect) pathway in the striatal-thalamic-cortical circuit associated with automaticity (Petzinger et al., 2013). These changes may include normalization of corticomotor excitability (Fisher et al., 2008), as well as increased dopamine D2 receptor binding potential in the dorsal striatum of adults in the early stages of PD (Fisher et al., 2013; Petzinger et al., 2013). In addition to effects on corticomotor excitation and BDNF levels, exercise may also induce gray matter volume changes in PD (Hirsch, Iyer, & Sanjak, 2016). For example, twenty individuals with PD who completed six weeks of balance training showed improvements in balance and associated gray matter changes in

several brain regions (anterior precuneus, inferior parietal, ventral premotor, anterior cingulate, and middle temporal gyrus), as well as a time-dependent volume increase in the right cerebellum (Sehm et al., 2014). Further research is needed to elucidate potential mechanisms of exercise-induced brain and behavioral changes in PD, with the goal of designing tailored exercise interventions to improve the motor and non-motor symptoms of the disease, while also supporting overall physical fitness and brain health, across all stages of the disease.

In summary, aerobic and resistance training have the greatest amount of empirical support with regard to the positive impact of exercise on the motor symptoms of PD, with alternative forms of exercise being explored more recently. The majority of studies to date have focused primarily on the physical benefits of exercise, rather than specifically targeting NMS such as mood, cognition, and sleep. Given the known anxiolytic, cognition-, and sleep-enhancing effects of exercise in the general population (Asmundson et al., 2013; Kredlow, Capozzoli, Hearon, Calkins, & Otto, 2015; Smith et al., 2010; B. M. Wipfli, Rethorst, & Landers, 2008), exercise may be an especially favorable adjunctive intervention for individuals with PD to support overall physical health and motor functioning, and also to potentially improve distressing NMS, which often emerge in the early stages of the disease. Further, to the extent that exercise may promote neuroplasticity in PD, particularly within basal ganglia circuitry and prefrontal regions, it may ultimately prevent or at least delay further disease progression.

Specific Aims and Hypotheses

The three studies presented here were designed to achieve the following goals: (1) to examine the relation between anxiety and cognition among adults with PD, (2) to determine the utility and feasibility of a transdiagnostic cognitive-behavioral intervention to treat anxiety in PD, and (3) to synthesize the literature on aerobic and resistance exercise in older adults and in PD and highlight the potential therapeutic effects of exercise as an adjunctive treatment for symptoms of mood, cognition, and sleep in PD.

Study One: The Relation of Anxiety and Cognition in PD

The increasing research focus on NMS in PD has underscored the high degree of comorbidity among these symptoms, even in the early stages of the disease (Naismith & Lewis, 2011; Stankovic et al., 2016). In order to better identify and treat these symptoms in clinical practice, a more thorough understanding of the relations among NMS is essential. In particular, mood and dysexecutive symptoms may emerge in early stages of the disease, due to disruption in brainstem and frontostriatal systems, respectively (Chaudhuri et al., 2006; Foltynie, Brayne, Robbins, & Barker, 2004; Prediger et al., 2012; Williams-Gray, Foltynie, Brayne, Robbins, & Barker, 2007). Study One examined the relation between anxiety and specific aspects of cognition (executive function and attention) among a large sample of adults with mild to moderate idiopathic PD. It was hypothesized that anxiety would correlate with cognitive performance in PD, such that individuals who perform more poorly on cognitive tests would report higher anxiety than those with better cognitive performance. Poor cognitive performance may indicate more

advanced PD pathology, and pre-existing anxiety may interfere with one's ability to perform optimally on cognitive testing.

Study Two: The Utility and Feasibility of Cognitive-Behavioral Treatment for Anxiety in Parkinson's Disease: A Pilot Study

With emerging research in PD on the classification, recognition, and pathophysiology of anxiety in PD, we can hope to use this information to develop effective, evidence-based treatments to improve affective symptoms in this population. Pharmacological treatments for anxiety in PD represent one strategy, although they do not work for many adults with PD, and also have the potential for adverse side effects. The goal of Study Two was to pilot a transdiagnostic cognitive-behavioral intervention in persons with PD who also met criteria for at least one anxiety disorder. This study critically evaluated the utility and feasibility of this intervention using a multiple-baseline single-case experimental design, allowing examination of post-treatment changes in anxiety and secondary outcome measures (e.g., depression, sleep, cognition, quality of life). Treatment adherence and satisfaction were also evaluated. It was hypothesized that CBT would reduce anxiety at post-treatment and a 6-week follow-up, and also improve secondary outcomes, including depressive symptoms and quality of life. It was also hypothesized that CBT would alleviate cognitive symptoms, as well as disease-specific motor symptoms-- e.g., freezing of gait or tremor-- because those symptoms may be exacerbated by anxiety. The third prediction was that study participants would report satisfaction with treatment, which may further contribute to symptomatic change.

Study Three: The Therapeutic Potential of Exercise to Improve Mood, Cognition, and Sleep in PD

Research in the general population suggests that CBT may not improve symptoms of anxiety or depression for all individuals (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Loerinc et al., 2015). As an alternative intervention for disturbances of mood, as well as of cognition and sleep, aerobic and resistance exercise present especially feasible and appealing treatment approaches for those with PD. Robust evidence in the general population indicates that exercise yields positive effects on mood (reducing both anxiety and depression), cognition, and sleep (Asmundson et al., 2013; Bherer, Erickson, & Liu-Ambrose, 2013; Kredlow et al., 2015; Smith et al., 2010; Stathopoulou, Powers, Berry, Smits, & Otto, 2006). In PD, aerobic exercise has largely been used to improve physical symptoms, but it likely has the potential to also improve NMS; research studies must be designed to specifically measure potential changes in mood, cognition, and sleep. The goal of Study Three was to synthesize the research on the effects of aerobic and resistance exercise on mood, cognition, and sleep, as shown in healthy older adults and in individuals with PD. The review was intended to provide a rationale for the targeted use of exercise interventions to ameliorate symptoms of mood, cognition, and sleep in PD.

Significance

This research project proposes to advance the study of anxiety in PD, with the goal of better recognizing, classifying, and treating this as well as other NMS (cognition

and sleep) in PD. To date, research on affective symptoms in PD has focused primarily on depression, with anxiety often considered only as a secondary or exploratory outcome, despite the significant negative effects of anxiety on quality of life (Hanna & Cronin-Golomb, 2012). The current project has PD-related anxiety as its primary focus.

First, the results from Study One expand our knowledge of the relations among anxiety and cognition in PD, in order to inform future diagnosis and treatment of these symptoms. Second, the pilot study of CBT for anxiety in PD critically evaluates the utility and feasibility of an intensive, but time-limited, intervention. To the best of our knowledge, this is the first study of individual transdiagnostic CBT in PD to focus exclusively on anxiety, rather than depression or some combination of the two. Another innovative aspect of Study Two was that CBT was conducted in the clinic or over the internet according to participant preference, which has significant implications for the dissemination of psychological treatments among older adults with neurologic disorders. The hope is that these findings will provide the impetus for further treatment development for anxiety and NMS in PD, including the eventual implementation of larger, randomized controlled trials to establish evidence-based interventions for anxiety, as well as for comorbid symptoms of mood, cognition, and sleep. Finally, as CBT may not be available or feasible for many persons with PD and may not be effective for some, the potential of aerobic and resistance exercise is considered as alternative non-pharmacological treatment with the ability to improve not only mood, but also cognition and sleep in PD, with simultaneous benefits for physical functioning and overall health.

In conclusion, these three studies together significantly expand current knowledge of anxiety in PD, with regard to both the manifestation and treatment of this symptom. This work emphasizes the increasing need for research and clinical focus on NMS in PD, especially anxiety, in order to better recognize and diagnose these symptoms and to develop disease-specific treatments to optimize quality of life and daily functioning.

CHAPTER 2: STUDY ONE – THE RELATION OF ANXIETY AND COGNITION IN PARKINSON'S DISEASE[1]

Introduction

Afflicting approximately 1% of the population over age 60 (Mayeux, 2003; Prediger et al., 2012), Parkinson's disease (PD) is associated with classic motor symptoms as well as with a variety of non-motor symptoms, including cognitive dysfunction and neuropsychiatric symptoms (Cronin-Golomb, 2013). Non-motor symptoms are often comorbid with one another, with increased comorbidity associated with greater disease severity as indexed by motor and functional measures (Shulman et al., 2001). These non-motor symptoms significantly contribute to a poor quality of life in individuals with PD (Duncan et al., 2014), often to a greater extent than the motor symptoms (Bonnet & Czernecki, 2013; Qin et al., 2009), but they remain understudied and under-diagnosed (Shulman et al., 2002). In particular among the non-motor symptoms, anxiety and cognitive dysfunction are highly prevalent in PD, even in the early stages of the disease. Emerging research is beginning to more closely consider cognitive impairment and affective disorders in this population (Bogdanova & Cronin-Golomb, 2012, 2013; Pluck & Brown, 2002; Santangelo et al., 2009), but the literature remains limited (Poletti, De Rosa, & Bonuccelli, 2012).

Although the relation between anxiety and cognitive function is not well characterized in PD, anxiety has long been associated with impaired cognitive

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performance in non-PD populations, particularly on attentionally demanding tasks (Derakshan & Eysenck, 2009). In older adults, including those with mild cognitive impairment, anxiety has been associated with cognitive deficits (Forsell, Palmer, & Fratiglioni, 2003) and has also been shown to predict cognitive decline in individuals without depression or cognitive impairment (Sinoff & Werner, 2003). There is some evidence that those who develop anxiety disorders later in life (age 55 and above; an age group that includes most individuals with PD) may exhibit poorer overall cognition than those with early-onset anxiety disorders (DeLuca et al., 2005), suggesting that anxious individuals with PD may be at an increased risk for cognitive dysfunction due to their age alone. Specifically, individuals with anxiety disorders exhibited impairments in executive function and episodic memory (Airaksinen, Larsson, & Forsell, 2005), and older adults with generalized anxiety disorder showed impairments in short-term and working memory, information processing speed, inhibition and problem-solving, and immediate and delayed memory, compared to control adults (Butters et al., 2011; Caudle et al., 2007; Mantella et al., 2007). These findings suggest that anxiety and cognition are likely to also be related in PD.

The lack of research on affective symptoms in PD is concerning, as clinically significant anxiety occurs in up to 40% of individuals with PD (Aarsland, Marsh, & Schrag, 2009; Walsh & Bennett, 2001), and anxiety disorders occur at higher rates in PD than in the overall population (Nuti et al., 2004; Walsh & Bennett, 2001). Anxiety in PD contributes to reduced subjective quality of life (Carod-Artal, Ziomkowski, Mourao Mesquita, & Martinez-Martin, 2008; N. N. Dissanayaka et al., 2010; Hanna & Cronin-

Golomb, 2012; Havlikova et al., 2011; Leentjens, Dujardin, Marsh, Martinez-Martin, et al., 2011; McKinlay et al., 2008; Pontone et al., 2009) and greater self-perceived disability (Witjas et al., 2002). Of further concern in PD, anxiety may compromise information processing ability and thereby negatively affect gait, potentially leading to falls (Ehgoetz Martens, Ellard, & Almeida, 2015). Anxiety can also co-occur with depression in PD (N. N. Dissanayaka et al., 2010; M. A. Menza et al., 1993), and clinically significant depressive symptoms occur at rates of 35% in this population (Reijnders, Ehrt, Weber, Aarsland, & Leentjens, 2008). Consideration of comorbid depression is important, given that depression in PD has been associated with cognitive decline (Starkstein, Mayberg, Leiguarda, Preziosi, & Robinson, 1992), and with executive dysfunction and working memory deficits, even in early disease stages (Dirnberger & Jahanshahi, 2013; Uekermann et al., 2003).

Cognitive dysfunction occurs in the majority of individuals with PD (Mamikonyan et al., 2009). Up to 57% of those with PD are affected by mild cognitive impairment within the first 3-5 years after diagnosis (Williams-Gray et al., 2007), and up to 14% of individuals with PD over age 65 develop some type of cognitive impairment each year (Galvin, 2006). Cognitive deficits in PD are associated with greater motor severity and typically include executive dysfunction, visuospatial and constructional deficits, and attention/working memory deficits (Dirnberger & Jahanshahi, 2013; Muslimovic, Post, Speelman, & Schmand, 2005; Pfeiffer, Lokkegaard, Zoetmulder, Friberg, & Werdelin, 2014). Visuospatial, attentional, and executive deficits are the most typical in PD individuals with mild cognitive impairment (PD-MCI) (Aarsland, Bronnick,

& Fladby, 2011). In a recent study of individuals with mild to moderate PD with neither dementia nor mild cognitive impairment, measures of attention and executive function (frontal-type tests) were the most sensitive to cognitive compromise (Miller, Neargarder, Risi, & Cronin-Golomb, 2013). Understanding cognitive deficits in the early stages of the disease is important because they may predict the progression of cognitive dysfunction to dementia (Azuma, Cruz, Bayles, Tomoeda, & Montgomery, 2003; Kehagia, Barker, & Robbins, 2010; Levy et al., 2002; Williams-Gray et al., 2009; Williams-Gray et al., 2007).

Regarding potential mechanisms, similar brain regions and neurotransmitter systems have been implicated in the development of anxiety and cognitive dysfunction in PD and in the overall population, suggesting that the symptoms may be related in PD, at least in part, as a result of shared underlying neurocircuitry. First, disrupted frontostriatal circuitry likely contributes to the executive deficits in non-demented individuals with PD, including deficits in flexibility, planning, and working memory (Kehagia, Barker, et al., 2010). Specifically, these impairments have been associated with prefrontal dopaminergic dysregulation (Cools, Barker, Sahakian, & Robbins, 2001; Narayanan, Rodnitzky, & Uc, 2013) and basal ganglia dysfunction (Kehagia, Barker, et al., 2010; Obeso et al., 2002; Obeso et al., 2000). At the same time, widespread Lewy-body pathology occurs in PD in brain areas associated with anxiety, such as the amygdala, which has major projections to the prefrontal cortex (Braak et al., 1994; Braak et al., 2004; Pontone et al., 2009; Prediger et al., 2012), suggesting potential disruption to affective and cognitive functioning. Emerging work also points to a potential role of

dopaminergic degeneration in the ventral tegmental area in the pathophysiology of non-motor symptoms in PD, namely depression, anxiety, and executive dysfunction (Alberico, Cassell, & Narayanan, 2015).

The sources of mild cognitive deficits in early-stage PD may also include structural changes in frontal and temporoparietal regions as well as non-dopaminergic dysfunction (Hanna-Pladdy, Jones, Cabanban, Pahwa, & Lyons, 2013). Noradrenaline and serotonin have been implicated in the development of anxiety in PD and the general population (Millan, 2003; Prediger et al., 2012; Ressler & Nemeroff, 2000). Specifically, noradrenergic dysfunction has been implicated in deficits in attentional set-shifting, such as the task-switching deficits observed in individuals with PD (Kehagia, Cools, Barker, & Robbins, 2009; Kehagia, Murray, & Robbins, 2010). In PD, noradrenergic dysfunction has been associated with depression and anxiety (Remy et al., 2005), and also with cognitive impairment and dementia (Del Tredici & Braak, 2013). Likewise, serotonergic dysfunction occurs early in PD and may contribute to anxiety, considering the projections from the serotonergic raphe nuclei to corticolimbic regions (Prediger et al., 2012). Serotonergic neuronal loss has the potential to compromise cognition as well (Halliday, Leverenz, Schneider, & Adler, 2014), based on reduced levels of serotonin observed in PD in key brain regions, such as the hippocampus and frontal cortex (Scatton, Javoy-Agid, Rouquier, Dubois, & Agid, 1983).

To date, the limited research on affective symptoms and cognitive function in PD has investigated the effects of depression and apathy on cognition, with relatively minimal attention given to the study of anxiety and cognition in this population (Poletti et

al., 2012). In the present study, we sought to expand our understanding of this relation in a relatively large sample of individuals with PD. We focused on executive functioning (set-shifting, phonemic fluency) and attention/working memory, as deficits in these domains are usually the cognitive symptoms that are documented in mild to moderate PD (Miller et al., 2013). The main hypothesis was that higher anxiety levels would correlate with poorer performance on neuropsychological measures of executive function and attention.

Method

Participants

Participants included 77 non-demented individuals with PD (39 men, 38 women; mean age = 62.9 years, SD 7.4), who were referred from the Parkinson's Disease Center of Boston Medical Center and local PD support groups. These individuals were participants in studies that used partly overlapping measures of cognition, as well as the same measures of anxiety. The study protocols were approved by the Boston University Institutional Review Board, with consent obtained according to the Declaration of Helsinki.

Participants with PD met the clinical criteria for mild to moderate idiopathic disease, following the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria (A. J. Hughes, Daniel, Kilford, & Lees, 1992). Exclusion criteria included coexisting serious chronic illness (including psychiatric or neurological); use of psychoactive medications besides antidepressants and anxiolytics, which are commonly

prescribed in PD; history of intracranial surgery, traumatic brain injury, alcoholism or other drug abuse; and visual acuity poorer than 20/40. All participants were non-demented, as indicated by scores of 25 or better on a standard cognitive screening measure, the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), and performance on the several cognitive tests described below.

In the PD group, motor disability was staged using the Hoehn & Yahr scale (Hoehn & Yahr, 1967). There were 15 participants in Stage I (unilateral), 51 in Stage II (mild bilateral), and 11 in Stage III (moderate bilateral). Of the 77 participants, 40 had motor symptom onset on the left body side (LPD), 36 on the right side (RPD), and one had bilateral onset. All were tested in their "on" medication state. Disease and motor disability was rated with the Unified Parkinson's Disease Rating Scale (UPDRS: (Fahn & Elton, 1987)). UPDRS scores were available for 45/77 participants. UPDRS total score (sections 1-3) was used as a measure of overall disease severity, and the motor subscale (section 3) was used as a measure of motor symptom severity. Levodopa equivalent dosages (LED) were calculated using a standard formula (Tomlinson et al., 2010); medication information was available for 39/77 participants. Of these 39 participants, five were taking anti-anxiety medication, and three were taking antidepressant medication. Table 1 provides a summary of participant characteristics.

Procedure and Measures

Following the administration of the MMSE, participants completed a series of neuropsychological tests and mood questionnaires. The neuropsychological tests

assessed current cognitive functioning primarily in the domains of executive functioning, working memory, and attention because these were the tests for which we had been collecting data across studies for several years, which permitted us to examine a large sample. Not all participants received all tests.

Tests of attention and working memory included the Trail Making Test A, and Digit Span Forward and Backward. Tests of executive functioning included the Trail Making Test B and Phonemic Fluency; Category Fluency was also administered.

We administered the Digit Span subtest from the Wechsler Memory Scale III (Wechsler, 1997) to assess attention (Forward and Backward conditions) and working memory (Backward condition). Score for each condition was the total number of correct trials. The Trail-Making Test (TMT) (Tombaugh, 2004) was given to evaluate attention, set-shifting, and executive function. The task was to quickly draw lines connecting numbers in order (TMT-A; attention), and alternate between numbers and letters in order (TMT-B; set-shifting, executive function). Score for each was time to completion. To isolate set-shifting measured by TMT-B, a derived TMT-difference score was calculated (TMT-B – TMT-A), which removes the psychomotor component of the task that is captured in TMT-A (O'Rourke et al., 2011). To further assess executive function, participants engaged in the Word Association Test for phonemic fluency (Delis, Kaplan, & Kramer, 2001). They were instructed to name as many unique words beginning with the letters *F, A,* and *S* (phonemic fluency; FAS) as possible. The categorical fluency trial was also administered, which required participants to name as many unique animals (categorical fluency; Animals) as possible. The time limit for each trial was 60 seconds.

Score for phonemic fluency was the total number of correct responses, summed across the *F*, *A*, and *S* trials. Score for categorical fluency was the total number of correct responses.

To measure anxiety symptoms, participants were administered the Beck Anxiety Inventory (BAI) (Beck & Steer, 1993). The BAI is a 21-item self-report measure of anxiety, on which higher scores indicate more anxiety symptoms. Participants also were given the Beck Depression Inventory II (BDI) (Beck, Steer, & Brown, 1996) to assess current depressive symptoms. The BDI is a 21-item self-report measure of depressive symptoms, with higher scores indicative of higher levels of depression.

Data Analysis

Statistical analyses were conducted with IBM SPSS Statistics, Version 22. Correlational analyses were conducted to determine whether neurocognitive functions were related to symptoms of anxiety in the PD sample. The relation between anxiety and cognitive performance was examined using correlational analyses. The skew in the BAI score distribution dictated the use of non-parametric analyses (Spearman's correlations). The sample size for each analysis was dependent upon the number of individuals in the sample who had been administered those particular cognitive tests. For the 77 PD participants, the sample size for each analysis ranged from 57 to 62. By test, the sample sizes were as follows: TMT-A: 62; TMT-B: 62; FAS: 59; Animals: 57; Digit Span Forward: 58; Digit Span Backward: 58. To account for the number of analyses and correlations between outcome variables, we used a conservative alpha level of .01

because some of the tests belonged to the same cognitive domain. Because some participants did complete all of the cognitive tests, a conservative alpha level was used to minimize Type I error rate.

Results

Within-Group Levels of Anxiety and Depression

The mean BAI in the sample was 10.0 (SD 7.7). Twelve of the 77 PD participants reported clinically significant levels of anxiety on the BAI when using a highly specific cutoff score of 18 (Higginson, Fields, & Troster, 2001). Four of the 12 had clinically significant depression scores (BDI-II ≥17). In this subgroup of 12, mean BDI-II was 15.2 (SD 7.9), mean age was 65.8 years (SD 9.8), mean education was 14.4 years (SD 2.4), mean disease duration was 10.9 years (SD 8.4), and all were in H&Y stages 2 or 3. Of these 12 with clinically significant anxiety, nine completed TMT-A and TMT-B, and seven completed Verbal Fluency (FAS and Animals) and Digit Span.

The mean BDI-II in the sample was 8.2 (SD 6.2). Clinically significant levels of depression were reported by eight of the participants on the BDI-II, using a highly specific cutoff score of 17 (Higginson et al., 2001). Four of the eight had clinically significant anxiety scores (BAI ≥18).

Within the PD group, levels of anxiety did not differ for men vs. women ($t(75) = .09$, $p=.93$) or by side of motor symptom onset (LPD, RPD; $t(74) = 1.07$, $p=.29$). Depression levels did not differ between men and women with PD ($t(75) = 1.71$, $p=.09$) or by side of motor symptom onset (LPD, RPD; $t(74) = .03$, $p=.98$). Age at testing did

not correlate with anxiety (ρ=-.14, p=.23). Data were accordingly collapsed across gender, side of motor symptom onset, and age for the following analyses.

Within-Group Correlational Analyses

Anxiety correlated with certain clinical characteristics, as shown in Table 2. These included disease stage (H&Y), disease severity (UPDRS total), and depression, with higher anxiety associated with more advanced stage, greater severity, and higher depression. Anxiety also correlated with education and disease duration at a trend level, with higher anxiety associated with lower education and longer disease duration. Anxiety was not associated with medication usage (LED) or motor symptom severity. Depression correlated with disease severity (ρ =.47, p=.001) and there was a trend for a correlation with motor symptom severity (ρ=.32, p=.03), but not with age, education, disease duration, medication usage, or disease stage (all ps>.05; see Table 3).

Because demographic and mood variables may influence neuropsychological performance, we conducted correlational analyses to examine these potential effects in our PD sample. Age, education, medication usage (LED), motor symptom severity, and overall disease severity (UPDRS total) did not correlate with cognitive performance (all ρs≤ |.26|, ps≥.04); UPDRS and LED correlational analyses were conducted with the subset of participants for whom those data were available. Disease stage (H&Y) correlated with performance on TMT-B (ρ=.37, p=.003), and there were trends for TMT B-A (ρ=.29, p=.02) and category fluency (ρ=-.31, p=.02), but not for other cognitive tests (all ρs≤ |.22|, ps ≥.087). There were trends for disease duration to correlate with TMT-B

(ρ=.29, p=.02) and TMT B-A (ρ=.30, p=.02), but not for other cognitive tests (all ρs< |.20|, ps ≥.15).

Anxiety significantly correlated with performance on TMT-B (ρ=.37, p=.003; Figure 1), and remained significant after removing the psychomotor component of the task (TMT B-A: ρ=.34, p=.007; Table 4). Anxiety did not correlate with performance on the tests of phonemic fluency, categorical fluency, attention, or working memory (Table 4). Depression did not correlate with performance on any of the cognitive measures (Table 5). The pattern of findings remained the same after excluding the eight participants with clinically significant depression scores, such that there was a trend for anxiety to correlate with TMT-B (ρ=.32, p=.016) and TMT B-A (ρ=.33, p=.016), but not with other cognitive measures (all ρs≤ |.23|, ps ≥.11).

Discussion

We examined the relation between anxiety and cognitive functioning in a large, well-characterized sample of non-demented individuals with mild to moderate idiopathic PD. Higher anxiety was significantly associated with more advanced disease stage and severity, and there was a trend for anxiety to also be associated with lower education and longer disease duration. Anxiety also correlated with depression, and depression was associated with greater disease severity, with a trend for an association with motor symptoms as indexed by the UPDRS motor subscale. Regarding cognitive function, higher anxiety correlated with poorer set-shifting (TMT-B) among PD participants even after removing the psychomotor component of the cognitive task (TMT B-A). Anxiety

level did not correlate with performance on tests of attention, working memory, phonemic fluency, or categorical fluency. Depression did not correlate with cognitive performance, which is likely related to floor effects as the mean depression score in our sample was well within normal limits.

We had originally predicted an association between anxiety and executive and attentional dysfunction in PD. Our results are consistent with a recent study by Martens and colleagues (2016) that reported a correlation between anxiety and TMT B-A in PD, but no significant correlations between anxiety and the digit span subtests. Our findings with a relatively large number of measures of executive function and attention (including digit span) accord with and expand upon those of the study of Martens and colleagues, highlighting the specific association between anxiety and set-shifting in mild to moderate PD. The relation between anxiety and TMT-B is consistent with attentional control theory (Eysenck, Derakshan, Santos, & Calvo, 2007), which asserts that anxiety decreases attentional control and increases attention to threat, thereby compromising cognitive processes including inhibition and shifting. Consistent with this theory, in a sample of community-dwelling older adults, individuals with increased anxiety showed poorer processing speed/shifting attention and inhibition abilities (Beaudreau & O'Hara, 2009), which is in keeping with the association we observed between anxiety and set-shifting in our PD sample.

An earlier paper from our lab examined anxiety and cognition as related to side of motor symptom onset in PD (Bogdanova & Cronin-Golomb, 2012). A consistent finding was the relation between disease duration and anxiety, which was observed in the 2012

sample and at a trend level in the present sample, suggesting that the relation between anxiety and cognition may evolve as the disease progresses. The current study, relative to the 2012 study, included a larger sample of individuals with mostly mild anxiety in early disease stages, with analyses collapsed across side of motor symptom onset. We also included discussion of depression and motor symptoms when possible and used a derived metric to better isolate set-shifting and account for motor slowing. Of note, the present sample was similar to the 2012 sample in age and gender distribution, but current participants were milder overall, as indexed by shorter disease duration (6.5 years compared to 8.7) and less advanced disease stage (H&Y stages 1-3 compared to stages 2-3), which underscores the importance of studying anxiety and cognition even in the early stages of PD.

It is important to note that neuropsychological tests vary in their sensitivity to cognitive impairment in PD (Miller et al., 2013); hence, it is possible that some of our cognitive measures were not sensitive enough to capture the relation between anxiety and mild cognitive deficits in our sample of high-functioning, non-demented PD participants with mostly quite mild anxiety symptoms. In a sample of 42 non-demented PD participants and 28 control participants, 36% of the PD group showed deficits (defined at 1.5 SD below the control-group mean) on TMT-B, while only 15% showed deficits on Digit Span Forward and Digit Span Backward, suggesting that TMT-B performance may be affected to a greater extent than Digit Span in early PD (Miller et al., 2013). Anxiety may impair cognitive performance, especially on complex or attentionally demanding tasks (Derakshan & Eysenck, 2009), which may explain the observed association

between anxiety and TMT-B, and the lack of association between anxiety and a relatively simple task (Digit Span Forward) in our sample. Although Digit Span Backward is also a demanding task, there was greater variability in our sample on TMT-B (SD=45.8) than Digit Span Backward (SD=2.8), which may have reduced the power to discern an association between anxiety and working memory. Likewise, although phonemic fluency is often impaired in early PD (Miller et al., 2013), in our present sample there was considerably less variability in performance of this test (SD=11.5) than for TMT-B. Also, the reduced power of non-parametric analyses, the use of which was dictated by the data characteristics, may have limited our ability to detect significant correlations between anxiety and measures of fluency or attention.

Our study was subject to limitations. First, our cognitive assessment was restricted to tests of executive function, attention, and categorical fluency. We drew upon neuropsychological data from several years of consecutive participants, and these were the tests that were common across that time period. The advantage of the selection of the tests was the large sample size for whom anxiety and cognition in a particular domain could be examined. Future research on anxiety and cognition in PD should include a more comprehensive assessment of cognitive function, and in particular, measures of complex visuospatial function and reasoning, as deficits in these domains are regularly observed in PD (Amick, Miller, Neargarder, & Cronin-Golomb, 2012; Amick, Schendan, Ganis, & Cronin-Golomb, 2006; Bogdanova & Cronin-Golomb, 2012). Second, our sample was assessed with only one measure of anxiety, the BAI, which includes several somatically-based items, e.g. “wobbliness in legs,” “unsteady,” “hands trembling,”

"shaky," which are similar to PD motor symptoms (e.g., tremor or feelings of unsteadiness) (Leentjens et al., 2008; Leentjens, Dujardin, Marsh, Richard, et al., 2011). Mitigating this concern, we have found no difference in the ability of the BAI and its less somatically-laden counterpart, the State-Trait Anxiety Inventory, to predict quality of life in mild to moderate PD (Hanna & Cronin-Golomb, 2012). Future studies may consider inclusion of recently developed PD-specific anxiety scales, such as the Parkinson Anxiety Scale (Leentjens et al., 2014). Third, our sample consisted of non-demented and mainly high-functioning individuals with PD who reported mostly mild to moderate levels of anxiety. The relation may be different in individuals with more advanced PD or more severe anxiety. Inclusion of a PD control group (e.g., non-anxious vs. highly anxious PD participants) may elucidate the effects of anxiety on cognition when controlling for the cognitive dysfunction associated with the disease itself (e.g. executive deficits due to frontostriatal disruption). Finally, information about disease severity (UPDRS) was available for the majority, though not all, of our participants with PD (45/77), which limits our interpretation of the relation between anxiety, cognition, and motor symptom severity. Among the subset with UPDRS scores, motor symptom severity did not correlate with anxiety or cognition, nor was there a relation between anxiety and cognition, likely due to floor effects, as the BAI mean was quite low (6.6). We included the participants without UPDRS data in order to increase the range of BAI scores and examine the relation between anxiety and cognition in a larger PD sample.

Taken together, our results suggest that anxiety may be related to poorer performance on measures of set-shifting even in high-functioning individuals with mild

to moderate PD. With a better understanding of the manifestation of non-motor symptoms in PD subgroups, we can hope to increase recognition of anxiety and cognitive dysfunction, particularly in the early stages of the disease, in order to inform subsequent treatment options. This is important because, as we have documented, anxiety may deleteriously affect quality of life to a greater extent than do the motor symptoms of PD (Hanna & Cronin-Golomb, 2012). With research dedicated to a more comprehensive and systematic evaluation of anxiety and cognition in PD at various stages of the disease, we can work toward developing treatment approaches to address the often devastating effects of mood and cognitive impairments in PD, and ultimately improve daily functioning and quality of life for people living with this disorder.

Table 1. Demographic, Clinical, and Neuropsychological Characteristics. Means (M) and Standard Deviations (SD), Unless Otherwise Noted

Age	62.9 (7.4)
Men:Women	39:38
Education	17.1 (2.6)
MMSE[a]	28.8 (1.2)
Disease Duration	6.5 (5.4)
H&Y[b]	2 (1-3)
UPDRS Total[c]	27.0 (10.7)
UPDRS Motor Subscale[d]	16.4 (7.3)
LED[e]	361 (231)
BAI	10.0 (7.7)
BDI-II	8.2 (6.2)
TMT-A (sec)	33.6 (15.0)
TMT-B (sec)	79.0 (45.8)
TMT B–A (sec)	45.4 (38.2)
FAS (total)	43.9 (11.5)
Animals (total)	22.4 (5.9)
Digit Span Forward (total)	11.1 (2.6)
Digit Span Backward (total)	7.5 (2.8)

[a]Mini-Mental State Examination
[b]Hoehn & Yahr stage: Median (range)
[c]Unified Parkinson's Disease Rating Scale (UPDRS) Total (sections 1-3); UPDRS scores were available for 45/77 participants.
[d]Unified Parkinson's Disease Rating Scale (UPDRS) Motor Subscale (section 3).
[e]Levodopa-equivalent dosages (LED); medication information was available for 39/77 participants.
BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory-II; TMT-A=Trail Making Test A; TMT-B=Trail Making Test B; FAS=phonemic fluency; Animals=categorical fluency.

Table 2. Spearman's Correlations between Anxiety (BAI) and Participant- and Disease-related Variables in PD

VARIABLE	rho	p-value	N
Age	-.14	.23	77
Education	-.28	.02	77
Disease Duration	.29	.01	77
H&Y	.31**	.007	77
UPDRS total	.41**	.005	45
UPDRS motor	.15	.31	45
LED	.04	.83	39
Depression	.58**	<.001	77

Table 3. Spearman's Correlations between Depression (BDI-II) and Participant- and Disease-related Variables in PD

VARIABLE	rho	p-value	N
Age	-.12	.29	77
Education	-.22	.053	77
Disease Duration	.03	.77	77
H&Y	.22	.061	77
UPDRS total	.47**	.001	45
UPDRS motor	.32	.03	45
LED	-.03	.87	39

** $p<0.01$
PD=Parkinson's Disease; BAI=Beck Anxiety Inventory; H&Y=Hoehn & Yahr; LED=Levodopa-equivalent dosage (available for 39/77 participants with PD); UPDRS=Unified Parkinson's Disease Rating Scale (available for 45/77 participants with PD)

Table 4. Spearman's Correlations between Anxiety (BAI) and Neuropsychological Performance in PD

VARIABLE	rho	p-value	N
TMT-B	.37**	.003	62
TMT B-A	.34**	.007	62
FAS	-.14	.28	59
Animals	-.24	.07	57
TMT-A	.07	.61	62
Digit Span Forward	.09	.50	58
Digit Span Backward	-.19	.16	58

Table 5. Spearman's Correlations between Depression (BDI-II) and Neuropsychological Performance in PD

VARIABLE	rho	p-value	N
TMT-B	.21	.099	62
TMT B-A	.18	.16	62
FAS	-.08	.57	59
Animals	-.25	.062	57
TMT-A	.12	.34	62
Digit Span Forward	-.03	.80	58
Digit Span Backward	-.17	.21	58

** $p<0.01$
PD=Parkinson's Disease; BAI=Beck Anxiety Inventory; FAS=phonemic fluency; Animals=categorical fluency.

Figure 1.

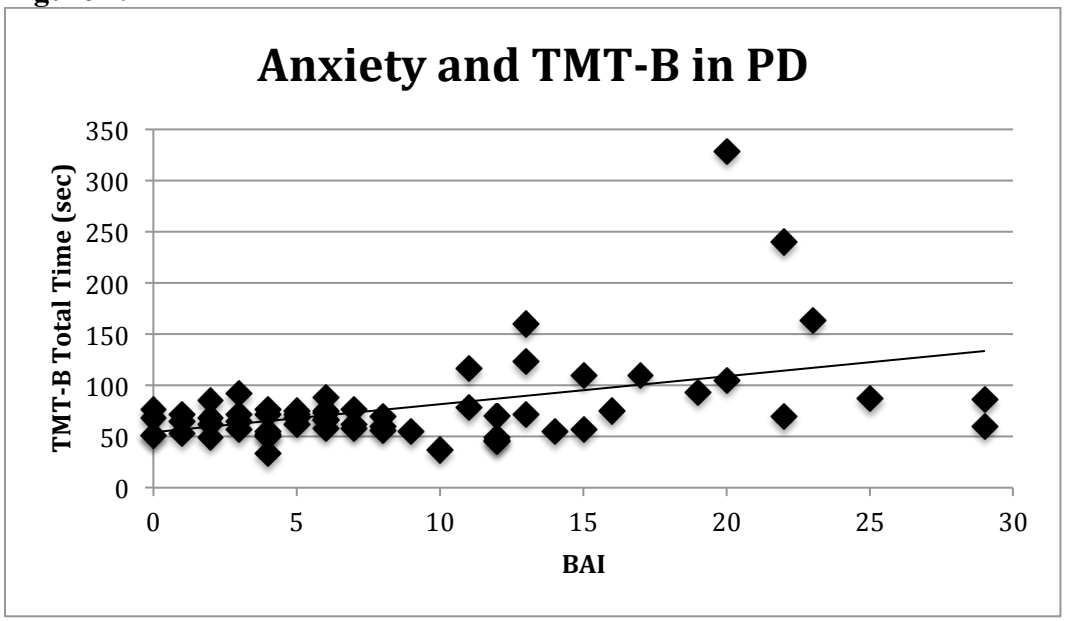


Figure 1. The line demonstrates a significant correlation between BAI and TMT-B among PD participants (ρ=.37, p=.003). PD = all Parkinson's disease participants; BAI=Beck Anxiety Inventory; TMT-B=Trail Making Test B.

CHAPTER 3: STUDY TWO – THE UTILITY AND FEASIBILITY OF COGNITIVE-BEHAVIORAL TREATMENT FOR ANXIETY IN PARKINSON'S DISEASE: A PILOT STUDY

Introduction

Anxiety is one of the most prevalent and distressing non-motor symptoms of Parkinson's disease (PD); yet it remains under-studied and inadequately treated (Chen & Marsh, 2014; N. Dissanayaka et al., 2015). The prevalence of anxiety disorders in PD is estimated to be 31%, with the most common disorders being generalized anxiety disorder (14%), social phobia (13.8%), anxiety not otherwise specified (13.3%), specific phobia (13%), and panic disorder (6.8%) (Broen, Narayen, Kuijf, Dissanayaka, & Leentjens, 2016). There is also emerging evidence of subtypes of anxiety and depression in PD (R. G. Brown et al., 2011), as well as anxiety symptoms that are specific to PD, such as distress, worry, and embarrassment related to motor symptoms (N. N. Dissanayaka, J. D. O'Sullivan, et al., 2016), which has important implications for diagnosis and treatment. The neurobiological mechanisms of anxiety in PD likely involve multiple neurotransmitter systems, suggesting that anxiety is not solely a reaction to the motor symptoms (Prediger et al., 2012). The high prevalence is concerning because anxiety is often comorbid with other non-motor symptoms (M. A. Menza et al., 1993; Naismith & Lewis, 2011), and significantly compromises quality of life, even among recently diagnosed patients, early in the disease course (Duncan et al., 2014; Hanna & Cronin-Golomb, 2012). Together, the prevalence and negative impact highlight the urgent need

for clinical research focused on anxiety in PD with the goal of better recognizing and treating this symptom across all stages of the disease.

To date, there has been very little treatment outcome research on anxiety in PD. As of July 2013, there were no randomized controlled trials of any kind for the treatment of anxiety in PD (Seppi et al., 2011; Troeung et al., 2013), and the limited research on affective symptoms in PD has focused more on depression than anxiety (N. N. Dissanayaka et al., 2014; S. Yang et al., 2012). Even more concerning is the fact that non-depressed individuals with PD and anxiety disorders are less likely to be treated with medication compared to individuals with comorbid anxiety and depression (Pontone et al., 2013). In this study of 250 individuals with PD, 53% of the participants with anxiety disorders were not receiving pharmacologic treatment (Pontone et al., 2013). Selective serotonin reuptake inhibitors (SSRIs) are often the standard pharmacologic treatment for anxiety in PD, while benzodiazepines may not be recommended due to potential for increased falls and cognitive dysfunction (Chen & Marsh, 2014; B. Connolly & Fox, 2014; N. Dissanayaka et al., 2015). Across two depression trials, SSRIs (citalopram) and tricyclic antidepressants (nortriptyline and desipramine) have yielded secondary improvements on anxiety in PD, although concern remains about the potential side effects of these drugs, which include bradykinesia, erectile dysfunction, orthostatic hypotension, and cardiac arrhythmias (D. Devos et al., 2008; M. Menza et al., 2009; Troeung et al., 2013). Many older adults may wish to avoid adding another medication to their regimen to avoid harmful interactions (Mintzer & Burns, 2000; Qato et al., 2008). It is also important to note that psychotropic drugs are not specifically designed for use in

PD and may exacerbate PD symptoms and/or interact harmfully with PD medications (B. S. Connolly & Fox, 2012). Overall, there remains a limited evidence base to guide the pharmacologic treatment of anxiety in PD (Seppi et al., 2011).

Non-pharmacological treatments offer an encouraging alternative treatment for anxiety in PD, with particular promise for cognitive-behavioral therapy (CBT; (Armento et al., 2012; Egan et al., 2015; Pachana et al., 2013)). Psychosocial interventions for depression and anxiety in PD have included CBT, psychodrama, education, behavior therapy, and multidisciplinary rehabilitation, with CBT yielding reductions in depression and anxiety among depressed PD patients or those who endorsed elevated anxiety symptoms on a self-report rating scale (S. Yang et al., 2012). In single-case and small pilot studies, individual and group CBT have shown the potential to alleviate anxiety and depression among individuals with PD and psychiatric diagnoses of anxiety and/or depression, with interventions delivered in person or by phone (Calleo et al., 2015; N. N. W. Dissanayaka et al., 2016; Feeney et al., 2005; Heinrichs et al., 2001; Mohlman et al., 2010; Veazey et al., 2009). In a waitlist-controlled trial, group CBT reduced levels of depression and anxiety among 18 participants with PD and comorbid diagnoses of depression and/or anxiety, with effects maintained at a 6-month follow-up (Troeung et al., 2014). A group mindfulness intervention also showed preliminary efficacy in ameliorating anxiety and depression and improving cognition and motor symptoms in PD (N. N. Dissanayaka, F. Idu Jion, et al., 2016).

These promising findings on CBT for anxiety in PD are consistent with the more extensive evidence for the efficacy of CBT for depression in this population. A small,

uncontrolled study reported that individual CBT reduced depression among eight individuals with PD, with 57% achieving remission at post-treatment (Farabaugh et al., 2010). In the first RCT of CBT for depression in PD, Dobkin and colleagues reported that ten weeks of CBT alleviated depression and also showed positive effects on secondary outcomes of anxiety, quality of life, coping, and PD-specific symptoms (UPDRS total score and motor subscale), relative to a clinical monitoring control group (Dobkin, Menza, Allen, Gara, et al., 2011). Results were similar in a smaller, uncontrolled trial of phone-delivered CBT for depression in PD (Dobkin, Menza, Allen, Tiu, et al., 2011). Together, these studies suggest that CBT may have similar efficacy when used to directly target anxiety in PD and underscore the need for treatment outcome research focused on anxiety.

Finally, it will be important to consider dissemination of non-pharmacological treatments for anxiety in PD. Reported barriers to utilization of psychological treatment in PD include lack of local services, reduced physical mobility, and lack of transportation (Dobkin et al., 2013). As described above, telephone-delivered CBT interventions have shown promising preliminary effects for reducing anxiety and depression in PD (Dobkin, Menza, Allen, Tiu, et al., 2011; Veazey et al., 2009). Similarly, in a pilot study of nine PD participants with elevated anxiety and/or depression scores on the Hospital Anxiety and Depression Scale, internet-delivered CBT yielded improvements in depression, but not anxiety, at post-treatment (Kraepelien et al., 2015). The protocol was self-guided and based on behavioral activation, with minimal therapist contact (<15 minutes/week) (Kraepelien et al., 2015). To improve participant engagement and satisfaction, the

authors suggested specific modifications for future interventions, including increased participant-therapist interaction, caregiver involvement, and more user-friendly technology (Kraepelien et al., 2015).

The aim of the present study was to examine the utility and feasibility of a transdiagnostic cognitive-behavioral treatment for anxiety disorders in PD. The study implemented a manualized CBT protocol that has demonstrated efficacy in the treatment of anxiety and depression in non-PD populations (Farchione et al., 2012). A single-case, multiple-baseline experimental design with three baseline conditions was used to examine within-subject variability and individual responses to specific intervention components, based on weekly measures of anxiety and depression. It was predicted that the intervention would reduce anxiety among PD participants and also yield positive effects on secondary outcome measures, including depression, quality of life, cognition, sleep, and any motor symptoms that may be exacerbated by anxiety.

Method

Participants

Participants were nine individuals who met the clinical criteria for mild to moderate idiopathic PD (Hoehn & Yahr motor stage: range I-II) (Hoehn & Yahr, 1967), following the United Kingdom Parkinson's Disease Society Brain Bank diagnostic criteria (A. J. Hughes et al., 1992). Inclusion criteria were (a) met diagnostic criteria for any anxiety disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; (Association, 2013)), (b) at least eight years of formal

education, (c) psychotropic medication stability (at least 6 weeks prior to the intake and during study), (d) high-speed internet access and a webcam if completing therapy sessions online. Exclusion criteria were: (a) serious or chronic medical or neurological illness if not well-managed, other than PD, (b) history of moderate to severe traumatic brain injury, (c) current or recent (past 90 days) history of alcohol or substance use disorder, with the exception of nicotine, marijuana, and caffeine, (d) current suicidal or homicidal ideation or intent, (e) dementia (MMSE <25), (f) corrected binocular visual acuity poorer than 20/50, (g) average "off" time >50% of the day (periods of time when PD medication wears off, resulting in worsening of symptoms), (h) current DSM-5 diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or substance/medication-induced disorder, or a principal diagnosis of specific phobia, (i) recent experience with an adequate trial of cognitive-behavioral therapy (CBT), defined as 8 sessions within the past 5 years, (j) concurrent psychosocial treatment (i.e. therapy) focused on anxiety or depression. One participant (P8) had a history of deep brain stimulation (DBS). Demographic information is reported in Table 6.

Research Design

This study implemented a single-case, multiple baseline across subjects experimental design (Barlow, Nock, & Hersen, 2009; Hayes, Barlow, & Nelson-Gray, 1999) to evaluate symptom change during treatment. Single-case experimental designs (SCEDs) have high internal validity (Barlow & Hersen, 1973) and allow for flexibility to adapt treatment to meet the unique needs of each individual participant (Nock, Michel, & Photos, 2007). The multiple baseline design is especially well-suited to examine the

utility and feasibility of a novel intervention, given its ability to establish functional relationships between individual symptomatic changes and specific treatment modules (Barlow et al., 2009; Hayes et al., 1999). Participants were randomized to one of three baseline conditions (two, four, or six weeks) with three participants per condition, in accordance with sample size recommendations (Barlow et al., 2009). Primary outcome measures of anxiety and depression were assessed weekly to track symptom change.

Procedures

Participants were recruited through local neurology clinics, the Fox Trial Finder, local flyers, and word-of-mouth. After phone screening, eligible individuals were scheduled for the intake. See Figure 2 for participant flow. All participants gave written informed consent, and all procedures were approved by Boston University's Internal Review Board. Participants completed four primary assessments of approximately 3-5 hours and twelve weekly hour-long sessions of cognitive-behavioral treatment. During the first assessment, participants were screened for visual acuity and dementia (per the Modified Mini Mental State Examination (mMMSE; (Stern, Sano, Paulsen, & Mayeux, 1987))). The mMMSE scores were converted to the traditional MMSE scale for screening purposes, and all participants scored 25.75 or greater. All assessments and therapy sessions were conducted at the Center for Anxiety and Related Disorders (CARD) at Boston University. At the approximate halfway point of the study, the protocol was amended to give participants the option to complete therapy sessions via a secure videoconferencing platform (WebEx^{TM}), in an effort to reduce burden of travel and improve recruitment rates. For participants who elected the online option, the four

primary assessments were conducted in the participants' homes. Participants incurred no charge for the 12 therapy sessions, and received financial compensation after each of the four primary assessments.

The lead investigator of the study (GOR) conducted all assessments and therapy sessions (with the exception of in-person UPDRS assessments described below). She was a Master's level doctoral student at the time of data collection with training in ADIS administration and UP delivery from senior clinicians and advanced graduate students at CARD and UPDRS training from neurologists and physical therapists at Boston Medical Center and at BU's College of Health and Rehabilitation Sciences: Sargent College.

Four Primary Assessments (intake/pre-baseline, post-baseline/pre-treatment, post-treatment, 6-week follow-up): These assessments lasted 3-5 hours each and consisted of a semi-structured diagnostic interview, self-report questionnaires, and brief neuropsychological measures. If the participant met diagnostic criteria for at least one DSM-5 anxiety disorder, he/she was then randomized to a two-, four-, or six-week baseline phase. To reduce participant burden and fatigue, self-report questionnaires for secondary outcome measures were available online via Qualtrics, a secure online platform used regularly in clinical research.

Baseline Phase (2, 4, or 6 weeks): Participants completed brief weekly self-report measures of anxiety and depression online via Qualtrics. Questionnaires were reviewed weekly by the examiner to assess stability in scores and to monitor for issues of risk. Once stability in weekly scores was observed during the baseline phase, participants completed the second primary assessment. The baseline phase was extended for four

participants (P2, P5, P8, P9). P2 and P5 showed variability in anxiety scores during the first 4 weeks of the baseline, requiring extension of the baseline phase by three weeks (P2) and one week (P5). P8 was randomized to the 4-week baseline condition, but her phase was extended by three weeks due to PD-symptom variability (increased OFF time) and scheduling conflicts. For these three participants (P2, P5, P8), the last 4 weeks of the baseline are used for comparison to the intervention phase. P9 (randomized to the 6-week baseline, which was extended by one week) showed variability during the first 4 baseline weeks and failed to complete the one of the anxiety measures during week 3. The last 6 weeks of the baseline condition are used for her analyses, with the exception of the Overall Anxiety Severity and Impairment Scale (OASIS), for which only 6 datapoints were collected across the 7 weeks, all of which were utilized as a baseline.

Intervention Phase (12 weeks): Participants engaged in twelve 50-60 minute weekly sessions of cognitive-behavioral therapy (CBT). The CBT followed the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP; (Barlow et al., 2011)). The UP comprises five core treatment modules to target emotional processing: present-focused awareness, cognitive flexibility, emotional avoidance and emotion-driven behaviors, awareness and tolerance of physical sensations, and interoceptive and situational emotion exposures, as well as modules on motivation, psychoeducation, and relapse prevention. Weekly homework was assigned and reviewed each session, and progress was tracked by charting weekly anxiety and depression scores in session. See Table 7 for an outline of weekly session content. Psychoeducation about anxiety and PD was incorporated as needed. At the halfway point in treatment, a 20-30 minute

informational session was conducted with a partner or family member of the participant, if the participant and the partner both agreed to this option. Seven of the nine participants chose this option (all except P2 and P8). During this brief session, the therapist met individually with the partner or family member (either in person, via WebEx™, or by phone) and introduced psychoeducation about emotions and cognitive appraisal/reappraisal to facilitate increased practicing of these skills by the participant. All sessions were supervised by a licensed clinical psychologist. All sessions were audiotaped (or videotaped via WebEx™), and just over 10% (12 of 108 session tapes) were randomly chosen for review by a certified UP trainer to ensure adherence to the treatment protocol and provide feedback to the therapist, based on a checklist of predetermined goals. Overall adherence ratings for all sessions were 85% or greater, with modal adherence of 100%. All qualitative ratings ranged from good to excellent.

Measures

Diagnostic interview: Diagnostic information was obtained with the Anxiety Disorders Interview Schedule (ADIS-5; (T. A. Brown & Barlow, 2013)), a semi-structured diagnostic interview for DSM-5 anxiety disorders, with additional sections for depression, trauma, and substance use. Each diagnosis was assigned a clinical severity rating on a scale from 0 (no symptoms) to 8 (severe symptoms) with ratings of four or greater indicative of clinically significant symptoms. To participate in the study, participants must have received a severity rating of at least 4 for at least one anxiety disorder during the intake. Only diagnoses with ratings ≥4 were assessed at subsequent assessments.

Primary outcome measures: The following measures of anxiety and depression were administered at all assessments and weekly during the baseline and intervention phases: Beck Anxiety Inventory (BAI; (Beck & Steer, 1993)), Overall Anxiety Severity and Impairment Scale (OASIS; (Norman, Cissell, Means-Christensen, & Stein, 2006)), State-Trait Anxiety Inventory (STAI; (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983)), Beck Depression Inventory (BDI-II; (Beck et al., 1996)), Overall Depression Severity and Impairment Scale (ODSIS; (Bentley, Gallagher, Carl, & Barlow, 2014)), Geriatric Depression Scale (GDS; (Yesavage et al., 1982)).

Secondary outcome measures: The following measures were administered at the four primary assessments. Mood and anxiety scales included the Anxiety Sensitivity Index (ASI; (Reiss, Peterson, Gursky, & McNally, 1986)), Apathy Scale (AS; (Starkstein, Mayberg, Preziosi, et al., 1992)), Pain Catastrophizing Scale (PCS; (Sullivan, Bishop, & Pivik, 1995)), Panic Disorder Severity Scale (PDSS; (Shear, Clark, & Feske, 1998)), Penn State Worry Questionnaire (PSWQ; (Meyer, Miller, Metzger, & Borkovec, 1990)), Social Interaction Anxiety Scale (SIAS; (Mattick & Clarke, 1998)), and Social Phobia Inventory (SPIN; (Connor et al., 2000)).

PD-specific rating scales included the Freezing of Gait Questionnaire (FOG; (Giladi et al., 2000)), Parkinson's Disease Quality of Life Questionnaire (PDQ-39; (Peto, Jenkinson, Fitzpatrick, & Greenhall, 1995)), Parkinson's Disease Sleep Scale (Trenkwalder, Kohnen, et al., 2011), Unified Parkinson's Disease Rating Scale (MDS-UPDRS; (Goetz, Tilley, Shaftman, Stebbins, Fahn, Martinez-Martin, Poewe, Sampaio, Stern, Dodel, Dubois, Holloway, Jankovic, Kulisevsky, Lang, Lees, Leurgans, LeWitt,

Nyenhuis, Olanow, Rascol, Schrag, Teresi, van Hilten, & LaPelle, 2008)). To maximize reliability and minimize potential examiner bias, an independent evaluator (IE) administered UPDRS assessments for the five participants who were assessed at CARD. The IE was blind to study hypotheses, well trained in human subjects research, and well trained in UPDRS assessment by collaborators at Sargent College and Boston Medical Center. For participants assessed in their homes (and treated via WebEx^{TM}), UPDRS assessments were administered by the lead examiner (GOR), who had also been trained in UPDRS assessment with collaborators at Sargent College and Boston Medical Center.

Additional scales included the Falls Self-Efficacy Scale (FES; (Tinetti, Richman, & Powell, 1990)), Short-Form McGill Pain Questionnaire (McGill-SF; (Melzack, 1987)), and the Telepresence in Videoconference Scale (administered at mid- and post-treatment only (Bouchard & Robillard, 2000, 2006)).

Brief neuropsychological tests of executive function and attention included Digit Span (forward and backward), Trail Making Test A & B, Verbal Fluency (letter and categorical) (Delis et al., 2001; Lezak, Howieson, & Loring, 2004; Wechsler, 1997). Two brief measures of treatment satisfaction (Client Satisfaction Questionnaire (CSQ-8 (Larsen, Attkisson, Hargreaves, & Nguyen, 1979); Post-treatment feedback form, see Appendix A) were administered at post-treatment.

Data Analysis

As is standard in SCEDs, visual inspection was the primary analytic strategy (Barlow et al., 2009; Hayes et al., 1999; Kazdin, 2003). The relative change in slope between assessment points was used to determine the effects of specific treatment

components on observed symptom changes. Observed changes in the slope or level of the dependent variables (weekly measures of anxiety and depression) during phase shifts (transitions from baseline to intervention/follow-up), compared to either previous within-subject or simultaneous between-subject baseline phases, were used to determine if the observed changes in symptoms were functionally related to the study phase (treatment).

To complement visual inspection, reliable change (RC) scores were computed for primary and secondary outcome measures per the method described in Au et al. (under review). For each participant, change scores were calculated for baseline (last baseline score – first baseline score), pre-post treatment (post-treatment score – last baseline score), and pre-follow-up (6-week follow-up score – last baseline score). A standard error of the difference (S_{diff}) was then calculated for each measure per the following equation: $S_{diff} = \text{sqrt}[2(SE)^2]$, where $SE = SD$ X $\text{sqrt}(1 - r_{xx})$, and where SE=standard error of measurement; sqrt=square root; SD=standard deviation of the measure (from published norms or larger samples either in PD or clinical populations); r_{xx}=reliability coefficient from published data. Due to the small sample size of the present study, SDs and internal consistency coefficients were taken from published studies with larger samples (Antony, Coons, McCabe, Ashbaugh, & Swinson, 2006; Bentley et al., 2014; Campbell-Sills et al., 2009; Delbaere et al., 2010; Donnell & McNally, 1990; Giladi et al., 2009; Goetz, Tilley, Shaftman, Stebbins, Fahn, Martinez-Martin, Poewe, Sampaio, Stern, Dodel, Dubois, Holloway, Jankovic, Kulisevsky, Lang, Lees, Leurgans, LeWitt, Nyenhuis, Olanow, Rascol, Schrag, Teresi, van Hilten, LaPelle, et al., 2008; Hawker, Mian, Kendzerska, & French, 2011; Heimberg, Mueller, Holt, Hope, & Liebowitz, 1992;

Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997; Kabacoff, Segal, Hersen, & Van Hasselt, 1997; Leentjens, Dujardin, Marsh, Richard, et al., 2011; O. Moore, Peretz, & Giladi, 2007; Rector, Szacun-Shimizu, & Leybman, 2007; Shear et al., 2001; Stanley, Novy, Bourland, Beck, & Averill, 2001; Starkstein, Mayberg, Preziosi, et al., 1992; Sullivan, 2009; Sullivan et al., 1995; Trenkwalder, Kohnen, et al., 2011; Williams et al., 2012; Wright, Asmundson, & McCreary, 2001; Yardley et al., 2005). 95% confidence intervals (CIs) around change scores were then computed for each measure by multiplying S_{diff} by 1.96.

RC scores were used to determine if observed changes during the baseline and treatment phases were greater than would be expected due to chance alone. For secondary outcome measures, RC scores were computed for quality of life (PDQ-39), motor symptom severity (MDS-UPDRS: Part III), disorder-specific questionnaires (e.g. GAD=PSWQ; Panic disorder=ASI, PDSS; SOC=SIAS, SPIN), and any other questionnaires for which the participant endorsed clinically significant scores at the intake. The following scores were used to determine clinical significance: AS≥14 (Starkstein, Mayberg, Preziosi, et al., 1992), ASI>23 (Maller & Reiss, 1992), FES>23 (Delbaere et al., 2010), FOG >6 (O. Moore et al., 2007), McGill-SF >14 (Wright et al., 2001), PCS≥30 (Sullivan, 2009), PDSS≥8 (Shear et al., 2001), PDSS-2>10.5 (Kovács et al., 2016), PSWQ>50 (Therrien & Hunsley, 2012), SIAS≥34 (E. J. Brown et al., 1997), SPIN≥19 (Connor et al., 2000). For measures with no identified cutoffs (FOG, McGill-SF), a conservative approach was adopted such that scores that fell above the published mean at the intake were analyzed for pre-post and pre-follow-up changes. For the

neuropsychological measures, change was explored using the 20% method (Raymond, Hinton-Bayre, Radel, Ray, & Marsh, 2006), chosen due to lack of a matched control group and our focus on idiographic analysis. A change score of 20% or greater relative to the intake score was considered clinically significant. Exploratory, qualitative analyses were used to examine treatment satisfaction and acceptability of the intervention.

Results

Figures 3-8 plot the scores on the weekly measures of anxiety and depression across all nine participants, with each figure containing one participant from each baseline condition. Tables 9-10 report individual change scores and 95% CIs for primary outcome measures of anxiety and depression during baseline, intervention, and follow-up phases.

Functional Analysis of Baseline Data

Weekly anxiety scores remained relatively consistent regardless of baseline length. The one exception was observed variability on the STAI-S during the baseline for P7, P8, P9, which precludes analysis of pre-post or pre-follow-up changes on this specific index, as any variability during those comparisons may have been related to external factors, similar to patterns observed during baseline. Likewise, depression scores remained relatively stable across all participants during the baseline phase, except for variability on the BDI-II for P4 and P7. Neither of these participants met diagnostic criteria for a depressive disorder during the study, suggesting that their scores on the

BDI-II during baseline reflect normal within-subject variability; though this variability does preclude conclusions about potential effects of the intervention on subclinical depressive symptoms for these two participants. For those who demonstrated a significant change in the level or slope of weekly anxiety and depression scores (P1, P2, P4, P5, P6, P7, P9), the change did not occur until the intervention and/or follow-up phases regardless of baseline condition (see graphs for P1 (2-week baseline), P2 (4-week baseline), and P9 (6-week baseline)). These findings suggest that the changes in anxiety or depression among the seven responders were functionally related to the intervention, and not to external factors or simply the passage of time.

Functional Analyses of Primary Outcome Measures

Anxiety

From the start to the end of the baseline, anxiety scores were largely consistent or trended slightly upward (e.g., P1) across all nine participants, with the exception of significant decreases in STAI-S for P7, P8, and P9. Occasional sharp changes in anxiety during baseline were observed for some participants (e.g., P9 (BAI, STAI-S increases in weeks 2-3), and P2 (BAI decrease in week 3)), but the scores quickly stabilized. During the intervention, visual inspection showed a reduction (change in level or slope) in at least one anxiety measure for seven of the nine participants (all except P3 and P8). Statistically significant reductions in anxiety were observed for seven of the nine participants (P1, P2, P4, P5, P6, P7, P8) at either post-treatment or follow-up (Table 2). The statistically significant change in STAI-S for P9 at follow-up cannot be solely attributed to the intervention due to similar variability reported during her baseline phase

on that same measure; however, her post-treatment and follow-up scores on this measure do not overlap with any of the scores during the baseline, suggesting some positive effect of the intervention. Seven of the nine participants also reported improved symptoms on the diagnostic interview (Table 8), such that they no longer met criteria for at least one anxiety disorder at post-treatment and/or follow-up (e.g., P1, P2, P4, P6, P9; P5 and P7 for GAD only), while others reported improvements in symptoms (e.g., P5, P7, P8 for panic disorder at post-treatment only).

Isolated spikes in anxiety were observed for some participants during treatment (e.g., week 11 for P1, weeks 10-12 for P2, weeks 5-7 and 12 for P4, week 9 for P7, weeks 4 and 9 for P9), which were related to specific external factors (e.g., family stressors, physical pain, the holidays, winter weather, missed sessions, illness) or treatment components (e.g., exposures). For example, P2 showed a rapid response to treatment, which corresponded with sessions on motivation and psychoeducation during weeks 2 and 3. For P5, BAI levels rose at the start of treatment (sessions 1-5), which coincided with external stressors for her (the departure of her husband on a month-long trip). Her husband returned by session 6, and of note, her BAI scores continued to trend steadily downward for the remainder of treatment (sessions 6-12) even after his return. For P8, an initial increase in the slope on BAI and STAI-S (weeks 1-5) coincided with increased OFF periods related to DBS reprogramming, and there was a subsequent decline in anxiety for the remainder of treatment (weeks 5-12). Throughout treatment, P8 reported several medically-warranted adjustments in dopaminergic dose and changes to DBS settings, several of which significantly worsened her motor symptoms (e.g., increased

dyskinesias). These changes likely affected her anxiety ratings, but these changes were consistent from weeks 1-10 of the intervention phase, and the downward trend in anxiety scores began in week 5.

Depression

Depression scores remained stable or trended slightly upward for seven of the nine participants during baseline (P1, P2, P3, P5, P6, P8, P9), other than occasional, isolated changes (e.g., P6 (sharp drop during week 4) and P9 (increase during weeks 3-5)). However, two participants (P4, P7) showed significant decreases in depression scores (BDI-II) during baseline, which limits interpretation of any changes observed on this measure at post-treatment and follow-up for these participants.

Visual inspection showed a change in level and/or slope on at least one primary depressive measure during treatment or follow-up for seven participants (P1, P2, P5, P6, P7, P8, P9), and all seven showed statistically significant reductions in depressive symptoms at post-treatment and/or follow-up, relative to the baseline. Sharp increases in depressive symptoms during treatment (e.g., weeks 5-6 for P4, week 10 for P7, weeks 5-6 for P8, week 4 for P9) were observed to correspond with treatment components (e.g., exposures), external stressors, or poor responses to DBS/PD-medication adjustments for P8 only (e.g., increased OFF time and severe dyskinesias, which reportedly contributed to her increased depression). P4 reported a decline in depressive symptoms on the BDI-II during treatment that was significant at post-treatment and follow-up, but this change cannot be fully accounted for by the intervention due to the downward trend observed on this measure during baseline. However, P4 showed a gradual decline in GDS scores

during treatment that reached statistical significance at follow-up, relative to the stable GDS scores observed during baseline. Two of the participants (P3, P8) met diagnostic criteria for a comorbid depressive disorder at the intake. P3 reported no changes at post-treatment or follow-up on the clinical interview and continued to meet diagnostic criteria for dysthymia (CSR≥4). P8 met criteria for major depression at post-treatment and follow-up, but reported a slight improvement in depressive symptoms at follow-up.

Secondary Outcome Measures – Disorder-Specific Questionnaires

Four (P1, P2, P4, P7) of the nine participants reported significant and consistent improvements on disorder-specific questionnaires at post-treatment and follow-up (Table 11). One additional participant (P8) reported significant improvement on one disorder-specific questionnaire (PDSS) at follow-up only, as well as non-significant improvement on one measure of social phobia (SPIN) at post-treatment and also at follow-up, though to a lesser extent. Two participants (P5, P6) reported non-significant improvements on most disorder-specific questionnaires at post-treatment and follow-up, with the one exception being no changes in worry (PSWQ) for P5. On a measure of social phobia (SPIN), P6's score dropped to 16 at post-treatment and follow-up, which is below the clinical cutoff of 19. Two of the nine participants (P3, P9) did not report any significant changes on disorder-specific questionnaires; P3's PSWQ scores fell just below the clinical cutoff of 50 at all assessment points.

Other notable improvements were observed for three participants (P2, P5, P7) who endorsed elevated symptoms on additional intake questionnaires that did not correspond with their principal anxiety diagnoses. At post-treatment and follow-up, P2

reported a significant reduction on a measure of social phobia (SPIN) on which he scored at the clinical cutoff at the intake. P5 reported significantly reduced symptoms of social anxiety on the SIAS at follow-up, but not post-treatment, relative to her intake score, which fell just above the cutoff. At post-treatment, but not follow-up, P7 reported significantly reduced symptoms of panic disorder (PDSS) after scoring above the clinical cutoff on this measure at the intake.

Secondary Outcome Measures – Quality of Life, Motor Symptoms, Freezing of Gait, Fear of Falling, Apathy, Sleep, Pain, & Cognition

One participant (P4) reported significantly improved quality of life at post-treatment and follow-up. There were no significant changes in quality of life among the other eight participants, but two participants (P1, P9) reported modest (non-significant) improvements at post-treatment and follow-up. There were no consistent effects of the intervention on motor symptoms. At post-treatment, P8's demonstrated improved motor symptoms, but this finding is difficult to interpret given her adjustments during treatment to DBS programming and PD-related medications. Two other participants demonstrated minimal (non-significant) improvements in motor symptoms at post-treatment and follow-up (P5, P6), while two other participants showed worse motor symptoms at either post-treatment (P7) or follow-up (P2). Three participants endorsed elevated freezing of gait at the intake (P3, P7, P8), and one (P8) reported significantly worse freezing of gait at the follow-up. Otherwise, there were no changes in freezing among these participants at post-treatment or follow-up. Two participants endorsed elevated fear of falling at the

intake (P1, P4) and both reported significantly reduced fear of falling at post-treatment and follow-up.

Six participants endorsed elevated apathy at the intake. Two of the six (P4, P9) reported significantly reduced apathy at post-treatment and/or follow-up, while one participant (P3) reported significantly worse apathy at post-treatment and follow-up. Seven participants reported elevated sleep disruption at the intake, and only one reported significant improvement at post-treatment and follow-up (P4). Two participants (P1, P8) reported significantly worse sleep at follow-up only. There were no significant changes in sleep for the other four participants. Two participants (P7, P8) endorsed elevated pain at the intake, and there were no significant changes in their pain levels at post-treatment or follow-up. See Tables 11 and 12 for change scores for secondary outcome measures.

Regarding cognition, six of the nine participants (P3, P4, P5, P6, P7, P9) improved on TMT-A at either post-treatment or follow-up, but those who showed improvement at post-treatment (P3, P4, P7, P9) did not maintain the gains at follow-up (Table 13). On TMT-B, three participants (P1, P8, P9) significantly improved at post-treatment and/or follow-up, while five participants (P2, P3, P5, P6, P7) significantly declined at post-treatment and/or follow-up. Three participants (P1, P6, P9) improved on lexical fluency at post-treatment and/or follow-up with no changes among the other six participants. For categorical fluency, three participants improved (P6, P8, P9) and two declined (P1, P5) at post-treatment and/or follow-up. One participant (P3) significantly improved on Digit Forward at post-treatment, but there were no changes on this measure for the remaining eight participants at post-treatment or follow-up. On Digit Backward,

four participants (P1, P2, P3, P6) significantly improved at post-treatment and/or follow-up, and two participants declined, either at post-treatment (P4) or follow-up (P8).

Treatment Satisfaction and Telepresence Ratings

All participants rated the intervention as either "very acceptable" (4/5) or "extremely acceptable" (5/5) (mean= 4.6/5), and all participants were either "very satisfied" (4/5) or "extremely satisfied" (5/5) (mean=4.6/5). Mean score on CSQ-8 was 30.9 (range=29-32) out of a possible 32. Across the four internet participants, mean telepresence scores were 80.72% at mid-treatment and 80.75% at post-treatment (0-100% scale), indicating >80% overall agreement that videoconference sessions seemed natural, that participants felt present with the therapist in session, and that participants were absorbed in the sessions as they occurred.

Discussion

To our knowledge, this trial of individual CBT for anxiety in PD is the first to implement a multiple-baseline, single-case experimental design using a 12-week, transdiagnostic CBT protocol, delivered both in-person and via the secure videoconferencing. A recently published article reported that six sessions of manualized CBT reduced anxiety and caregiver burden in 12 PD participants and their caregivers (N. N. W. Dissanayaka et al., 2016); the CBT protocol emphasized behavioral elements and implemented a dyadic approach, with treatment delivered to patients and caregivers simultaneously. Results from the present study add to these findings by indicating that twelve sessions of individual CBT yielded clinically significant reductions in anxiety at

either post-treatment or a 6-week follow-up, relative to the baseline phase, for seven of the nine PD participants, all of whom met diagnostic criteria for a DSM-5 anxiety disorder at baseline. All seven responders also reported improvements in anxiety on the diagnostic interview, and no longer met diagnostic criteria for at least one of their principal anxiety diagnoses at post-treatment and/or follow-up. Two participants (P5, P7) with co-principal anxiety diagnoses at baseline no longer met diagnostic criteria for GAD at post-treatment or follow-up but continued to meet diagnostic criteria for panic disorder and agoraphobia (P5) and social anxiety disorder (P7). An eighth participant reported improvements in anxiety at the follow-up only, and the ninth participant showed no response to the intervention. Seven of the nine participants also reported reduced depressive symptoms at post-treatment and/or follow-up. Levels of acceptability and satisfaction with treatment were high across all participants, regardless of treatment modality (e.g., in-person or internet-delivered sessions).

The effects of the intervention on secondary outcomes were highly variable. There were minimal and/or inconsistent effects on quality of life, motor symptoms, freezing of gait, apathy, sleep, pain, and most aspects of cognition (set-shifting, verbal fluency, attention, working memory). Six participants showed improved psychomotor speed at post-treatment or follow-up, but post-treatment gains were not maintained at follow-up. Of the two participants who endorsed fear of falling at the intake, both reported reduced fear at post-treatment and follow-up.

Consistent with our hypotheses, the intervention yielded significant reductions in anxiety and depression for the majority of participants. The intervention was also highly

feasible with minimal dropout rates. However, we also predicted that the intervention would positively affect additional secondary outcomes, including quality of life, cognition, sleep, and any motor symptoms that may be worsened by anxiety. These latter hypotheses were not supported, other than improved psychomotor speed, and reduced fear of falling. Maintenance of psychomotor speed gains was unclear, but the fear of falling finding warrants further exploration. Both participants with elevated fear of falling at the intake improved at post-treatment and follow-up, suggesting that the positive effects of the intervention on anxiety generalized to their fear of falling.

The lack of significant effects on quality of life, cognition, sleep, and motor symptoms may be related to ceiling effects, as most study participants were high-functioning and highly educated individuals in mild to moderate disease stages, leaving little room for improvement on secondary outcomes. It is also possible that secondary outcome measures were not sensitive enough to capture any subtle changes in this high-functioning participant group. In addition, some secondary outcome measures may be directed linked to neuropathological changes and therefore, may require more targeted interventions. Sleep disruption, for example, is very common and heterogeneous in PD, related to nighttime motor symptoms, nocturia, depression, medication effects, dysfunction in various neurotransmitter systems (Suzuki, Miyamoto, Miyamoto, Iwanami, & Hirata, 2011), and even increased α -synuclein pathology in brainstem and limbic regions (Kalaitzakis, Gentleman, & Pearce, 2013).

Strengths of the study included the use of a rigorous single-case experimental design, stringent inclusion criteria including presence of at least one DSM-5 anxiety

disorder, use of an efficacious transdiagnostic CBT protocol, assessment of therapist adherence to protocol, and the flexibility for participants to choose in-person or internet-delivered therapy sessions. The promising effects of this intervention on anxiety and depression warrant further investigation. First, future work will need to examine predictors of treatment response. One important consideration will be comorbid apathy, which is distinct from depression and present in approximately 40% of individuals with PD (den Brok et al., 2015). Of note, the one individual who showed no response to the intervention reported frequent amotivation and elevated apathy at the intake and pre-treatment assessments (AS=19, 26), and reported worse apathy at post-treatment and follow-up. Given that CBT relies so heavily on homework compliance and out-of-session practice, it is likely that his apathy acted as a significant barrier to treatment response. Future studies may benefit from incorporating additional sessions on motivation for individuals with comorbid apathy. The second participant who showed a minimal treatment response had a history of DBS and much more frequent OFF periods, compared to the other participants. Research that examines the relation between anxiety and motor symptoms will be helpful in informing future treatments for individuals with anxiety, history of DBS, and motor fluctuations.

Most importantly, this study highlights the utility and feasibility of in-person and internet-delivered CBT, as results did not differ by treatment modality. The protocol was modified to allow for internet-delivered sessions due to slow and difficult recruitment, as has been reported in previous treatment trials for depression and anxiety in PD (Troeung et al., 2014). Indeed, Dobkin and colleagues have described several barriers to seeking

mental healthcare in PD, including dismissal of mood symptoms, cost, lack of PD-specific local options, lack of referral, mobility issues, embarrassment, and transportation difficulties (Dobkin et al., 2013); their study also found a high interest in telehealth among PD respondents, which underscores the important findings from this study. The incorporation of a telehealth option facilitated access for individuals who otherwise would not have been able to participate. Moreover, the four telehealth participants reported high treatment satisfaction, and all showed a significant response to treatment.

Limitations of the study included limited generalizability and lack of independent evaluators for the clinician-administered diagnostic interviews. Single-case experimental designs emphasize internal validity and allow for the flexibility to tailor a novel intervention to the individual, which was well-suited for this pilot study. To build upon this work, controlled studies with larger samples are needed, with the eventual goal of a large RCT. Future modifications to the CBT protocol that may be particularly helpful in this population are 1) additional modules on motivation or increased caregiver involvement (Kraepelien et al., 2015), especially for individuals with high baseline apathy, 2) monitoring of homework compliance, 3) shorter treatment course for individuals who show a rapid response to treatment, 4) supplemental modules or adaptation of weekly handouts to optimize organization for any individuals with executive dysfunction at baseline. Specific CBT modules, such as psychoeducation and motivation, may also be helpful as a brief adjunctive treatment for individuals with situational anxiety related to psychosocial stressors, for example. Future work should also consider the potential of CBT to be combined with pharmacotherapies (Cuijpers et

al., 2014) or exercise (Merom et al., 2008) to maximize treatment response in PD. There is also the possibility of simultaneously treating anxiety, freezing of gait, and cognitive set-shifting in PD, given the recently observed association between these symptoms (Martens et al., 2016). Intervention trials that recruit individuals with elevated anxiety and FOG will better elucidate potential treatment effects on these symptoms, as the majority of participants in the present study did not report elevated FOG.

Taken together, additional treatment studies are critically needed with a focus on anxiety in PD, both for in-person and internet-delivered interventions, in order to replicate the current findings and eventually implement an RCT to evaluate generalizability. This study demonstrated the utility and feasibility of transdiagnostic CBT for anxiety in PD, when delivered in person or via secure videoconferencing. The intervention also reduced mild to moderate depressive symptoms among the majority of participants. Exploratory examinations of treatment effects on additional secondary outcomes were much more mixed and require further study. We hope the findings will provide the impetus for larger treatment trials with a focus on anxiety in this population, with the goal of establishing evidence-based psychological treatment options for individuals with PD and increasing dissemination of these treatments to assist individuals in accessing mental healthcare and developing long-term skills to manage anxiety across all stages of the disease.

Table 6.

Participant	Age (yrs)	Education (yrs)	Sex	Side of Onset	Disease Duration (yrs)	Anxiety/ Depression Diagnosis (CSR)	In-person vs. Internet-delivered Tx	Baseline Length
P1	67	18	F	Right	4.4	GAD (4)	In-person	2
P2	55	14	M	Right	3.5	PD (4)	In-person	4
P3	65	16	M	Right	15.4	GAD (5); DYS (5)	In-person	6
P4	79	18	M	Bilateral	7.9	OTHER SPEC ANX (LSA) (6); SOC (5)	In-person	2
P5	59	16	F	Right	4.9	PD (5); AG (6); GAD (4)	Internet	4
P6	64	20+	M	Left	10.4	SOC (4)	Internet	6
P7	56	14	F	Right	1.6	SOC (5); GAD (5)	Internet	2
P8	33	19	F	Left	9.0	PD (6); AG (6); SOC (6); GAD (6); MDD (5)	In-person	4
P9	73	16	F	Left	2.5	GAD (4)	Internet	6

CSR = Clinical Severity Rating; GAD = generalized anxiety disorder; SOC = social anxiety disorder; LSA=limited-symptom panic attack; DYS=persistent depressive disorder (dysthymia); PD=panic disorder. MDD=major depressive disorder. Tx=Treatment.

Only clinically significant anxiety/depression diagnoses (CSR ≥4) are reported, and only these diagnoses were reassessed at subsequent assessments.

Table 7. Content Outline for CBT Sessions (Barlow et al., 2011).

Session	Major Topic	Content/Goals
1	Introduction	Establish rapport, review presenting complaints, introduce treatment program (format, procedures, monitoring forms)
2	Motivation	Discuss motivation to maximize treatment engagement, set specific treatment goals
3	Psychoeducation	Discuss functional nature of emotions, introduce three-component model of emotions and emotion-driven behaviors, discuss triggers and consequences of emotions and emotional reactions, discuss learned experiences
4	Emotional Awareness (Part 1)	Introduce and practice nonjudgmental, present-focused awareness
5	Emotional Awareness (Part 2)	Continue to practice emotional awareness techniques using a musical mood induction
6	Cognitive Appraisal & Reappraisal	Discuss relationship between thoughts and emotions, introduce automatic appraisals, discuss common thinking traps, practice cognitive reappraisal
7	Emotion Avoidance & Emotion-Driven Behaviors	Introduce and discuss emotion avoidance and emotion avoidance strategies, discuss emotion-driven behaviors, develop alternative action tendencies
8	Awareness & Tolerance of Physical Sensations	Identify physical sensations associated with emotions, discuss role of physical sensations in emotional response, conduct symptom exercises to elicit uncomfortable physical sensations
9	Emotion Exposure	Discuss purpose of exposures, develop emotional and situational avoidance hierarchy, design emotion exposures
10	Emotion Exposure	Conduct emotion exposure
11	Emotion Exposure	Conduct emotion exposure
12	Relapse Prevention/Review	Review skills and treatment progress, identify and troubleshoot triggers, encourage skill generalization, set new goals and discuss ways to maintain treatment gains

Table 8. Clinical Severity Ratings for Anxiety and Depressive Disorder Diagnoses.

	Intake		**Pre-Tx**		**Post-Tx**		**6-Week Follow-Up**	
	DX	*CSR*	*DX*	*CSR*	*DX*	*CSR*	*DX*	*CSR*
P1	GAD	4	GAD	4	GAD	1	GAD	1
P2	PD	4	PD	4	PD	1	PD	0
P3	GAD	5	GAD	5	GAD	5	GAD	5
	DYS	5	DYS	5	DYS	5	DYS	5
P4	OTHER SPEC ANX (LSA)	6	OTHER SPEC ANX (LSA)	6	OTHER SPEC ANX (LSA)	2	OTHER SPEC ANX (LSA)	2
	SOC	5	SOC	4	SOC	2	SOC	2
P5	PD	5	PD	5	PD	4	PD	4
	AG	6	AG	6	AG	5	AG	5
	GAD	4	GAD	4	GAD	3	GAD	3
P6	SOC	4	SOC	4	SOC	4	SOC	3
P7	SOC	5	SOC	5	SOC	4	SOC	4
	GAD	5	GAD	5	GAD	3	GAD	3
P8	PD	6	PD	6	PD	5	PD	6
	AG	6	AG	6	AG	6	AG	6
	SOC	6	SOC	6	SOC	6	SOC	6
	GAD	6	GAD	6	GAD	6	GAD	6
	MDD	5	MDD	6	MDD	5	MDD	4
P9	GAD	4	GAD	4	GAD	2	GAD	2

P=Participant; CSR=Clinical Severity Rating; SOC=social anxiety disorder; GAD=generalized anxiety disorder; OTHER SPEC ANX=other specified anxiety disorder; LSA=limited-symptom panic attacks; DYS=persistent depressive disorder (dysthymia); PD=panic disorder. MDD=major depressive disorder.
*Only clinically significant diagnoses (CSR>=4) reported at the intake are listed, and only those diagnoses were reassessed at the subsequent timepoints.

Table 9a. Anxiety Change Scores (CS) with 95% CIs.

	BAI 95% CI = CS±8.93	**OASIS** 95% CI = CS±4.46
P1		
BL	3 (-5.93, 11.93)	1 (-3.46, 5.46)
Pre-Post	-9 (-17.93, -0.07)*	-6 (-10.46, -1.54)*
Pre-FU	-10 (-18.93, -1.07)*	-6 (-10.46, -1.54)*
P2		
BL	4 (-4.93, 12.93)	2 (-2.46, 6.46)
Pre-Post	-9 (-17.93, -0.07)*	-5 (-9.46, -0.54)*
Pre-FU	-10 (-18.93, -1.07)*	-5 (-9.46, -0.54)*
P3		
BL	1 (-7.93, 9.93)	2 (-2.46, 6.46)
Pre-Post	0 (-8.93, 8.93)	1 (-3.46, 5.46)
Pre-FU	-1 (-9.93, 7.93)	3 (-1.46, 7.46)
P4[#]		
BL	-4 (-12.93, 4.93)	-4 (-8.46, 0.46)
Pre-Post	-10 (-18.93, -1.07)*	-8 (-12.46, -3.54)*
Pre-FU	-7 (-15.93, 1.93)	-7 (-11.46, -2.54)*
P5		
BL	3 (-5.93, 11.93)	-2 (-6.46, 2.46)
Pre-Post	-5 (-13.93, 3.93)	0 (-4.46, 4.46)
Pre-FU	-8 (-16.93, 0.93)	-4 (-8.46, 0.46)
P6		
BL	-4 (-12.93, 4.93)	1 (-3.46, 5.46)
Pre-Post	-5 (-13.93, 3.93)	-4 (-8.46, 0.46)
Pre-FU	-3 (-11.93, 5.93)	-5 (-9.46, -0.54)*
P7^		
BL	5 (-3.93, 13.93)	1 (-3.46, 5.46)
Pre-Post	-4 (-12.93, 4.93)	-6 (-10.46, -1.54)*
Pre-FU	-8 (-16.93, 0.93)	-4 (-8.46, 0.46)
P8		
BL	4 (-4.93, 12.93)	3 (-1.46, 7.46)
Pre-Post	0 (-8.93, 8.93)	-4 (-8.46, 0.46)
Pre-FU	-9 (-17.93, -0.07)*	-5 (-9.46, -0.54)*
P9		
BL	-18 (-26.93, -9.07)*	-2 (-6.46, 2.46)
Pre-Post	-1 (-9.93, 7.93)	-2 (-6.46, 2.46)
Pre-FU	0 (-8.93, 8.93)	-3 (-7.46, 1.46)

*Improvement significant at $p<.05$
BL=last baseline score – first baseline score
Pre-post=post-treatment score – last baseline score
Pre-FU=6-week follow-up score – last baseline score

Table 9b. Anxiety Change Scores (CS) with 95% CIs.

	STAI-S 95% CI = CS±10.47	**STAI-T** 95% CI = CS±11.70
P1		
BL	2 (-8.47, 12.47)	2 (-9.70, 13.70)
Pre-Post	-30 (-40.47, -19.53)*	-13 (-24.70, -1.30)*
Pre-FU	-30 (-40.47, -19.53)*	-23 (-34.70, -11.30)*
P2		
BL	6 (-4.47, 16.47)	6 (-5.70, 17.70)
Pre-Post	-19 (-29.47, -8.53)*	-21 (-32.70, -9.30)*
Pre-FU	-18 (-28.47, -7.53)*	-21 (-32.70, -9.30)*
P3		
BL	1 (-9.47, 11.47)	-5 (-16.70, 6.70)
Pre-Post	-5 (-15.47, 5.47)	0 (-11.70, 11.70)
Pre-FU	3 (-7.47, 13.47)	3 (-8.70, 14.70)
P4[#]		
BL	9 (-1.47, 19.47)	0 (-11.70, 11.70)
Pre-Post	-5 (-15.47, 5.47)	1 (-10.70, 12.70)
Pre-FU	1 (-9.47, 11.47)	1 (-10.70, 12.70)
P5		
BL	-5 (-15.47, 5.47)	-1 (-12.70, 10.70)
Pre-Post	-22 (-32.47, -11.53)*	-16 (-27.70, -4.30)*
Pre-FU	-28 (-38.47, -17.53)*	-20 (-31.70, -8.30)*
P6		
BL	-3 (-13.47, 7.47)	-2 (-13.70, 9.70)
Pre-Post	-1 (-11.47, 9.47)	-2 (-13.70, 9.70)
Pre-FU	-2 (-12.47, 8.47)	-2 (-13.70, 9.70)
P7^		
BL	-18 (-28.47, -7.53)*	2 (-9.70, 13.70)
Pre-Post	0 (-10.47, 10.47)	-6 (-17.70, 5.70)
Pre-FU	-2 (-12.47, 8.47)	-16 (-27.70, -4.30)*
P8		
BL	-14 (-24.47, -3.53)*	1 (-10.70, 12.70)
Pre-Post	4 (-6.47, 14.47)	-5 (-16.70, 6.70)
Pre-FU	-9 (-19.47, 1.47)	-5 (-16.70, 6.70)
P9		
BL	-20 (-30.47, -9.53)*	-6 (-17.70, 5.70)
Pre-Post	-7 (-17.47, 3.47)	-4 (-15.70, 7.70)
Pre-FU	-18 (-28.47, -7.53)*	-10 (-21.70, 1.70)

*Improvement significant at $p<.05$
BL=last baseline score – first baseline score
Pre-post=post-treatment score – last baseline score
Pre-FU=6-week follow-up score – last baseline score

#P4 slightly increased his parkinsonian medications to address motor symptoms during the middle of treatment.
^At the follow-up, P7 reported retrospectively that she increased her psychotropic medication dose from 20mg to 30mg for "about a week" during the middle of treatment in response to increased frustration about an ongoing physical pain issue (unrelated to anxiety). She was unable to provide the exact dates when she adjusted the dose, but likely in the 1-2 weeks prior to session 9. She denied noticing any effect of the increased dose and as a result returned to the original 20mg dose shortly after making the change.

Table 10. Depression Change Scores (CS) with 95% CIs.

	BDI-II** 95% CI = CS±6.49 95% CI = CS±4.56	**ODSIS** 95% CI = CS±3.42	**GDS**** 95% CI = CS±5.33 95% CI = CS±4.08
P1			
BL	1 (-3.56, 5.56)	2 (-1.42, 5.42)	3 (-1.08, 7.08)
Pre-Post	-5 (-9.56, -0.44)*	1 (-2.42, 4.42)	-5 (-9.08, -0.92)*
Pre-FU	-5 (-9.56, -0.44)*	-2 (-5.42, 1.42)	-9 (-13.08, -4.92)*
P2			
BL	1 (-3.56, 5.56)	1 (-2.42, 4.42)	-1 (-5.08, 3.08)
Pre-Post	-6 (-10.56, -1.44)*	-4 (-7.42, -0.58)*	-3 (-7.08, 1.08)
Pre-FU	-5 (-9.56, -0.44)*	-4 (-7.42, -0.58)*	-2 (-6.08, 2.08)
P3			
BL	0 (-6.49, 6.49)	3 (-0.42, 6.42)	-1 (-6.33, 4.33)
Pre-Post	0 (-6.49, 6.49)	-1 (-4.42, 2.42)	2 (-3.33, 7.33)
Pre-FU	1 (-5.49, 7.49)	-3 (-6.42, 0.42)	2 (-3.33, 7.33)
P4			
BL	-8 (-12.56, -3.44)*	-3 (-6.42, 0.42)	2 (-2.08, 6.08)
Pre-Post	-10 (-14.56, -5.44)*	-2 (-5.42, 1.42)	-4 (-8.08, 0.08)
Pre-FU	-13 (-17.56, -8.44)*	-2 (-5.42, 1.42)	-5 (-9.08, -0.92)*
P5			
BL	0 (-4.56, 4.56)	0 (-3.42, 3.42)	-1 (-5.08, 3.08)
Pre-Post	-5 (-9.56, -0.44)*	0 (-3.42, 3.42)	-3 (-7.08, 1.08)
Pre-FU	-4 (-8.56, 0.56)	0 (-3.42, 3.42)	-3 (-7.08, 1.08)
P6			
BL	1 (-3.56, 5.56)	1 (-2.42, 4.42)	-3 (-7.08, 1.08)
Pre-Post	-6 (-10.56, -1.44)*	-3 (-6.42, 0.42)	-5 (-9.08, -0.92)*
Pre-FU	-4 (-8.56, 0.56)	-3 (-6.42, 0.42)	-3 (-7.08, 1.08)
P7			
BL	-6 (-10.56, -1.44)*	0 (-3.42, 3.42)	-1 (-5.08, 3.08)
Pre-Post	-2 (-6.56, 2.56)	0 (-3.42, 3.42)	-5 (-9.08, -0.92)*
Pre-FU	-2 (-6.56, 2.56)	0 (-3.42, 3.42)	-4 (-8.08, 0.08)
P8			
BL	-3 (-9.49, 3.49)	0 (-3.42, 3.42)	NA
Pre-Post	-4 (-10.49, 2.49)	1 (-2.42, 4.42)	
Pre-FU	-11 (-17.49, -4.51)*	0 (-3.42, 3.42)	
P9			
BL	-4 (-8.56, 0.56)	-1 (-4.42, 2.42)	1 (-3.08, 5.08)
Pre-Post	-16 (-20.56, -11.44)*	-5 (-8.42, -1.58)*	-10 (-14.08, -5.92)*
Pre-FU	-10 (-14.56, -5.44)*	-3 (-6.42, 0.42)	-11 (-15.08, -6.92)*

*Improvement significant at $p<.05$

**Two confidence intervals were calculated for the BDI-II and GDS: one for participants (P3, P8) who met criteria for a current depressive disorder (BDI-II=6.49; GDS=5.33),

and the second for all other participants who did not meet diagnostic criteria for a current depressive disorder (BDI-II=4.56; GDS=4.08).
NA=GDS was not administered to P8 due to her younger age.
BL=last baseline score – first baseline score
Pre-post=post-treatment score – last baseline score
Pre-FU=6-week follow-up score – last baseline score

Table 11a. Change Scores for Secondary Outcome Measures (Disorder-Specific Questionnaires).

	PSWQ 95% CI = CS±10.23	**ASI** 95% CI = CS±9.45	**PDSS** 95% CI = CS±5.19
P1 *Intake-Post* *Intake-FU*	 -15 (-25.2, -4.8)* -18 (-28.2, -7.8)*	 NA	 NA
P2 *Intake-Post* *Intake-FU*	 NA	 -10 (-19.5, -0.6)* -16 (-25.5, -6.6)*	 0 (-5.2, 5.2) -4 (-9.2, 1.2)
P3 *Intake-Post* *Intake-FU*	 6 (-4.2, 16.2) 6 (-4.2, 16.2)	 NA	 NA
P4 *Intake-Post* *Intake-FU*	 NA	 -19 (-28.5, -9.6)* -16 (-25.5, -6.6)*	 -12 (-17.2, -6.8)* -13 (-18.2, -7.8)*
P5 *Intake-Post* *Intake-FU*	 -1 (-11.2, 9.2) 3 (-7.2, 13.2)	 -7 (-16.5, 2.5) -5 (-14.5, 4.5)	 -4 (-9.2, 1.2) -3 (-8.2, 2.2)
P6 *Intake-Post* *Intake-FU*	 NA	 NA	 NA
P7 *Intake-Post* *Intake-FU*	 -15 (-25.2, -4.8)* -15 (-25.2, -4.8)*	 NA	 -8 (-13.2, -2.8)* -5 (-10.2, 0.2)
P8+ *Intake-Post* *Intake-FU*	 0 (-10.2, 10.2) -2 (-12.2, 8.2)	 6 (-3.5, 15.5) -2 (-11.5, 7.5)	 -5 (-10.2, 0.2) -8 (-13.2, -2.8)*
P9 *Intake-Post* *Intake-FU*	 -4 (-14.2, 6.2) 0 (-10.2, 10.2)	 NA	 NA

*Improvement at $p<.05$

+: P8 follow-up completed at eight weeks post-treatment due to scheduling constraints.

Table 11b. Change Scores for Secondary Outcome Measures (Disorder-Specific Questionnaires and Quality of Life).

	SIAS 95% CI = CS±12.03	**SPIN** 95% CI = CS±11.60	**PDQ-39** 95% CI = CS±17.49
P1 *Intake-Post* *Intake-FU*	NA	NA	-9.1 (-26.6, 8.4) -8.3 (-25.8, 9.2)
P2 *Intake-Post* *Intake-FU*	NA	-19 (-30.6, -7.4)* -18 (-29.6, -6.4)*	-3.1 (-20.6, 14.4) 3.4 (-14.1, 20.9)
P3 *Intake-Post* *Intake-FU*	NA	NA	-2.1 (-19.6, 15.4) 1.7 (-15.8, 19.2)
P4 *Intake-Post* *Intake-FU*	-4 (-16.0, 8.0) -7 (-19.0, 5.0)	-5 (-16.6, 6.6) -9 (-20.6, 2.6)	-18.0 (-35.5, -0.5)* -21.8 (-39.3, -4.3)*
P5 *Intake-Post* *Intake-FU*	-9 (-21.0, 3.0) -17 (-29.0, -5.0)*	NA	-0.9 (-18.4, 16.6) -3.5 (-21.0, 14.0)
P6 *Intake-Post* *Intake-FU*	-5 (-17.0, 7.0) -5 (-17.0, 7.0)	-9 (-20.6, 2.6) -9 (-20.6, 2.6)	10.6 (-6.9, 28.1) 6.5 (-11.0, 24.0)
P7 *Intake-Post* *Intake-FU*	-14 (-26.0, -2.0)* -8 (-20.0, 4.0)	-14 (-25.6, -2.4)* -20 (-31.6, -8.4)*	-5.9 (-23.4, 11.6) 6.2 (-11.3, 23.7)
P8+ *Intake-Post* *Intake-FU*	6 (-6.0, 18.0) 5 (-7.0, 17.0)	-9 (-20.6, 2.6) -3 (-14.6, 8.6)	-4.3 (-21.8, 13.2) 3.8 (-13.7, 21.3)
P9 *Intake-Post* *Intake-FU*	NA	NA	-8.3 (-25.8, 9.2) -7.3 (-24.8, 10.2)

*Improvement at $p<.05$

+: P8 follow-up completed at eight weeks post-treatment due to scheduling constraints.

Table 12a. Change Scores for Secondary Outcome Measures (Apathy, Fear of Falling, FOG).

	AS 95% CI = CS±7.74	**FES** 95% CI = CS±3.55	**FOG** 95% CI = CS±5.52
P1 *Intake-Post* *Intake-FU*	NA	-5 (-8.6, -1.5)* -5 (-8.6, -1.5)*	NA
P2 *Intake-Post* *Intake-FU*	-1 (-8.7, 6.7) -7 (-14.7, 0.7)	NA	NA
P3 *Intake-Post* *Intake-FU*	9 (1.3, 16.7)^ 9 (1.3, 16.7)^	NA	-1 (-6.5, 4.5) 0 (-5.5, 5.5)
P4 *Intake-Post* *Intake-FU*	-9 (-16.7, -1.3)* -10 (-17.7, -2.3)*	-25 (-28.6, -21.5)* -22 (-25.6, -18.5)*	NA
P5 *Intake-Post* *Intake-FU*	NA	NA	NA
P6 *Intake-Post* *Intake-FU*	3 (-4.7, 10.7) 6 (-1.7, 13.7)	NA	NA
P7 *Intake-Post* *Intake-FU*	NA	NA	1 (-4.5, 6.5) -1 (-6.5, 4.5)
P8+ *Intake-Post* *Intake-FU*	-2 (-9.7, 5.7) -1 (-8.7, 6.7)	NA	3 (-2.5, 8.5) 9 (3.5, 14.5)^
P9 *Intake-Post* *Intake-FU*	-7 (-14.7, 0.7) -9 (-16.7, -1.3)*	NA	NA

*Improvement at $p<.05$.

^Worsening at $p<.05$.

+ P8 follow-up completed at eight weeks post-treatment due to scheduling constraints.

Table 12b. Change Scores for Secondary Outcome Measures (Pain, Sleep, Motor Symptoms).

	McGill-SF 95% CI = CS±11.55	**PDSS-2 #** 95% CI = CS±12.82	**MDS-UPDRS Part III** 95% CI = CS±13.49
P1 *Intake-Post* *Intake-FU*	NA	11 (-1.8, 23.8) 16 (3.2, 28.8)^	3 (-10.5, 16.5) 0 (-13.5, 13.5)
P2 *Intake-Post* *Intake-FU*	NA	0 (-12.8, 12.8) 4 (-8.8, 16.8)	9 (-4.5, 22.5) 17 (3.5, 30.5)^
P3 *Intake-Post* *Intake-FU*	NA	NA	1 (-12.5, 14.5) 3 (-10.5, 16.5)
P4 *Intake-Post* *Intake-FU*	NA	-16 (-28.8, -3.2)* -17 (-29.8, -4.2)*	3 (-10.5, 16.5) -6 (-19.5, 7.5) ||
P5 *Intake-Post* *Intake-FU*	NA	-5 (-17.8, 7.8) -2 (-14.8, 10.8)	-9 (-22.5, 4.5) -12 (-25.5, 1.5)
P6 *Intake-Post* *Intake-FU*	NA	2 (-10.8, 14.8) -1 (-13.8, 11.8)	-1 (-14.5, 12.5) -9 (-22.5, 4.5)
P7 *Intake-Post* *Intake-FU*	3 (-8.6, 14.6) -2 (-13.6, 9.6) <	NA	15 (1.5, 28.5)^ 7 (-6.5, 20.5)
P8+ *Intake-Post* *Intake-FU*	9 (-2.6, 20.6) 11 (-0.6, 22.6)	5 (-7.8, 17.8) 14 (1.2, 26.8)^	-14 (-27.5, -0.5)* -12 (-25.5, 1.5)
P9 *Intake-Post* *Intake-FU*	NA	-3 (-15.8, 9.8) 0 (-12.8, 12.8)	3 (-10.5, 16.5) 2 (-11.5, 15.5)

*Improvement at $p<.05$.

^Worsening at $p<.05$.

#P1: PDSS-2 intake questionnaire missing one item.

|| P4, two items missing on follow-up UPDRS

< P7 McGill-SF completed at approximately 8 weeks follow-up rather than 6 weeks.

+ P8 follow-up completed at eight weeks post-treatment due to scheduling constraints.

Table 13. Neuropsychological Outcomes.

	TMT-A	TMT-B	FAS	Animals	Digit Forward	Digit Backward
P1						
Intake-Post	4.1%	-28.9%*	-2.4%	-25.9% ^	9.1%	100% *
Intake-FU	13.8%	5.6%	26.2%*	-37.0% ^	18.2%	33.3% *
P2						
Intake-Post	4.9%	7.3%	19.4%	-11.5%	0%	40.0%*
Intake-FU	-15.5%	21.8% ^	13.9%	-3.8%	0%	20.0%
P3						
Intake-Post	-22.1%*	30.8% ^	-10.5%	9.4%	40.0%*	83.3%*
Intake-FU	-7.4%	8.3%	-3.5%	0%	20.0%	0%
P4						
Intake-Post	-32.0%*	-9.4%	-6.5%	0%	16.7%	-25.0% ^
Intake-FU	-9.0%	-5.0%	-19.4%	20.0%	8.3%	-12.5%
P5						
Intake-Post	-18.0%	-4.2%	-14.8%	0%	-7.1%	-9.1%
Intake-FU	-25.5%*	32.5% ^	-3.7%	-21.7% ^	7.1%	9.1%
P6						
Intake-Post	-15.9%	44.0% ^	3.5%	28.6%*	0%	40.0%*
Intake-FU	-22.8%*	-8.3%	36.8%*	19.0%	-16.7%	0%
P7						
Intake-Post	-29.8%*	26.8% ^	5.3%	13.3%	0%	16.7%
Intake-FU	-0.8%	32.3% ^	-5.3%	0%	-10.0%	0%
P8+						
Intake-Post	-2.8%	-21.2%*	0%	23.8%*	-8.3%	10.0%
Intake-FU	-1.3%	-22.1%*	6.7%	28.6%*	-8.3%	-30.0% ^
P9						
Intake-Post	-36.3%*	-24.5%*	39.5%*	21.1%*	7.7%	10.0%
Intake-FU	-16.4%	8.9%	23.7%*	21.1%*	-7.7%	10.0%

*Improvement >20%
^Worsening >20%.
+ P8 follow-up completed at eight weeks post-treatment due to scheduling constraints.

Figure 2. Participant Flow

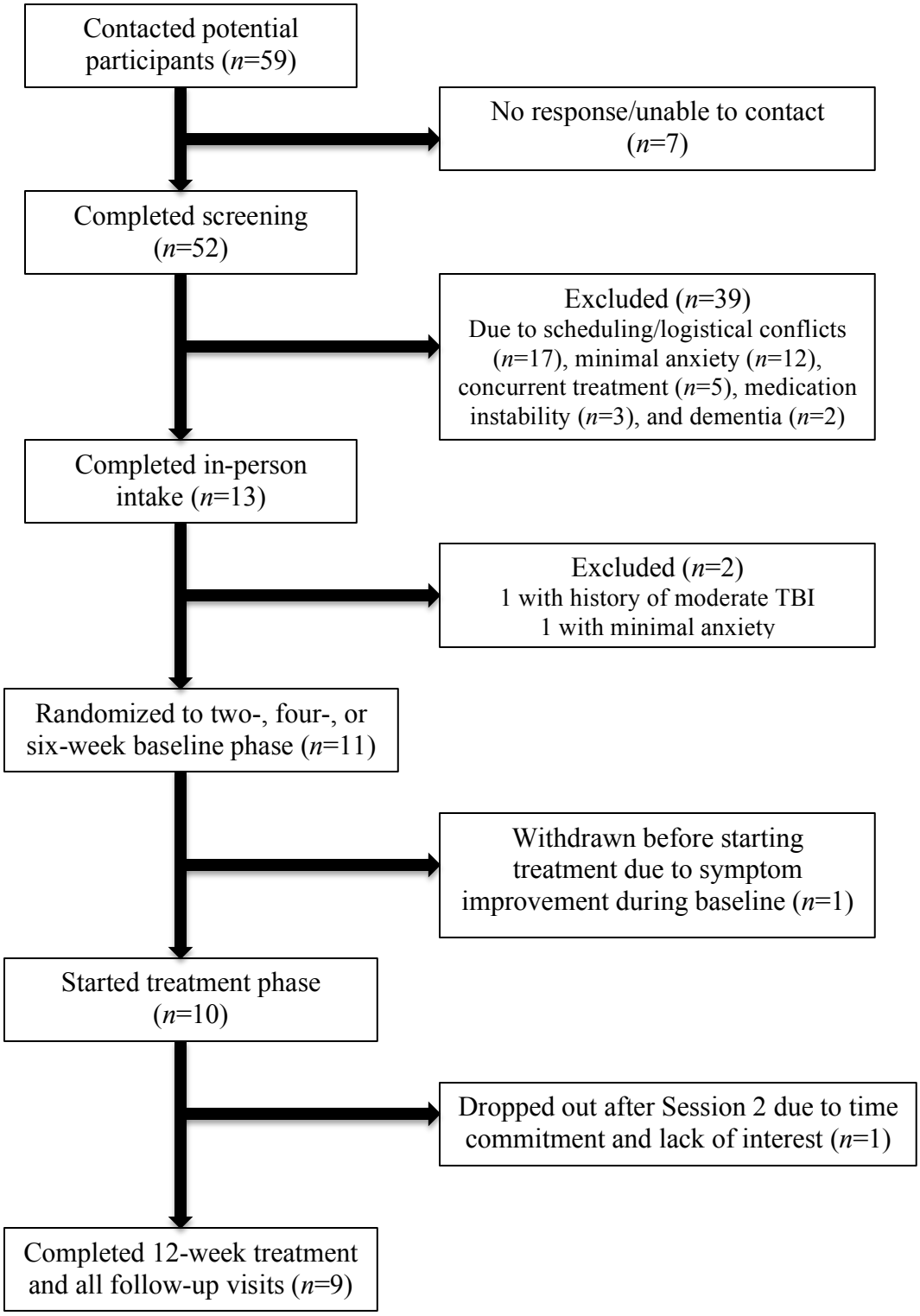


Figure 3. Weekly Self-Report Anxiety Scores: P1, P2, P3

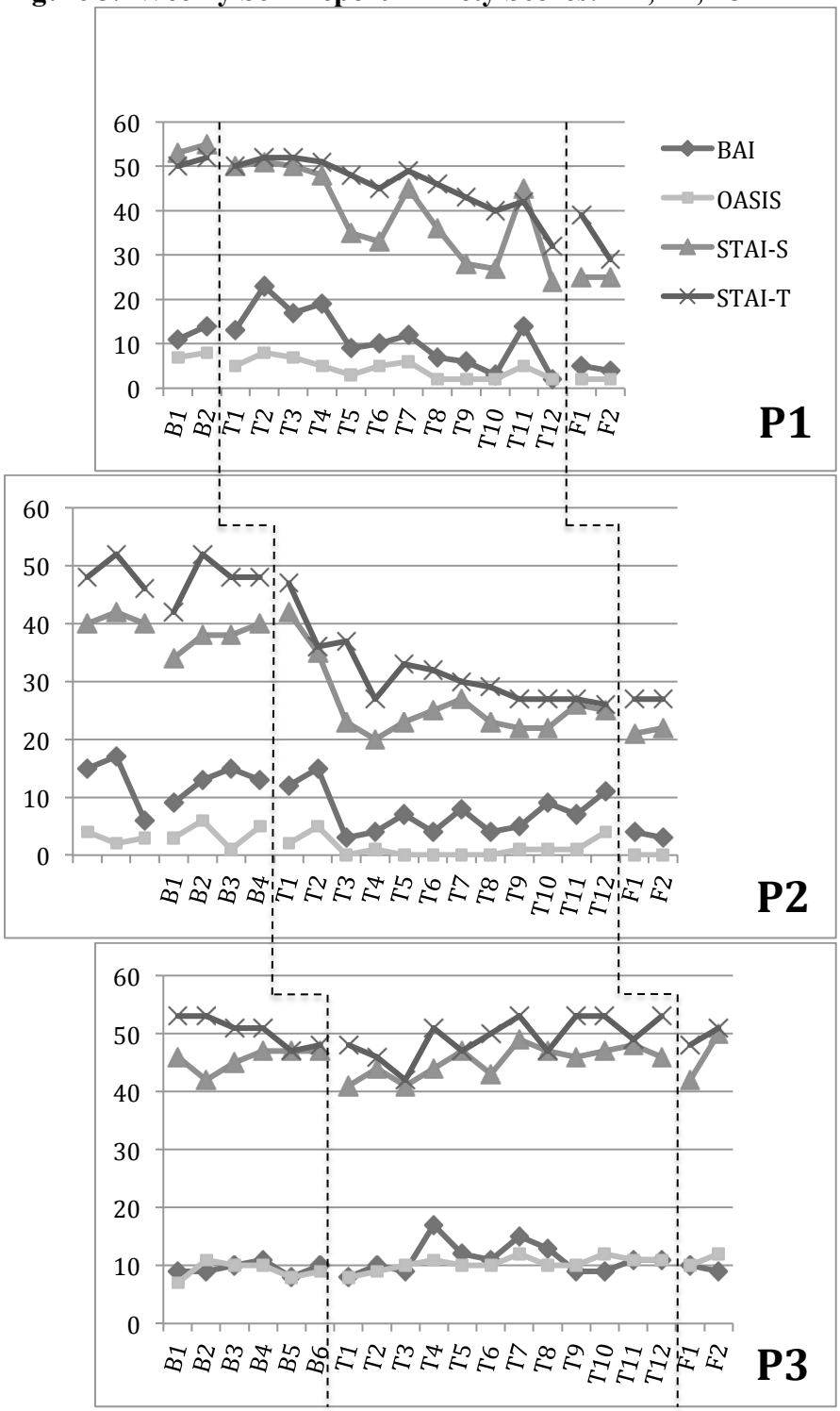


Figure 4. Weekly Self-Report Depression Scores: P1, P2, P3

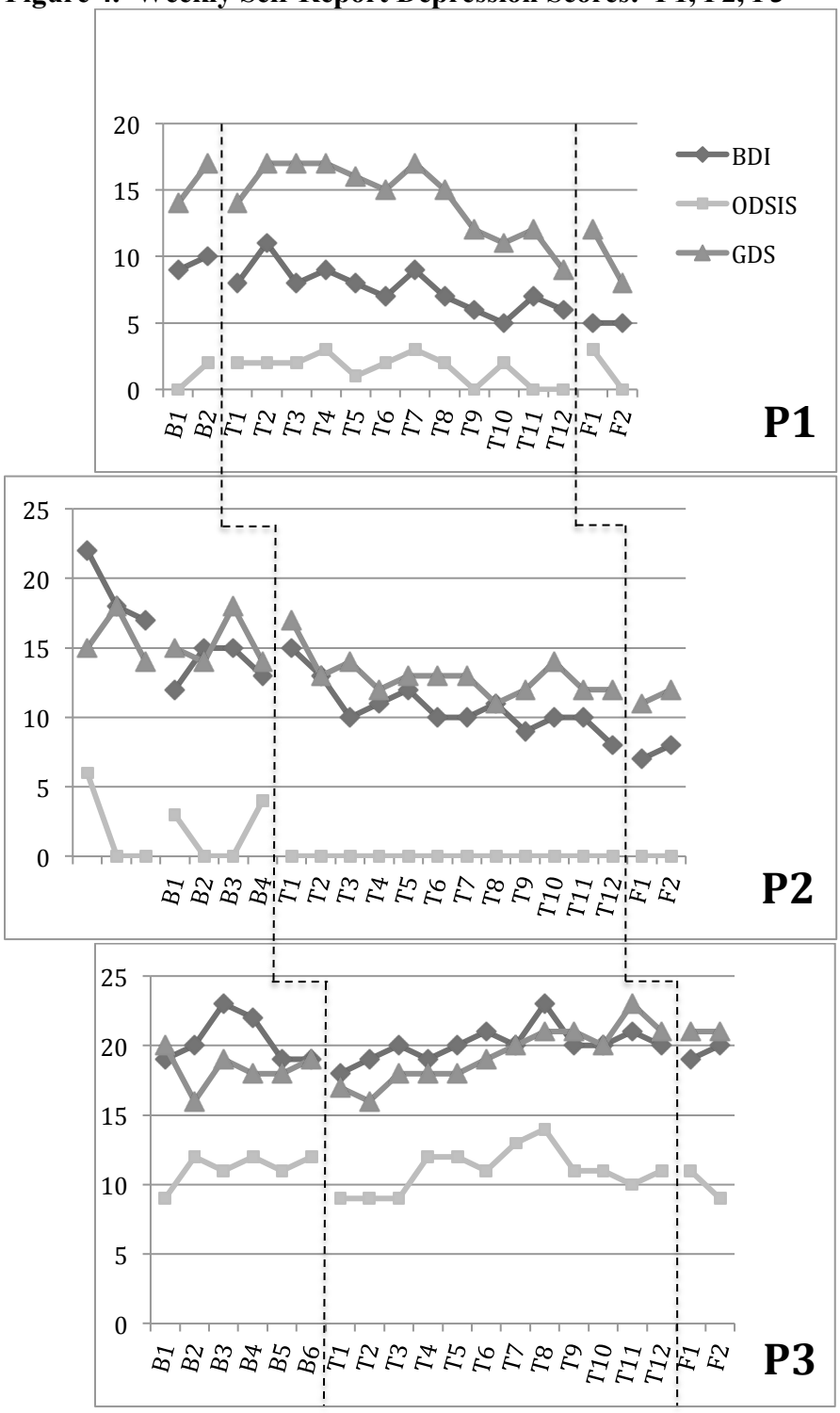


Figure 5. Weekly Self-Report Anxiety Scores: P4, P5, P6

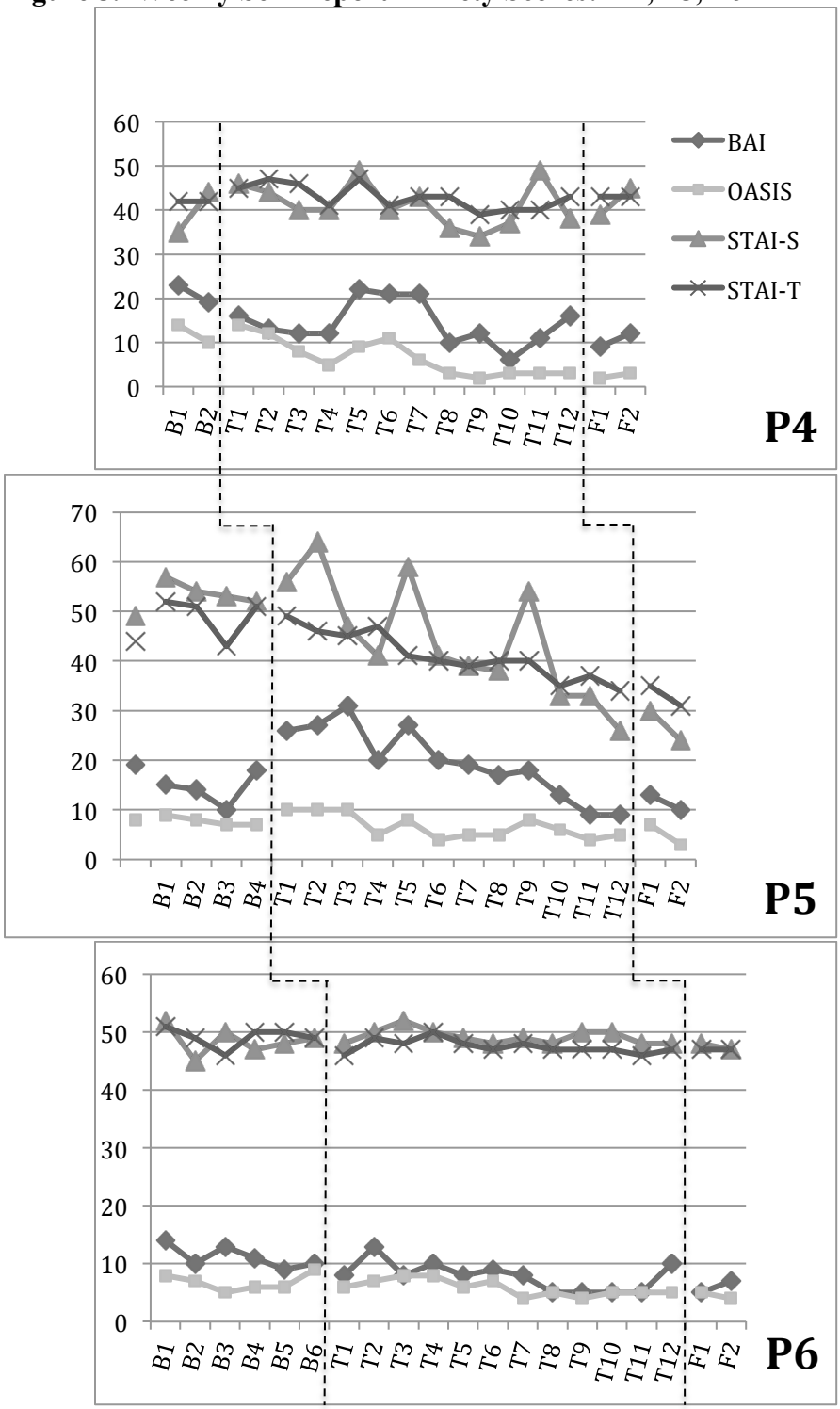


Figure 6. Weekly Self-Report Depression Scores: P4, P5, P6

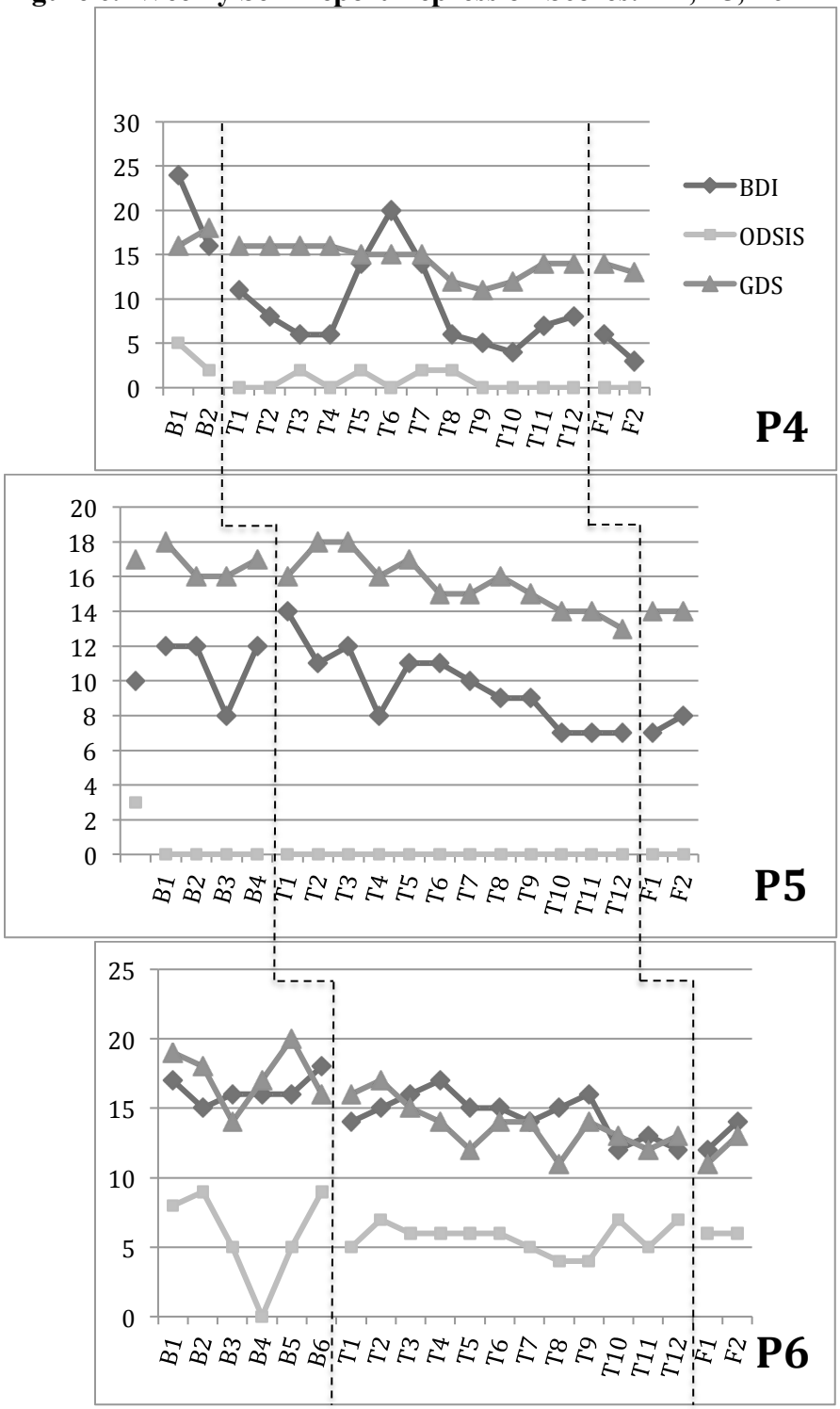


Figure 7. Weekly Self-Report Anxiety Scores: P7, P8, P9

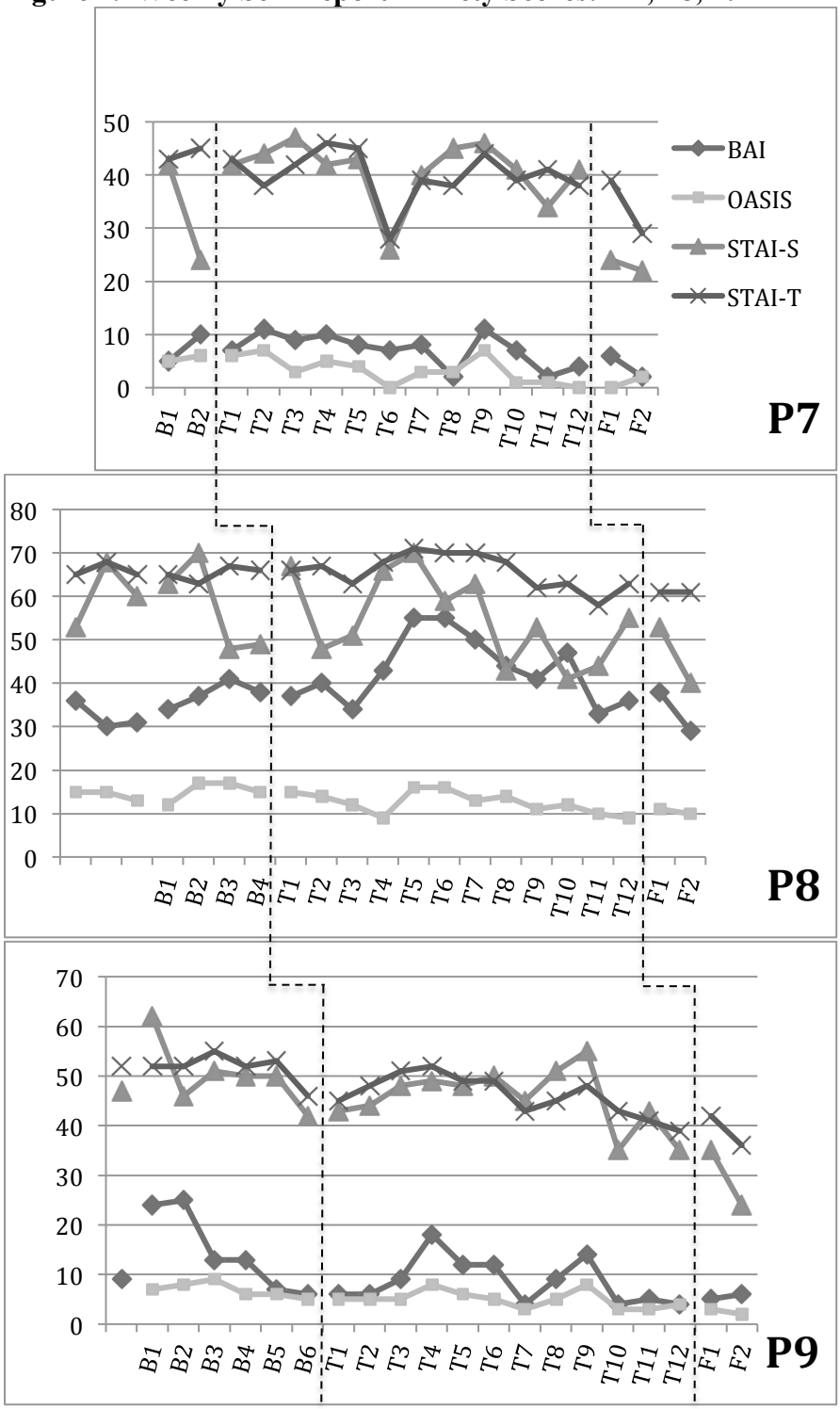
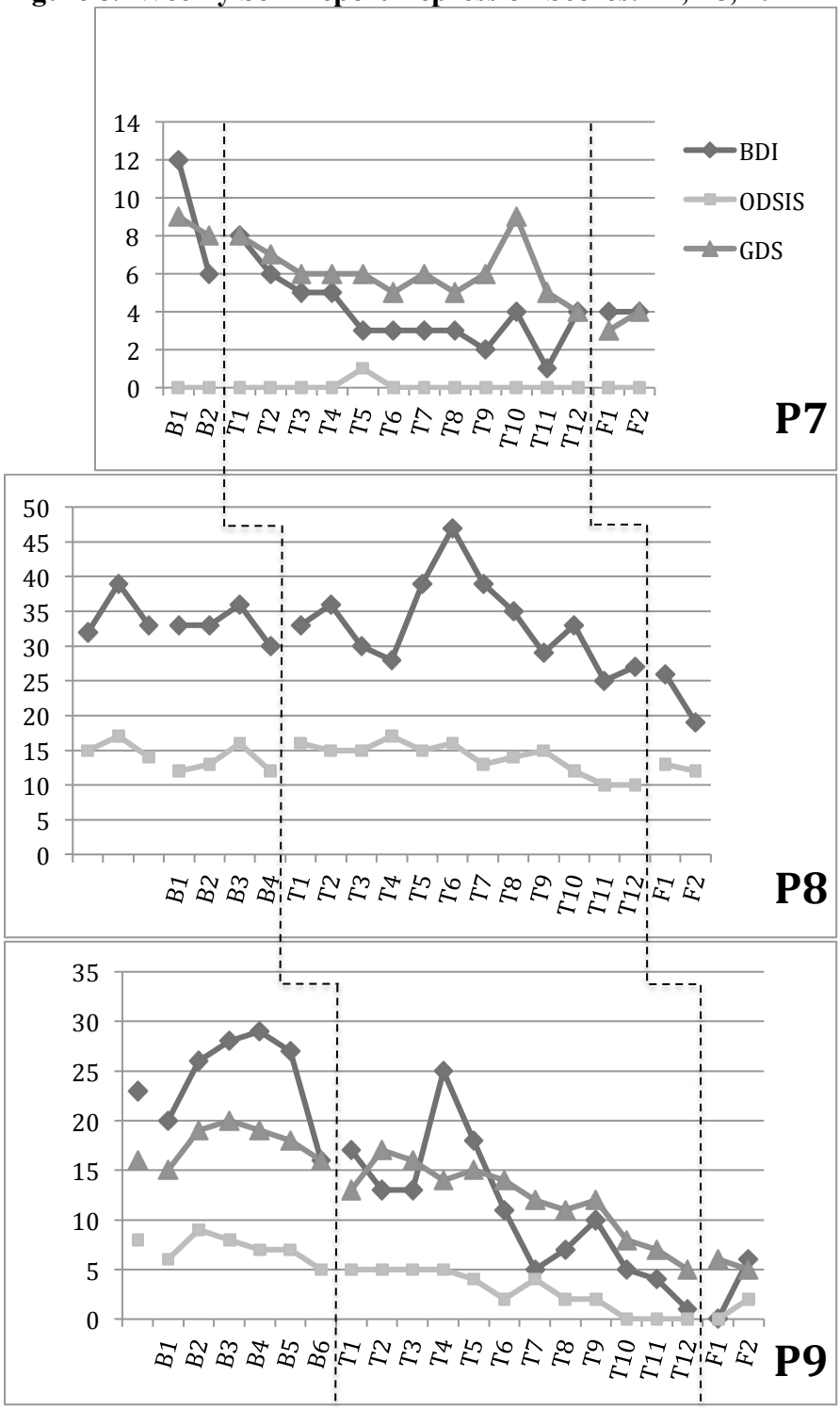


Figure 8. Weekly Self-Report Depression Scores: P7, P8, P9



Appendix A. Post-treatment Feedback Form.

Please answer the questions below as honestly as possible to provide feedback for us about the intervention.

1. Overall, how acceptable was the intervention to you? Did you think the treatment approach and activities made sense and were reasonable? (Circle answer).

Not at all acceptable	Slightly acceptable	Moderately acceptable	Very acceptable	Extremely acceptable
1	2	3	4	5

2. Overall, how satisfied were you with the intervention? (Circle answer).

Not at all satisfied	Slightly satisfied	Moderately satisfied	Very satisfied	Extremely satisfied
1	2	3	4	5

3. In your own words, please tell us what you thought of the intervention overall.

4. What elements of the intervention did you find most helpful?

5. What elements of the intervention did you find least helpful?

6. Are there any changes that you would recommend?

7. What are the most important things that you learned from this intervention?

CHAPTER 4: STUDY THREE – THE THERAPEUTIC POTENTIAL OF EXERCISE TO IMPROVE MOOD, COGNITION, AND SLEEP IN PARKINSON'S DISEASE[2]

Introduction

Although traditionally conceptualized as a motor disorder, Parkinson's disease (PD) is also associated with a variety of non-motor symptoms. These symptoms – including disturbances of mood, cognition, and sleep – substantially reduce quality of life, often to a greater extent than the motor symptoms (Cronin-Golomb, 2013; Duncan et al., 2014; Hanna & Cronin-Golomb, 2012; McKinlay et al., 2008). Also of note, traditional dopaminergic treatments for PD may exacerbate or contribute, at least in part, to mood, cognitive, and especially sleep symptoms in this population (Park & Stacy, 2009). In this article, we present the evidence supporting aerobic exercise and strength training as promising broad-spectrum interventions for these specific non-motor symptoms in PD, beyond the well-established benefits for core motor symptoms. To date, most exercise programs in PD have focused on improving physical function, including gait, mobility, and balance, and on targeting disease-specific physical impairments, such as bradykinesia, rigidity, and strength (Corcos et al., 2013; Goodwin et al., 2008; Tomlinson et al., 2012). In general, exercise, including aerobic and resistance training, improves physical function and motor symptoms in PD (Allen et al., 2010; Allen, Sherrington, Paul, & Canning, 2011; Canning et al., 2015; Earhart & Falvo, 2013; Gobbi et al., 2009; Goodwin et al., 2011; Grazina & Massano, 2013; Lamotte G., 2015;

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Li et al., 2012; Mehrholz et al., 2010; van der Kolk & King, 2013). Given these benefits to core symptoms, exercise has a potential to be one of those rare adjunct interventions to treat principal non-motor symptoms of PD without worsening the primary motor disorder.

In this manuscript, we review the efficacy of aerobic and strengthening exercise interventions in PD relative to more conventional treatments of mood, cognition, and sleep. The following electronic databases were searched: PubMed (1990 to July 6th 2015), Google Scholar (1990 to July 6th 2015), and Cochrane Library (1990 to July 6th 2015); citation tracking was also used to identify relevant references. Specifically, we included studies if they met the following criteria: 1) at least one target population was adults with PD; 2) aerobic exercise and/or resistance exercise was used in at least one of the exercise conditions; 3) at least one outcome measure was included to examine mood (depression or anxiety), cognition, or sleep; 4) the paper was available in English as of July 6, 2015. To inform these findings, we also discuss the relevant literature on aerobic and resistance exercise in healthy older adults, as well as neurologic populations. Although many forms of exercise may be beneficial, we limited our review to studies that included aerobic exercise and/or strengthening exercises, as the evidence in these areas is more developed in healthy older adults and in persons with PD from both a clinical and mechanistic perspective. Also of note, additional non-motor symptoms manifest in PD, including fatigue and autonomic, gastrointestinal, and sensory symptoms (Chaudhuri et al., 2006), but the literature investigating the effects of exercise on these symptoms

remains very limited; accordingly, the present article focuses on the potential benefits of exercise interventions on mood, cognition and sleep only.

Treatment of Mood Symptoms in PD

Mood disturbance (here referring to depression and anxiety) develops in many individuals with PD, even in the early stages of the disease (Ishihara & Brayne, 2006), contributing to poorer quality of life (Duncan et al., 2014; Gallagher & Schrag, 2012; Hanna & Cronin-Golomb, 2012) and caregiver burden (Schrag et al., 2006). Major depression is estimated to occur in 20-40% of individuals with PD (Lieberman, 2006; Veazey, Aki, Cook, Lai, & Kunik, 2005), and clinically significant anxiety in approximately 40% (Aarsland et al., 2009; Pontone et al., 2009; Walsh & Bennett, 2001); prevalence of psychiatric symptoms in PD reviewed in (Gallagher & Schrag, 2012)). Depression in PD is associated with poorer emotional well-being, communication, and activities of daily living (Holroyd, Currie, & Wooten, 2005; Oguru, Tachibana, Toda, Okuda, & Oka, 2010), as well as increased disability, falls, and caregiver distress, with some research indicating that depression may predict 10-year mortality (Bryant et al., 2012; T. A. Hughes, Ross, Mindham, & Spokes, 2004; Weintraub, Moberg, Duda, Katz, & Stern, 2004). Despite these high prevalence rates and associated distress and disability, clinical management of many non-motor symptoms, including depression and anxiety, remains inadequate (Seppi et al., 2011).

Anxiety is common but less studied and treated in PD than depression (Chen & Marsh, 2014; N. N. Dissanayaka et al., 2014; Seppi et al., 2011; Weintraub & Burn,

2011). In addition to generalized anxiety disorder, panic disorder, and simple and social phobias, individuals with PD also report recurrent situational anxiety related to their motor symptoms, including fear of falling or fear of crowded places due to freezing of gait (Aarsland et al., 2009; Pontone et al., 2009). Anxiety is associated with reduced quality of life in PD (Carod-Artal et al., 2008; N. N. Dissanayaka et al., 2010; Havlikova et al., 2011), even after controlling for the effects of motor symptoms (Bonnet & Czernecki, 2013; McKinlay et al., 2008), and to a greater extent than depression (Hanna & Cronin-Golomb, 2012).

The high prevalence, early manifestation, and negative impact of anxiety and depression in PD dictate the need to manage and improve these symptoms, which are under-treated and understudied (Frisina, Borod, Foldi, & Tenenbaum, 2008; Palanci et al., 2011; Pontone et al., 2013; Troeung et al., 2013; Weintraub, Moberg, Duda, Katz, & Stern, 2003). To date, antidepressants have generally yielded non-significant and variable effects for both depression (Rocha, Murad, Stumpf, Hara, & Fuzikawa, 2013; Troeung et al., 2013) and anxiety (Troeung et al., 2013) in PD. Some controlled studies suggest that certain selective serotonin reuptake inhibitors, dual reuptake inhibitors, and dopamine agonists may improve depression in PD, albeit with some risk of treatment-related side effects (e.g. fatigue, dry mouth, orthostatic hypotension, dyskinesia) (Barone et al., 2010; M. Menza et al., 2009; Richard et al., 2012). Benzodiazepines are not recommended for the treatment of anxiety in PD due to potential side effects, including autonomic, cognitive, sleep, and psychomotor impairments (B. S. Connolly & Fox, 2012; Gallagher & Schrag, 2012; Weintraub & Hoops, 2011). There is emerging evidence for

psychosocial alternatives to pharmacologic treatment of mood, with limited but promising data from cognitive behavioral therapy (CBT) (Armento et al., 2012; Charidimou, Seamons, Selai, & Schrag, 2011; Dobkin, Menza, & Bienfait, 2008; Farabaugh et al., 2010; Heinrichs et al., 2001; Troeung et al., 2013, 2014; Veazey et al., 2009; S. Yang et al., 2012).

The Potential of Exercise Interventions for Mood

Exercise interventions have demonstrated robust efficacy in the treatment of mood symptoms in the general population and in older adults, but few exercise trials in PD have included mood as an outcome measure. A meta-analysis of 11 randomized controlled trials (RCTs) with adults with major depression reported a large combined effect size for exercise, usually aerobic or resistance training, relative to non-active control conditions (Stathopoulou et al., 2006). More recent meta-analyses confirm a significant acute effect of exercise on depression relative to non-exercising control groups (Krogh, Nordentoft, Sterne, & Lawlor, 2011), with benefits generally following programs of at least moderate aerobic activity delivered several times a week, often in a group setting, with session durations of 20 to 45 minutes (Stathopoulou et al., 2006). Although promising, these meta-analyses are not without limitations, such as restricted power due to the small number of included trials, as well as the selection bias of individuals who volunteer to participate in exercise research (Krogh et al., 2011; Stathopoulou et al., 2006). Despite this, the benefits of exercise are conferred across a wide range of settings and symptom severities. For example, Mota-Pereira and

colleagues (Mota-Pereira et al., 2011) found that aerobic exercise (30-45 minute sessions, 5 days/week) offered significant improvement or remission of depression in outpatients who had failed two previous trials of antidepressant medication (see also (Salehi et al., 2014)). Aerobic exercise also has efficacy in combination with antidepressants or CBT (Merom et al., 2008; Mura, Moro, Patten, & Carta, 2014). Even in healthy adults without clinical depression, exercise interventions, including resistance exercise, have improved depressive symptoms (Conn, 2010b). In sum, exercise has been shown to reduce depression in the general population, suggesting that it may also benefit those with PD and depression, either as a stand-alone or adjunctive intervention to improve mood.

Besides its antidepressant effects, exercise is also anxiolytic (Asmundson et al., 2013; Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991). Strong effects on self-reported anxiety were documented in a meta-analysis of primarily non-clinical samples (B. M. Wipfli et al., 2008) with further evidence from clinical trials for panic disorder, generalized anxiety disorder, and social anxiety (Asmundson et al., 2013). These clinical trials have focused largely on aerobic exercise (usually completed 2-5 times per week, for 5-12 weeks), often in small samples, with unstandardized or unsupervised exercise sessions and/or lacking a non-exercising control group; nevertheless, the results are encouraging and suggest that aerobic exercise, in particular, may effectively treat anxiety disorders, either as a stand-alone intervention or as an adjunct treatment in combination with pharmacotherapy or CBT (Asmundson et al., 2013; Gaudlitz, Plag, Dimeo, & Strohle, 2015). More controlled studies are needed to determine the optimal exercise dose and modality required to achieve lasting anxiolytic effects.

Exercise has also been shown to improve mood in healthy older adults (e.g., (Bridle, Spanjers, Patel, Atherton, & Lamb, 2012)). For example, physical exercise, usually aerobic or resistance training completed 3 times per week for 20-60 minutes for 6-19 weeks, yielded positive short-term outcomes for depressive symptoms (Blake, Mo, Malik, & Thomas, 2009; Brenes et al., 2007); and compared to a non-exercising control group, aerobic (but not resistance) exercise was associated with reduced depressive symptoms, regardless of baseline level of depression (Penninx et al., 2002). Comparing an aerobic exercise program to pharmacological treatment, exercise (three 45-minute sessions/week) was equally effective at reducing depressive symptoms after 16 weeks of treatment, although the study did not control for the social interaction aspect of the exercise group (Blumenthal et al., 1999).

There is promising evidence that exercise may improve depression among adults with neurologic disorders (Adamson, Ensari, & Motl, 2015), but there remains limited research on the effects of aerobic and resistance exercise on mood in PD specifically (Table 14). In a large RCT with 231 adults with PD, six months of strengthening exercises (40-60 minutes, 3 times/week) yielded improved positive affect relative to a usual-care control group (Canning et al., 2015). In a second controlled trial, individuals with PD were randomized to either an early- or late-start group exercise program (combined cardiovascular and strength training, completed for 60 minutes, 3 days/week, for 24-48 weeks) (Park et al., 2014). Participants in the early-start group reported significantly fewer depressive symptoms after 48 weeks, relative to the delayed start group, although there was no control for the potential effects of weekly social interaction

on mood. In a comparative trial of three types of exercise (high-intensity treadmill training, lower-intensity treadmill training, and stretching/resistance training), no changes in depression were observed for any group after 3 months of exercise (30-50 minutes, 3 times per week), although participants reported only mild levels of depressive symptoms at baseline (Shulman et al., 2013). In a smaller study, aerobic exercise, completed twice per week for 12 weeks, improved mood, while maintaining functional ability, among 13 adults with early PD relative to non-exercising PD participants (Bridgewater & Sharpe, 1996). In a sample of 11 early- to mid-stage participants with PD, 5 participants (mean age=64.0) completed a 4-week general exercise program (60-minute sessions of combined aerobic and resistance training, 4 times/week), and 6 participants (mean age=62.8) completed an exercise-based behavioral treatment focused on increasing amplitude of movement (Dashtipour et al., 2015). Although there were no between group differences, the combined group showed improvement in depression and fatigue at all post-intervention assessments (weeks 4, 12, 24), suggesting benefits of both exercise approaches. In an uncontrolled trial, 49 individuals with PD (mean age=65.5) reported reduced depressive symptoms after six months of aerobic walking (3 times/week for 45 minutes per session), although depressive symptoms were very low among this sample (Uc et al., 2014). In general, the PD exercise studies that have included mood outcomes have included participants with minimal depressive symptoms, limiting their generalizability. Even so, these studies provide strong rationale for the targeted use of exercise to improve mood in PD.

Cognitive Impairment in PD

Like mood symptoms, cognitive impairments are common and heterogeneous in PD (Dalrymple-Alford et al., 2011; Kehagia, Barker, et al., 2010; Litvan et al., 2011; Litvan et al., 2012; Mamikonyan et al., 2009), even in the early stages of the disease, with widespread implications for quality of life and functional abilities such as driving (Amick, Grace, & Ott, 2007; H. Devos et al., 2013; Duncan et al., 2014; Kurtis, Rodriguez-Blazquez, & Martinez-Martin, 2013; Schiehser et al., 2009; Svenningsson, Westman, Ballard, & Aarsland, 2012; Uc et al., 2009). Cognitive disruptions can also co-occur with other non-motor symptoms, tending to be worse in PD with depression, for example (Fernandez et al., 2009; Santangelo et al., 2009). Up to 57% of individuals with PD experience some cognitive impairment within the first 3-5 years after diagnosis (Williams-Gray et al., 2007), including deficits in executive functioning, visuospatial function, and attention/working memory (Dirnberger & Jahanshahi, 2013; Muslimovic et al., 2005; Pfeiffer et al., 2014). Measures of attention and executive function ("frontal" tests) are often the most sensitive to cognitive compromise (Miller et al., 2013). Executive dysfunction often emerges early in the disease course and is thought to be associated with dopaminergic dysfunction in fronto-striatal regions, whereas memory impairment and visuoconstructional difficulties, along with cognitive decline and dementia, may be driven by cortical Lewy body pathology and cholinergic deficiency (Kehagia, Barker, & Robbins, 2013). With cognitive impairment beginning in the early stages of PD (Svenningsson et al., 2012), there is a corresponding need for early cognitive-enhancement strategies.

The Potential of Exercise Interventions for Cognitive Enhancement

There is reliable evidence for significant benefits conferred upon cognition by exercise programs (Etnier, Nowell, Landers, & Sibley, 2006; Smith et al., 2010). A meta-analysis of RCTs (29 studies, 2049 participants) has indicated that healthy older adults reliably achieve modest improvements in attention and processing speed, executive function, and memory following aerobic training (Smith et al., 2010). The exercise trials ranged in duration from 6 weeks to 18 months, with modal length of 2.5 to 4 months, but with relatively minimal range of exercise intensity or frequency across trials (most often 3 times per week at 70% peak oxygen uptake (VO_2)). Exercise typically comprised brisk walking and/or jogging relative to wait-list control or other comparison conditions (stretching and toning, health education, or relaxation). Greater benefits to attention and processing speed arose from trials that combined aerobic exercise with strength training, relative to aerobic only interventions. Likewise, aerobic training has been reported to improve cognition in healthy older adults, especially for executive-control processes (S. Colcombe & Kramer, 2003) – a finding particularly pertinent to the goal of improving executive dysfunction in PD (Dirnberger & Jahanshahi, 2013; Miller et al., 2013). There remains need for additional research to examine how aerobic exercise may affect various cognitive domains when maintained for extended periods of time (e.g. several years instead of months) (Smith et al., 2010).

Exercise may also improve general cognitive functioning and balance in older-adult neurological populations, including those with mild cognitive impairment, as well

as Alzheimer's disease (AD) and other dementia-causing disorders (Forbes, Thiessen, Blake, Forbes, & Forbes, 2013; Hernandez, Coelho, Gobbi, & Stella, 2010). This research is relevant to PD, given that cognitive impairment, including dementia, often emerges over the course of the disease (Apaydin, Ahlskog, Parisi, Boeve, & Dickson, 2002; Compta et al., 2011; Meireles & Massano, 2012) and that an AD-like pattern of brain atrophy in PD may predict cognitive decline (Weintraub et al., 2012). There is preliminary evidence that aerobic exercise may be associated with greater memory improvements among adults with mild cognitive impairment relative to cognitively intact adults (Smith et al., 2010). In a large sample of adults (≥ 50 years) with subjective memory impairment, a six-month exercise program (at least three 50-minute sessions of moderate-intensity aerobic exercise per week) yielded modest improvements on brief cognitive tests of memory, language, and praxis (Alzheimer Disease Assessment Scale – ADAS-Cog) over an 18-month follow-up period; participants in the exercise group also improved on word list delayed recall (Lautenschlager et al., 2008). It is important to note that the primary outcome measure in this study was a non-specific measure of overall cognitive function, rather than an index of a specific cognitive domain. Relative to a non-active control group, elderly individuals with AD (mean age=78.3) demonstrated improved balance and executive functioning (Clock Drawing Test and Frontal Assessment Battery) following dual-task exercise that paired motor and cognitive tasks (60-minute sessions completed 3 times/week for 4 months) (Pedroso et al., 2012). Aerobic training has also been reported to improve visual learning, working memory, and processing speed in psychiatric populations, including depression (Oertel-Knochel et al.,

2014). In sum, exercise has demonstrated cognitive benefits in healthy older adults and in adults with conditions that may be observed in PD (e.g., depression and dementia), supporting the potential cognition-enhancing role of exercise for PD.

There is initial evidence that these expectations will be realized in PD (Hindle, Petrelli, Clare, & Kalbe, 2013; Murray et al., 2014); see Table 15. Aerobic exercise may particularly impact executive function in PD (Petzinger et al., 2013), consistent with the findings in healthy older adults (S. Colcombe & Kramer, 2003). Twelve weeks of combined aerobic plus anabolic exercise, conducted twice weekly, resulted in selective improvement in frontal-based executive function (spatial working memory and verbal fluency, relative to spatial and pattern recognition memory) in 15 individuals with PD compared to 13 non-exercising PD control participants (all in mild to moderate disease stages and approximately 60 years old) (Cruise et al., 2011). Likewise, in relatively large studies of a long duration, 6 months of moderate-intensity aerobic exercise, conducted three times per week for 45-60 minutes, led to improved executive functioning for individuals with mild to moderate PD (mean age of approximately 65 in both studies), though only one of these studies used a non-exercising PD control group (Tanaka et al., 2009). Across these studies, moderate-intensity aerobic exercise, conducted 2-3 times per week, produced promising effects on executive function in the mild to moderate stages of PD, consistent with studies in healthy older adults (S. Colcombe & Kramer, 2003). In small preliminary case studies, 8 weeks of aerobic exercise, completed 3 times per week for 20-40 minutes, yielded improvements in executive function, verbal fluency, and working memory for three individuals with PD – one with high cognitive

performance at baseline (age 66), and two with cognitive impairments (ages 61 and 72) (Nocera, Altmann, Sapienza, Okun, & Hass, 2010; Tabak, Aquije, & Fisher, 2013). Further research is warranted to examine the underlying mechanisms driving these selective improvements, which may relate to increased cerebral perfusion, release of growth factors, or angiogenesis following aerobic exercise, as suggested by Tabak and colleagues (Tabak et al., 2013). Among healthy older adults, aerobic training, relative to non-aerobic, may even mitigate volume loss in prefrontal regions (S. J. Colcombe et al., 2006), which are associated with a variety of executive control processes. Of note, both prefrontal atrophy and executive dysfunction occur in PD, even in the early stages of the disease (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Dirnberger & Jahanshahi, 2013).

At the same time, recent evidence suggests that resistance exercise may also benefit cognition in PD. After 24 months of twice weekly progressive resistance exercise (60-90 minutes per session), adults with PD improved their performance on measures of working memory, inhibition, and attention (Digit Span, Stroop, Brief Test of Attention) (David et al., 2015). The comparison group completed stretching, balance, and non-progressive strengthening exercises (of the same duration and frequency) and improved on Digit Span and Stroop after 24 months (David et al., 2015). There were no between-group differences on any of the cognitive measures at 12 or 24 months, and the authors noted that their sample was relatively young, highly educated, and in mild-to moderate disease stages, thereby limiting the generalizability of their findings (David et al., 2015). Even so, these results provide clear rationale for future research to examine the targeted

use of resistance exercise to improve cognition in PD. Taken together, emerging research suggests that aerobic and resistance exercise may improve cognition in PD; however, there remains a need for larger, well-controlled studies on the cognitive effects of exercise interventions among adults with PD.

Sleep Disruption in PD

In the general population, the prevalence of insomnia symptoms ranges from 25% to 48% and insomnia diagnoses from 4.4% to 9.5% (Mallon, Broman, & Hetta, 2000; Morin, LeBlanc, Daley, Gregoire, & Merette, 2006; Ohayon, 2002; Ohayon, Carskadon, Guilleminault, & Vitiello, 2004). Sleep disruptions are common among older adults (Crowley, 2011) and are particularly problematic and multifactorial in PD (Barber & Dashtipour, 2012; Diederich & McIntyre, 2012; Havlikova et al., 2011), with reference to this problem dating back to James Parkinson's observations in his original essay (Parkinson, 2002). Fragmented sleep has been reported (Claassen & Kutscher, 2011; Comella, 2007; Factor, McAlarney, Sanchez-Ramos, & Weiner, 1990; Pappert, Goetz, Niederman, Raman, & Leurgans, 1999; Karina Stavitsky & Cronin-Golomb, 2011; K. Stavitsky, Saurman, McNamara, & Cronin-Golomb, 2010), attributed in part to nighttime motor symptoms (Grinberg, Rueb, Alho, & Heinsen, 2010; Poewe, 2008), with reports of sleep benefits upon control of these symptoms (Trenkwalder, Kies, et al., 2011; Wood, 2010). Individuals with PD may present with REM sleep behavior disorder, excessive daytime sleepiness, sleep onset and sleep maintenance insomnia, as well as sleep disordered breathing, restless leg syndrome, and nocturia (Diederich & McIntyre, 2012;

M. Menza, Dobkin, Marin, & Bienfait, 2010). Furthermore, sleep disturbances in PD are linked to mood and cognitive dysfunction (Borek, Kohn, & Friedman, 2006; Neikrug et al., 2013; K. Stavitsky, Neargarder, Bogdanova, McNamara, & Cronin-Golomb, 2012), likely related to neurodegenerative changes. The underlying disease pathology in PD is now thought to begin in the brainstem (Braak et al., 2004), where damage to specific nuclei (e.g., locus ceruleus, pedunculopontine nucleus) and neurotransmitters (e.g., norepinephrine, serotonin, dopamine, GABA, acetylcholine) likely affects sleep-wake and REM sleep modulation in PD years prior to the manifestation of motor symptoms (Bohnen & Albin, 2011; Diederich & McIntyre, 2012; Grinberg et al., 2010; M. Menza et al., 2010). Given the magnitude of the impact of sleep disruption on quality of life in PD (Duncan et al., 2014; Stocchi, Barbato, Nordera, Berardelli, & Ruggieri, 1998), there is need to address general, age-related, and disease-specific sleep disruptions in those with PD.

The Potential of Exercise Interventions for Sleep Disruption

Meta-analytic review of 25 studies indicates that regular exercise programs help adults achieve moderate-to-large sleep quality benefits, as per the self-reported Pittsburgh Sleep Quality Index (PSQI; (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989)), which includes subscales of daytime sleepiness as well as sleep disturbance, duration, efficiency, latency, and medication use (Kredlow et al., 2015). The moderate-to-large effects of regular exercise were observed for all PSQI subscales except sleep medication use. Across aerobic, anaerobic, and mixed studies, regular exercise had small effects on

total sleep time and sleep efficiency and a small-to-moderate effect on sleep onset latency, predominantly assessed using objective measures (e.g. electroencephalogram or polysomnography) (Kredlow et al., 2015). These benefits appear to be uniform across younger and older samples except for weaker effects on sleep-onset latency in older adults, consistent with its general worsening with age (Ohayon et al., 2004). Even individual sessions of exercise, evaluated across 41 studies (predominantly aerobic training), conferred benefit on objective measures of sleep, though with small effect sizes that varied in reliability (Kredlow et al., 2015). Moderate-intensity aerobic exercise (30- to 40-minute sessions, completed four times per week, for 16 weeks) yielded improvements in self-reported sleep quality (global PSQI score) among healthy older adults (ages 50-76) with sleep complaints, relative to wait-list control participants (King, Oman, Brassington, Bliwise, & Haskell, 1997).

There is some indication that the benefits of exercise for sleep extend to individuals with PD, including improved sleep, quality of life, and daily functioning (Nascimento et al., 2014; Rodrigues de Paula et al., 2006); see Table 16. In an RCT (with stratified randomization), 17 PD participants in mild to moderate stages (mean age=67.8) who completed six months of multimodal exercise (three 60-minute sessions per week of muscular resistance, balance/motor coordination, and aerobic fitness) reported enhanced sleep and functional abilities on standardized questionnaires compared to 17 PD control participants who did not exercise (Nascimento et al., 2014). The sleep questionnaire (Mini-Sleep Questionnaire) included items related to both insomnia and daytime sleepiness. Only the total score was used for data analysis, so it is not possible to

determine if exercise more strongly affected insomnia or daytime sleepiness. Likewise, after 36 group sessions of combined aerobic conditioning and muscular strengthening (75 minutes each, 3 times per week, for 3 months), twenty mild- to moderate-stage PD participants (mean age=61.5) reported significant improvements in quality of life, particularly within the domains of emotional reactions, social interactions, and physical ability, as well as reporting a trend toward improved sleep on a self-report questionnaire (Rodrigues de Paula et al., 2006). A significant limitation of both PD studies was the lack of objective sleep measures. Further research is needed to elucidate potential effects of exercise on daytime and nighttime sleep disturbances, including larger, well-controlled trials that include subjective and objective sleep outcome measures.

Potential Mechanisms of Action of Exercise on Mood, Cognition, and Sleep

Dopaminergic dysfunction in the hypothalamus and limbic regions may be associated with disturbances of mood, cognition, and sleep in PD (Chaudhuri, 2009; Chaudhuri & Odin, 2010; Chaudhuri & Schapira, 2009; Prediger et al., 2012). It is plausible then that exercise may improve these non-motor symptoms at least partially via dopaminergic mechanisms. More specifically, exercise may modulate dopaminergic and glutamatergic neurotransmission, and thereby attenuate basal ganglia hyperexcitability in PD (Fisher et al., 2008; Petzinger et al., 2010). Among exercising rats (n=10) relative to sedentary counterparts (n=9), aerobic exercise (6 weeks of wheel running) has been associated with increased dopamine synthesis and reduced inhibition of dopamine neurons in the substantia nigra pars compacta (Foley & Fleshner, 2008). Preliminary

evidence in humans suggests that aerobic exercise (three 60-minute treadmill sessions/week for 8 weeks) may lead to increased dopaminergic signaling (per imaging with positron emission tomography) and improved postural control in the early stages of PD (Fisher et al., 2013). Although non-motor outcomes were not included in this pilot study, the reported improvements in postural control are potentially relevant for non-motor symptoms given that common neural substrates may modulate balance control and anxiety (e.g., parabrachial nucleus network and associated connections to limbic regions) (Balaban, 2002; Balaban & Thayer, 2001; Prediger et al., 2012).

Besides its dopaminergic effects, regular exercise also has a wide variety of effects on non-dopaminergic neurotransmitter systems, including serotonergic, noradrenergic, and GABA-ergic systems, which is relevant for depression, anxiety, and sleep (DeBoer, Powers, Utschig, Otto, & Smits, 2012; Melancon, Lorrain, & Dionne, 2014). In rats that swam (n=18) 5 days a week for 10 weeks (typically 30 minutes per day), exercise was associated with increased hippocampal levels of serotonin and norepinephrine (He et al., 2012) – two neurotransmitters that have been implicated in modulation of anxiety, depression, and sleep (Millan, 2003; Monti, 2011; Palazidou, 2012; Prediger et al., 2012). In regard to the potential for improved cognition (Erickson et al., 2011), animal work indicates that serotonin is necessary in order to achieve exercise-induced neurogenesis in the hippocampus (n=30 per group) (Klempin et al., 2013). In human research, aerobic exercise (three 30-minute cycling sessions per week, for 7 weeks) has been associated with reduced depression and reduced blood serotonin, relative to a stretching-control group (B. Wipfli, Landers, Nagoshi, & Ringenbach, 2011).

This effect is similar to effects of selective serotonin reuptake inhibitors, although the sample consisted of healthy undergraduate students who were not pre-screened for anxiety or depression, which limits its generalizability. These findings suggest that aerobic exercise may increase levels of serotonin and norepinephrine in the brain, which may positively affect mood, cognition, and sleep. For example, cognitive dysfunction and sleep disturbances (e.g., insomnia, vivid dreaming, and sleep-disordered breathing) in PD are generally unresponsive to dopamine therapy (Lee & Koh, 2015), suggesting that these symptoms may develop, at least in part, through non-dopaminergic mechanisms. Likewise, anxiety in PD is associated with dysfunction in a variety of neurotransmitter systems, including noradrenergic and serotonergic, which may precede dopaminergic depletion (Prediger et al., 2012). Aerobic exercise, then, could act upon these non-dopaminergic systems to improve non-motor symptoms, particularly in the early stages of PD.

The mechanisms by which exercise may affect non-motor symptoms, especially cognition, in PD may be similar to structural and functional brain changes and proliferation of growth factors seen in exercising healthy adults. Higher aerobic fitness in healthy older adults (mean age=66.6) has been associated with greater gray matter volume in dorsolateral prefrontal cortex and improved executive function (Stroop test of inhibition) and spatial working memory (Weinstein et al., 2012). The association with prefrontal volume is relevant to PD as affected individuals may show prefrontal and hippocampal atrophy even in early stages of the disease (Bruck et al., 2004). Imaging with positron emission tomography has also revealed that prefrontal dysfunction in PD

(hypometabolism) contributes to difficulties with set-shifting (Sawada et al., 2012). Following a one-year walking intervention (three 40-minute sessions per week), aerobic fitness in older adults was associated with white matter changes in frontal and temporal regions, as well as improved short-term memory relative to an active control group (flexibility, toning, and balance) (Voss, Heo, et al., 2013). Also following one year of aerobic exercise, increased functional connectivity in the temporal lobe among healthy older adults (mean age=66.4) was associated with increased levels of growth factors, including brain-derived neurotrophic factor (BDNF), as well as insulin-like growth factor type 1, and vascular endothelial growth factor (Voss, Erickson, et al., 2013). Consistent with these findings, regular aerobic exercise in healthy older adults is thought to promote neuroplasticity and facilitate learning and memory through the release of neurotrophins, including BDNF, glia-derived neurotrophin (GDNF), nerve growth factor (NGF), and galanin (S. Colcombe & Kramer, 2003; Hirsch & Farley, 2009). In PD, aerobic exercise may increase the production of growth factors and promote gray and white matter changes, especially in prefrontal regions, both of which may contribute to improved cognitive function.

Animal and cellular studies further highlight the important effects of BDNF on neurogenesis, dendritic growth, and long-term potentiation (Altar, 1999; Gorski, Zeiler, Tamowski, & Jones, 2003; Huang et al., 1999; Lu, Pang, & Woo, 2005). Meta-analytic review of 29 human studies (1111 participants) indicates that single sessions of exercise induce BDNF activity and that there is a significant increase in this activity with regular exercise (Szuhany et al., 2015). These effects appear reliable enough that Szuhany and

colleagues (Szuhany et al., 2015) suggested that exercise can be considered as an intervention to induce BDNF for subsequent therapeutic benefit, although they note that future research is needed to examine the effects of exercise type (e.g., aerobic versus resistance training) on BDNF. Rodent and human studies indicate that BDNF may mediate both the mood and cognitive effects of exercise (Erickson, Miller, & Roecklein, 2012; Heyman et al., 2012; van Praag, Shubert, Zhao, & Gage, 2005; Vaynman, Ying, & Gomez-Pinilla, 2004), with a particular effect on executive function in older adults (Leckie et al., 2014), which is known to be compromised in PD (Dirnberger & Jahanshahi, 2013).

These mechanisms may relate to potential cognitive benefits of exercise in PD, given the known executive dysfunction and reduced BDNF expression in this population. Postmortem human studies and rodent studies indicate significantly reduced expression of BDNF in the substantia nigra in PD (Howells et al., 2000; Mogi et al., 1999; Parain et al., 1999; Porritt, Batchelor, & Howells, 2005), and surviving dopaminergic neurons in the substantia nigra express reduced BDNF compared to control cases (Howells et al., 2000). In a 6-hydroxydopamine (6-OHDA) rat model of PD, exercise (4 weeks of treadmill running, 30 minutes/day, 5 days/week) has been found to increase levels of BDNF in the striatum (Tajiri et al., 2010). In a recent human study of early-stage PD, 28 days of intensive aerobic exercise increased BDNF levels, improved motor symptoms (balance and gait) (Frazzitta et al., 2014), and potentially slowed motor symptom progression after a two-year follow-up (Frazzitta et al., 2015). Indeed, drawing largely from animal studies, Fumagalli and colleagues (Fumagalli, Racagni, & Riva, 2006)

posited that BDNF may function as a neuroprotective molecule and also a neuromodulator in PD, such that it is associated with the loss of dopaminergic neurons when inhibited, and with improved cognition when expressed. Exercise may improve hippocampal function via BDNF expression (Intlekofer & Cotman, 2013), and in non-PD rats (n=7 per group), BDNF expression has been associated with exercise-induced enhancement on learning and recall on the Morris water maze after one week of voluntary wheel running (Vaynman et al., 2004). Though there are limitations related to translating results in animal models of PD to humans with PD (Potashkin, Blume, & Runkle, 2010), animal work as well as emerging human research suggest that aerobic exercise may lead to improvements in cognition that may be mediated, at least in part, by increased production of BDNF (Ahlskog, 2011b). In sum, the potential effects of exercise-induced BDNF on cognition in PD are particularly promising.

These findings suggest that exercise has potential neuroprotective and neurorestorative effects in PD, which may be associated with subsequent improvements in overall brain health, mood, and especially cognition (Petzinger et al., 2013), though the majority of this evidence in PD comes from animal studies and small pilot studies. Other mechanisms may be active for the effects of exercise on sleep, and potentially include body temperature elevation (to promote slow wave sleep), increased cytokine levels, heart rate variability (and associated improvements in vagal modulation and parasympathetic control), as well as increased BDNF activity and associated changes in mood (Buman & King, 2010; Kredlow et al., 2015; Uchida et al., 2012). As sleep disruption is a core symptom of depression, and aerobic exercise improves depression, it

is plausible that exercise may benefit sleep as a function of improved mood, or *vice versa* (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Uchida et al., 2012). It may also be important to consider the potential effects of aerobic exercise on cholinergic function, as demonstrated in non-PD animal studies (Ang & Gomez-Pinilla, 2007). It is unknown whether these positive effects translate to persons with PD, but it warrants examination, given the association between cholinergic dysfunction and disturbances of sleep, mood, and cognition in PD (Bohnen & Albin, 2011; Diederich & McIntyre, 2012). Ultimately, sleep benefits from exercise may result from some of the same or alternative mechanisms as those that positively affect mood and cognition.

It is also important to consider potential mechanisms specific to resistance exercise in PD. Progressive resistance training in PD has yielded improvements in strength and motor symptoms, as well as cognition (David et al., 2015; Lamotte G., 2015). Future research should more closely examine the effects of resistance training on non-motor symptoms in PD, especially cognition, which may relate to reduced levels of homocysteine and/or increased levels of insulin-like growth factor I (David et al., 2012). At the same time, resistance training may facilitate motor improvements via increased neural drive and central neural changes, such as cross-education and reduced agonist-antagonist coactivation (Falvo, Schilling, & Earhart, 2008). These mechanisms may be relevant for PD given the reduced muscle activation observed in the disorder, which largely contributes to bradykinesia and muscle weakness (David et al., 2012). Drawing from functional neuroimaging studies, resistance training may also promote functional neuroplasticity in the cortex and basal ganglia, although all of these potential mechanisms

require further study in PD (David et al., 2012). For a review of potential mechanisms of resistance exercise in PD, please see (David et al., 2012).

Exercise Dose and Adherence in PD

Public health guidelines recommend a minimum of 150 minutes of moderate-intensity aerobic exercise plus 2-3 sessions of strengthening exercises per week for adults aged 18-65 (Haskell et al., 2007), but it is unknown whether this recommendation is also appropriate for individuals with PD. Optimal dosing of exercise in PD has not been determined. Current research efforts are beginning to examine this question, including an ongoing multi-site, randomized, controlled study designed to compare moderate-intensity to high-intensity aerobic training in PD (C. G. Moore et al., 2013). Intensive rehabilitation strategies (three daily exercise sessions, 60 minutes each, 5 days per week, for 4 weeks) that include aerobic exercise (heart rate reserve ≤60%; maximum speed of treadmill scrolling=3.5 km/hour) revealed increased BDNF levels and improved motor symptoms in the early stages of PD, suggesting the benefits of higher intensity exercise (Frazzitta et al., 2014) as well as potential benefits in cognition via BDNF. Other exercise trials in PD, however, reveal equivalent benefits related to physical function for both low (50 minutes at 40%-50% of heart rate reserve) and high (30 minutes at 70%-80% of heart rate reserve) intensity of aerobic exercise conducted 3 times a week for 3 months (Shulman et al., 2013). In studies examining the benefits of strength training, high-intensity resistance programs have been shown to be safe and efficacious and associated with greater improvements in quality of life relative to active control groups (Corcos et

al., 2013; Dibble et al., 2006; Dibble, Hale, Marcus, Gerber, & LaStayo, 2009). A progressive resistance training program (at least 5% increase in resistance as participants were able) was found to be more effective in improving motor symptoms than a strengthening program that was not progressive (no systematic increase in load), suggesting greater benefits of a high dosing (Corcos et al., 2013), although both programs produced improvements in cognition after 24 months (David et al., 2015). The only other non-motor outcome included in these studies was quality of life, which may capture secondary effects on mood, but otherwise, the effects of exercise intensity on mood and sleep in PD remain largely unknown and warrant further study (Lamotte et al., 2015).

Generally speaking, adherence to exercise programs among adults with PD is relatively high (often >80%) in the context of research where there is typically a great deal of emphasis on promoting adherence (Allen et al., 2012). Likewise, across exercise trials in PD, retention rates are largely above 80%, with studies typically conducted in clinic and lasting 8 weeks on average, though some studies have reported similar retention rates for trials of a longer duration (up to two years) (Allen et al., 2012; Corcos et al., 2013; Shulman et al., 2013). Persons with PD tolerate exercise programs quite well with relatively low dropout rates (~10-20%) and minimal adverse effects (Allen et al., 2012; Canning et al., 2015; Corcos et al., 2013; Park et al., 2014; Schenkman et al., 2012; Shulman et al., 2013; Uc et al., 2014). The majority of adverse events tend to consist of relatively mild musculoskeletal issues that resolve relatively quickly and do not require medical attention or restrict activities (Canning et al., 2015; Schenkman et al., 2012; Uc et al., 2014). This minimal-risk profile compares favorably to medications for non-motor

symptoms in PD (Liu et al., 2013), and provides further support for the use of exercise to simultaneously improve multiple motor and non-motor symptoms. At the same time, it should be noted that the largely supervised, in-clinic nature of current exercise studies in PD may limit generalizability of these findings to motivated research participants who have access to a highly structured research setting. Further research is warranted to better examine the longevity of effects and to effectively tailor the content, dose, and delivery of exercise programs to individuals at various stages of PD.

Treatment Stage and Exercise Intervention

Exercise has been shown to be beneficial to individuals with PD across Hoehn & Yahr stages I-IV, with most trials focusing on stages II and III (Ellis et al., 2008; Goodwin et al., 2008; Li et al., 2012; Monticone, Ambrosini, Laurini, Rocca, & Foti, 2015; van Eijkeren et al., 2008). At the same time, the potential neuroprotective and neurorestorative effects of exercise (Petzinger et al., 2013) underscore its importance early in the course of the disease (Ellis & Motl, 2013). Non-motor symptoms of PD, including disturbances in sleep and mood, can emerge years before the motor symptoms (Claassen et al., 2010; Claassen & Kutscher, 2011; Jacob, Gatto, Thompson, Bordelon, & Ritz, 2010). In particular, individuals in the early stages may present with depression or anxiety that may be more distressing or interfering than the motor symptoms (Bhidayasiri & Truong, 2012). Accordingly, exercise programs are particularly well suited to early implementation in PD with the potential for diffuse non-motor benefits (e.g. mood, sleep, cognition) and few side effects or adverse events. By implementing exercise

interventions to improve depression, for example, in the early stages of PD, we can hope to also affect associated comorbidities, such as anxiety, memory difficulties, and sleep disruption (N. N. Dissanayaka et al., 2011) and subsequently improve daily functioning and quality of life (e.g., (Lin et al., 2003)). Of note, sufficient dopamine replenishment, most often with carbidopa/levodopa, may be necessary to facilitate adherence and motivation for regular exercise and to avoid the formation of sedentary habits among individuals with PD (Ahlskog, 2011a, 2011b). The majority of exercise trials in PD have been conducted with participants on appropriate dosages of dopaminergic medication, and the combined effect of dopaminergic medication plus exercise in PD has yielded greater physical benefits relative to medication or exercise alone (Dibble, Foreman, Addison, Marcus, & LaStayo, 2015). These findings highlight the importance of dopamine replenishment to enhance motor functioning and allow adults with PD to exercise at sufficient doses and intensities. In sum, for as long as individuals with PD are able to safely engage in physical activity, exercise should be seriously considered as an intervention strategy with the potential for widespread benefits for both non-motor and motor symptoms.

Conclusion

The conceptualization of PD has shifted from that of a pure motor disorder, with a burgeoning research effort in the domain of non-motor symptoms (Cronin-Golomb, 2013; Weintraub & Burn, 2011). There is as yet limited research on the management of mood, cognitive, and sleep symptoms in PD (Seppi et al., 2011), with these symptoms

often being comorbid (Aarsland, Taylor, & Weintraub, 2014). As we expand our understanding of the etiology and manifestation of the non-motor symptoms, a shift in attention to identifying and prescribing effective treatment is warranted. If these symptoms do share underlying pathologies, it is possible that a single treatment may yield multi-faceted symptom improvement.

Aerobic and resistance exercise, in particular, offer especially promising treatment strategies for alleviating a spectrum of PD symptoms, including motor function, mood, cognition, and sleep. It is important to emphasize that exercise programs have generally been well tolerated in PD with few adverse events (Ellis et al., 2013; Li et al., 2012; States, Spierer, & Salem, 2011; van Eijkeren et al., 2008), attenuating concerns about the ability of individuals with PD to successfully complete prescribed exercise due to motor limitations.

In conclusion, exercise presents a particularly feasible treatment approach in PD with minimal side effects and the potential to yield broad-spectrum benefits related to mood, cognition, and sleep, particularly if implemented in the early stages of the disease. The known benefits of exercise in healthy older adults may very well translate to this population, driven by potentially overlapping mechanisms. As with the majority of PD studies, exercise research in PD has focused primarily on the motor symptoms and largely failed to consider its potential to improve non-motor symptoms. Future studies should include a variety of non-motor outcome measures to systematically examine the effects of exercise on these symptoms. With greater research and clinical attention devoted to the potential utility of exercise interventions in PD, we may meet the goal of

simultaneously treating motor and non-motor symptoms, and ultimately optimize quality of life for persons living with this disorder.

Table 14. Exercise interventions for mood in PD.

Authors	Study Design	Mean Age	Intervention	Sample Size	Exercise Frequency/ Duration/ Setting	Control Group	Mood Outcome Measures	Main Results	Limitations
Canning et al., 2015	RCT	71.0	40-60 minutes of strengthening	231	3X/wk for 6 months (in clinic + at home)	Usual-care	PANAS	Improved affect in exercise group compared to usual care	No attention control; Mood measures included as secondary outcomes
Park et al., 2014	RCT (delayed-start)	59.9	60 minutes of combined aerobic and resistance	31	3X/wk for 48 weeks (in clinic)	Delayed-start at 24 weeks	BDI	Greater reduction in depression in early-start group compared to late-start group at 48 weeks	Greater social interaction in early-start group relative to late-start group
Shulman et al., 2013	RCT	65.8	3 exercise groups: 1) 30 minutes of high-intensity treadmill exercise; 2) 50 minutes of low-intensity treadmill exercise; 3) stretching and resistance training	67	3X/wk for 3 months (in clinic)	Stretching and resistance exercise (comparative trial)	BDI	No change in depression within any group	No non-exercising comparison condition
Bridgewater & Sharpe, 1996	Pilot RCT	67.3 (EX); 66.5 (CON)	20-30 minutes of aerobic exercise (+ warm-up calisthenics and cool-down stretching)	26	2X/wk for 3 months (in clinic)	Usual care + attendance at "interest talks" once every 3 wks	LPDQ	Improved mood in exercise group	Small sample size; Less social interaction in control group
Dashtipour et al., 2015	Prospective, double-blinded randomized trial	63.4	60 minutes of combined aerobic and resistance	11	4X/wk for 4 weeks (in clinic)	Exercise based behavioral treatment (LSVT BIG)	BAI, BDI	Reduced depression in combined group	Small sample size; Combined data analysis across both groups
Uc et al., 2014[82]	Uncontrolled phase I/II trial	65.5	45 minutes of aerobic walking	49	3X/wk for 6 months (at home)	None	GDS	Reduced depression across all completers	Lack of a control group

BAI=Beck Anxiety Inventory. BDI=Beck Depression Inventory. CON=control group. EX=exercise group. GDS=Geriatric Depression Scale; LPDQ=Levine-Pilowsky Depression Questionnaire. LSVT BIG=Lee Silverman Voice Therapy. PANAS=Positive affect subscale of the Positive and Negative Affect Schedule. PD=Parkinson's disease. RCT=randomized controlled trial.

Table 15. Exercise interventions for cognition in PD.

Authors	Study Design	Mean Age	Intervention	Sample Size	Exercise Frequency/ Duration/ Setting	Control Group	Cognitive Outcome Measures	Main Results	Limitations
Cruise et al., 2011	Controlled trial	59.5 (EX); 60.6 (CON)	60 minutes of progressive aerobic and anabolic exercise	28	2X/wk for 3 months (in clinic)	Usual lifestyle	COWAT, MMSE, PRM and SRM, SOC, SWM	EX group improved on specific measures of executive function (SWM, COWAT)	No attention control; No random allocation to groups
Uc et al., 2014	Uncontrolled phase I/II trial	65.5	45 minutes of aerobic walking	49	3X/wk for 6 months (at home)	None	Complex Figure Copy and Recall, COWAT, Eriksen flanker task, JLO, MoCA, RAVLT, Stroop, TMT B-A, WCST	Improved performance on flanker task after exercise program	Lack of a control group
Tanaka et al., 2009	Quasi-experimental design	65.4	60 minutes of multimodal exercise (aerobics, flexibility, muscular resistance, motor coordination, balance)	20	3X/wk for 6 months (in clinic)	Usual lifestyle	Symbol Search, WCST	Improved executive function (WCST categories completed and perseverative errors) in the exercise group	Small sample size; Non-randomized control group; No attention control
Tabak et al., 2013	Case series	61, 72	60 minutes of aerobic exercise	2	3X/wk for 2 months (in clinic)	None	CTT, MoCA, PDCRS	Both participants improved on all measures of executive function after exercise	Case series design; Selection bias; No attention control
Nocera et al., 2010	Case study	66	20 minutes of aerobic exercise	1	3X/week for 2 months (in clinic)	None	COWAT, Digit Span Forward and Backward, MMSE, Picture Description, Stroop	Improved performance on Stroop, COWAT (especially animal fluency), Digit Span Backward, and Picture Description after exercise program	Case study design; Limited generalizability
David et al., 2015	RCT	59.0 (EX); 58.6 (CON)	60-90 minutes of progressive resistance exercise (PRET)	51	2X/wk for 24 months (in clinic)	Stretching, balance, and non-progressive strengthening (mFC)	BTA, Digit Span, Stroop	At 24 months: PRET improved on BTA, Digit Span, and Stroop; and mFC improved on Digit Span and Stroop; No between-group differences at 12 or 24 months	No non-exercising comparison condition; Limited generalizability (due to high education and younger age of participants)

BTA=Brief Test of Attention. CON=control group. COWAT=Controlled Oral Word Association Test. CTT=Color Trails Test 1 and 2. EX=exercise group. JLO=Judgment of Line Orientation Test. mFC=modified Fitness Counts. MMSE=Mini-Mental Status Examination. MOCA=Montreal Cognitive Assessment. PD=Parkinson's disease. PDCRS=Parkinson's Disease Cognitive Rating Scale. PRET=Progressive Resistance Exercise Training. PRM and SRM=Pattern and Spatial Recognition Memory (computerized versions) from the Cambridge Neuropsychological Test Automated Battery. RAVLT=Rey Auditory Verbal Learning Test. SOC=Stockings of Cambridge. SWM=Spatial Working Memory. TMT=Trail Making Test. WCST=Wisconsin Card Sorting Test.

Table 16. Exercise interventions for sleep in PD.

Authors	Study design	Mean Age	Intervention	Sample Size	Exercise Frequency/ Duration/ Setting	Control Group	Sleep Outcome Measures	Main Results	Limitations
Nascimento et al., 2014	RCT with stratified randomization	66.3 (PD, CON) 67.8 (PD, EX)	60 minutes of muscular resistance, balance/motor coordination, and aerobic fitness	34	3X/week for 6 months (in clinic)	Usual care	MSQ	Improvements in sleep disturbance (insomnia + daytime sleepiness) in exercise group	No objective measures of sleep; No attention control
Rodrigues de Paula et al., 2006	Uncontrolled trial	61.5	75 minutes of combined aerobic conditioning and muscular strengthening	20	3X/week for 3 months (in clinic)	None	NHP-S	Trend for improved sleep after exercise program	Lack of a control group; Small sample size; Non-specific and subjective measure of sleep

CON=control group. EX=exercise group. MSQ=Mini-Sleep Questionnaire (MSQ). NHP-S=Nottingham Health Profile (sleep domain). PD=Parkinson's disease.

CHAPTER 5: GENERAL DISCUSSION

In PD, anxiety is a prevalent non-motor symptom that compromises quality of life, even in early disease stages (Hanna & Cronin-Golomb, 2012); yet it remains understudied and undertreated, as studies of affective symptoms in PD have largely focused on depression (N. N. Dissanayaka et al., 2014; Seppi et al., 2011; S. Yang et al., 2012). To address these gaps in the literature, this set of three studies uniquely focused on anxiety in PD, including its relation to other non-motor symptoms, as well as potential treatment strategies to reduce anxiety in this population. The specific aims included the following: (1) examine the relation between anxiety and cognition in PD; (2) evaluate the utility and feasibility of a cognitive-behavioral intervention for anxiety in PD; and (3) review the literature on aerobic and resistance exercise as treatments for dysfunctions of mood, cognition, and sleep in PD to provide a rationale for the targeted use of future exercise interventions to alleviate these symptoms.

In Study One, we hypothesized that self-reported anxiety would be associated with impaired cognitive performance as indexed by measures of attention and executive function in a sample of high-functioning adults with mild to moderate PD. Executive dysfunction is commonly observed in PD, even in early disease stages, and is strongly associated with psychiatric symptoms, including depression, apathy, and hallucinations (Dirnberger & Jahanshahi, 2013), but few studies have investigated the relation between anxiety and cognition in PD (Poletti et al., 2012). An earlier study from our lab found that anxiety correlated with disease duration, and in RPD only, with cognitive

performance on verbal tasks (phonemic fluency, clock reading errors, naming, and intrusion errors on a memory task) (Bogdanova & Cronin-Golomb, 2012). Other than naming, these verbal tasks fall broadly within the domain of executive functioning, suggesting some relation between anxiety and executive deficits in PD. More generally, attentional control theory posits that anxiety compromises cognitive efficiency, specifically via interference of bottom-up processing on tasks requiring inhibition and shifting (Derakshan & Eysenck, 2009; Eysenck et al., 2007). Overall, though, there are few studies that have examined the relation between anxiety and cognition in PD despite the prevalence of these symptoms in early PD and their negative impact on quality of life (Hanna & Cronin-Golomb, 2012; Schrag, Jahanshahi, & Quinn, 2000).

In Study One, we sought to investigate the association between self-reported anxiety and executive and attentional functions in a large sample of adults with mild to moderate PD. We hypothesized that anxiety would negatively affect cognitive performance on tasks of executive functioning and attention/working memory in PD. Results from Study One showed that relatively minimal levels of anxiety among adults with mild to moderate PD were associated with a specific aspect of executive dysfunction, poorer set-shifting, even after removing the psychomotor component of the task. There were no associations between anxiety and attention, working memory, or verbal fluency. This finding is consistent with a recent work by Martens et al. (Martens et al., 2016), who reported that anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS), correlated with freezing of gait and set-shifting (TMT B-A), but not with other aspects of cognition (attention, working memory, retention of

information) in a large sample of adults with PD (n=461). In a second recently published paper, this research group reported that anxious PD participants (defined as >8 on the HADS-A) performed more poorly on tests of attention, working memory, and set-shifting than did non-anxious participants with PD, with no between-group differences on measures of verbal fluency, memory, or psychomotor speed (Ehgoetz Martens et al., 2016). It is important to note that in both of these studies, Martens and colleagues used a different measure of anxiety (HADS-A) than the measure used in our study (BAI) and still found an isolated association with set-shifting. Our results are also consistent with their report of no association between anxiety and verbal fluency or psychomotor speed. In our sample, we did not find an association between anxiety and the Digit Span subtests, which is likely related to ceiling effects in our high-functioning PD group. To illustrate, the means for Digit Span Forward (11.1) and Backward (7.5) in our sample aligned much more closely with the means of the non-anxious PD group in Martens' study (Digit Forward=10.6, Backward=7.2 in non-anxious group vs. Digit Forward=8.8, Backward=5.7 in anxious group) (Ehgoetz Martens et al., 2016).

Generally speaking, there remains concern about the use of current anxiety scales, including the BAI and HADS-A, in PD (Forjaz et al., 2013; Leentjens et al., 2008), suggesting a need for the development of PD-specific anxiety scales, such as the recently created Parkinson Anxiety Scale (PAS) (Leentjens et al., 2014). Future research studies should incorporate this scale in combination with comprehensive neuropsychological assessment of attention, executive functioning, language, visuospatial skills, and memory to better characterize the relation between anxiety and all aspects of cognition in PD. It

will also be critical to include PD participants with a wide range of anxiety severities across all stages of the disease, as well as those with and without diagnosed anxiety disorders according to DSM-5. By including non-anxious PD participants as well as anxious non-PD participants for control groups, we can aim to better understand how anxiety may be contributing to cognitive dysfunction in PD above and beyond what would be expected by either the disease or anxiety in isolation. Finally, longitudinal research may be helpful in clarifying how the relation between anxiety and cognition may change as the disease progresses.

Anxiety and Cognition in Early PD: Implications for Diagnosis and Treatment

The findings from Study One have important implications for the early diagnosis and management of non-motor symptoms in PD. Although PD is now increasingly recognized as a multifaceted neuropsychiatric disorder (Cronin-Golomb, 2013; Weintraub & Burn, 2011) rather than a pure movement disorder, anxiety still remains terribly under-diagnosed and under-treated (N. Dissanayaka et al., 2015; Shulman et al., 2002). By improving screening procedures and considering the comorbidity of anxiety with other symptoms, non-motor and motor, we may be better able to identify targets for intervention, especially in early disease stages.

To that end, additional screening for anxiety and cognitive dysfunction may be warranted by neurologists when possible, both qualitatively during the interview with the patient and also quantitatively via a brief self-report anxiety measure (e.g., PAS) and/or cognitive screen. For a brief cognitive screen, the Montreal Cognitive Assessment

(MoCA) has been recommended for use in PD (Chou et al., 2010; Dalrymple-Alford et al., 2010). The MoCA includes several items to assess executive functioning (Nasreddine et al., 2005), which could serve the dual purpose of identifying subtle executive dysfunction in early PD and alerting clinicians to the potential for elevated anxiety. Given the association we observed in Study One between anxiety and poorer set-shifting in early PD, neurologists may also consider administering the TMT as a brief cognitive screen during regular office visits for individuals with complaints of anxiety and/or cognitive dysfunction. Future research trials should also consider screening for potential comorbidities between anxiety and executive dysfunction, particularly if either of those outcomes is the primary variable of interest.

With better identification of these non-motor symptoms in early disease stages, clinicians may be able to intervene and delay or alter disease progression. Indeed, consistent with Study One, a recent study reported a specific association between anxiety, set-shifting, and freezing of gait in PD, and highlighted the possibility that treatment for anxiety could also reduce freezing (Martens et al., 2016). In Study Two, we were limited in our exploration of this hypothesis, as the majority of participants did not report elevated freezing of gait and performed within normal limits on the measure of set-shifting (compared to age-, education-, and in some cases, gender-matched normative samples; (Choi et al., 2014; Tombaugh, 2004; Tombaugh, Kozak, & Rees, 1999)). Future treatment studies on anxiety in PD could recruit individuals with elevated freezing of gait and/or reported cognitive dysfunction to better elucidate the potential of

interventions for anxiety to simultaneously improve comorbid motor and cognitive symptoms.

Future Directions for Cognitive-Behavioral Therapy for Anxiety in PD

With better recognition of anxiety in PD, we can also hope to intervene early in the disease course to reduce mood symptoms and improve quality of life. To do so, there is urgent need for the development of evidence-based treatments for anxiety in PD, especially non-pharmacological options, such as cognitive-behavioral therapy (CBT). CBT may be especially well-suited for implementation in early PD when individuals experience fewer physical and cognitive limitations, allowing them to fully engage in treatment, complete out-of-session practice, and develop long-term skills to manage anxiety throughout the disease course.

CBT has demonstrated strong efficacy as a treatment for anxiety disorders and stress in the general population, including preliminary evidence of efficacy in populations with medical conditions, such as cancer, HIV, and spinal cord injury (Hofmann et al., 2012). In PD, CBT has yielded positive effects on depression in a large RCT (Dobkin, Menza, Allen, Gara, et al., 2011), as well as promising preliminary effects on anxiety, mostly in smaller, uncontrolled pilot studies (N. N. W. Dissanayaka et al., 2016; Egan et al., 2015; Troeung et al., 2014). The findings from Study Two build upon this literature by demonstrating the clear utility and feasibility of CBT for individuals with mild to moderate PD, who also met criteria for at least one DSM-5 anxiety disorder. We aimed to critically evaluate the utility and feasibility of a transdiagnostic CBT protocol for

anxiety in PD, using a single-case, multiple-baseline, experimental design. Twelve sessions of CBT were highly feasible with minimal dropout rates, and all participants reported high acceptability and satisfaction with treatment. Seven of the nine participants reported a significant reduction in symptoms of anxiety and/or depression at either the post-treatment or 6-week follow-up assessment. The intervention was delivered in-person for five participants and via secure videoconferencing for the remaining four, and results did not differ by treatment modality.

Future studies should aim to replicate these findings in larger samples and also continue to explore telehealth as a viable treatment strategy in this population. Despite the promising literature on CBT in PD, anxiety continues to be terribly understudied and under-treated, and 83% of PD patients treated with medication reported minimal benefit on anxiety in a recent study (N. Dissanayaka et al., 2015). Together, these findings point to the importance of considering the use of non-pharmacological strategies for anxiety treatment in PD, such as CBT. To maximize treatment effectiveness, it will be imperative for future research to examine predictors of treatment response among those with PD, with the goal of best matching a specific treatment to the individual. Study Two highlighted the importance of assessing for apathy among persons with PD, which frequently presents as a non-motor symptom that is often unique in presentation from depression (den Brok et al., 2015). The one participant in our study who did not show any response to CBT (P3) reported significant levels of apathy at pre- and post-treatment, both on self-report questionnaires and in session. He also missed sessions on occasion

and reported frequent amotivation and difficulty completing homework exercises out-of-session, all of which likely contributed to his lack of treatment response.

The only other participant who showed a relatively minimal response to treatment (P8) had a history of deep brain stimulation (DBS), and reported several adjustments to DBS settings/PD medications during the intervention, which often worsened her motor symptoms and subsequently contributed to increased depression, per her report in session. Compared to all other participants, P8 was significantly younger and reported more frequent OFF time, greater motor fluctuations, and significantly higher anxiety across all study phases. Even so, the intervention was feasible and acceptable for her with reported high satisfaction, and there were downward trends in her anxiety and depression during the second half of treatment, beginning in weeks 5-6, despite consistent DBS/PD-medication changes from weeks 1-10. This suggests that the reductions in anxiety and depression were related at least in part to the effects of the intervention, despite the confound of medically-warranted DBS/dopaminergic medication adjustments.

Based on these findings, future adaptations to the protocol may help to maximize treatment response. First, it will be important consider adding supplemental modules or extra sessions on motivation for individual with high baseline apathy. Recent research has also highlighted the potentially critical role of caregiver participation in optimizing treatment response and reducing caregiver burden (N. N. W. Dissanayaka et al., 2016; Kraepelien et al., 2015). Caregiver involvement may be even more essential for individuals with comorbid apathy as an additional tool to facilitate out-of-session engagement and homework compliance. Future studies may also wish to systematically

evaluate homework compliance, which could function as a predictor or mediator of treatment response.

Study Two demonstrated preliminary efficacy of the CBT protocol for an individual with a history of DBS. During treatment, it was crucial to monitor changes to DBS settings/dopaminergic dose on a weekly basis and inquire about the effects of these symptoms on mood and anxiety. With this caveat in mind, future studies should expand inclusion criteria to include individuals with a history of DBS and consider adapting protocols as necessary for this subset of individuals (e.g., allowing for telehealth sessions for weeks when motor fluctuations are disabling, exploring how motor fluctuations change the experience of anxiety, and perhaps increasing the number of sessions depending on the severity of the anxiety). GAD is more common among patients with motor fluctuations compared to those without fluctuations, but this anxiety is not consistently associated with motor state (e.g., ON vs. OFF periods, (Leentjens et al., 2012)). This finding underscores the need to better understand this relation between anxiety and motor states in PD, and also highlights the need for future studies to include individuals with motor fluctuations in order to develop effective treatments and identify any necessary adaptations to the CBT protocol. Finally, as noted above, anxiety and subtle executive dysfunction may co-occur in early disease stages, as demonstrated in Study One. For individuals with comorbid anxiety and cognitive symptoms, CBT protocols may require modification related to the presentation of information to compensate for any difficulty with multi-tasking or divided attention. These modifications may include a session devoted to organization/planning, increased structure

and organization in session, repetition of information, provision of explicitly organized written materials/handouts, and systematic planning of homework exercises to maximize out-of-session practice.

Dissemination and Potential of Telehealth Interventions in PD

Future interventions for anxiety in PD must also fully consider the potential of telehealth as a way to increase dissemination of evidence-based treatments to individuals who may be unable or unwilling to commit to weekly trips to a therapist's office. Indeed, several barriers to accessing mental healthcare have been reported in PD, including lack of local services, physical impairments, and lack of transportation (Dobkin et al., 2013). Dobkin and colleagues also found that many individuals with PD were interested in telehealth options for mental health treatment, though there have been few studies that have addressed the feasibility and utility of this approach.

To date, telephone-delivered CBT has shown some promise for treatment of mood, primarily depression, in PD (Dobkin, Menza, Allen, Tiu, et al., 2011; Veazey et al., 2009). In addition, a recent pilot study of internet-delivered CBT reported a significant reduction in depression, but not anxiety, among PD participants who endorsed elevated depression or anxiety on the Hospital Anxiety and Depression Scale (>7) (Kraepelien et al., 2015). Although this study reported a relatively high dropout rate (3 out of 9 participants), the authors described the CBT as self-guided with minimal therapist contact (<15 minutes per week), suggesting that the treatment approach was less standardized and structured than typical CBT.

Study Two first underscored the difficulty with recruitment that has been observed in previous studies in this population (Troeung et al., 2014; Veazey et al., 2009). In response to significant difficulty with recruitment, we modified the study to include the option of internet-delivered sessions, which allowed several new participants to engage in treatment who otherwise would not have enrolled in the study. These telehealth participants comprised almost half of the sample (4/9), responded well to the intervention, and reported high satisfaction and acceptability of the treatment. Despite the small sample size, these findings provide additional rationale to further investigate telehealth options for treatment of anxiety in PD. Study Two demonstrated the utility and feasibility of internet-delivered CBT in this population, as all four telehealth participants completed the study and showed a positive response to treatment. With larger, controlled trials focused on internet-delivered CBT, we can more systematically explore the efficacy of this treatment approach, increase recruitment and access to care, and provide urgently needed mental healthcare to a greater number of PD individuals, including those with more advanced physical limitations or those living in rural areas.

Potential of Exercise Interventions for Anxiety in PD

Despite the promising evidence of CBT for anxiety in PD, some individuals may not respond to CBT or may not have access to CBT therapists. Hence, it is important to develop alternative non-pharmacological interventions. In Study Three, we comprehensively reviewed the literature on aerobic and resistance exercise in healthy older adults and in PD and argued for the potential of exercise interventions to

simultaneously improve motor symptoms, as well as mood, cognition, and sleep in PD. Aerobic and resistance exercise interventions have previously demonstrated feasibility and efficacy in PD, yielding positive effects on physical fitness, gait, bradykinesia, and quality of life (Dibble et al., 2009; Goodwin et al., 2008; Shulman et al., 2013). However, as we discussed in Study Three, the potential of aerobic and resistance exercise to directly target non-motor symptoms, such as anxiety, has not yet been fully explored. Preliminary findings in PD suggest that aerobic and resistance exercise may improve mood in PD, although exercise research has largely focused on depression, with mood measures often included as secondary outcomes (Bridgewater & Sharpe, 1996; Canning et al., 2015; Cusso, Donald, & Khoo, 2016; Dashtipour et al., 2015; Park et al., 2014; Uc et al., 2014). To illustrate the potential widespread effects of exercise on non-motor symptoms in PD, a recent controlled trial reported that 16 weeks of aerobic exercise (3x/week) improved aspects of executive functioning (relative to no change in stretch-balance or no-contact control groups) and language (greater improvement in aerobic group than in the stretch-balance group) (Altmann et al., 2016). They did not examine anxiety and reported no change in depression in the exercise groups, but noted an increase in depression in the control group only. Strengths of their study include inclusion of outcome measures of both mood and cognition, but further exercise trials are needed that specifically target anxiety in PD.

In non-PD populations, exercise has been shown to yield positive effects on both depression and anxiety, among clinical and non-clinical samples, though with smaller effects on anxiety than on depression (Asmundson et al., 2013; Conn, 2010a, 2010b;

Stathopoulou et al., 2006; Wegner et al., 2014). At the same time, a meta-analysis pointed to a lack of evidence for aerobic exercise as a superior stand-alone treatment for anxiety disorders relative to active control groups, including non-aerobic exercise, antidepressants, or CBT (Bartley, Hay, & Bloch, 2013). These findings suggest that exercise, known to positively affect motor symptoms and physical health in PD (Goodwin et al., 2008), may be most helpful as an adjunctive treatment for mood in PD, to be added to either CBT or medication, as shown in non-PD populations. For example, group CBT plus an adjunctive walking program improved depression, anxiety, and stress among adults with a range of anxiety disorders (Merom et al., 2008). A more recent review of eight RCTs, including the study by Merom et al., highlighted the evidence for the use of aerobic and non-aerobic exercise as adjunctive treatments for anxiety disorders, in combination with either antidepressants, occupational therapy and lifestyle changes, or group CBT (Jayakody, Gunadasa, & Hosker, 2014). Similar approaches of combined therapies should be explored in PD to maximize treatment response and tailor intervention programs to each individual.

To do so, we should consider individual presentations of motor and non-motor symptoms in PD, and encourage exercise interventions for their potential to positively affect not only anxiety, but also additional non-motor symptoms, including depression, reduced qualify of life, and fear of falling, all of which are frequently comorbid with anxiety in PD (Gallagher & Schrag, 2012; Hanna & Cronin-Golomb, 2012; Pontone et al., 2009). Study Two showed that comorbid depressive symptoms were frequently present, but often at mild levels, among PD participants with anxiety disorders. For these

participants, exercise may be an appropriate adjunctive treatment to reduce mild depressive symptoms in combination with CBT that more directly targets anxiety. An adjunctive exercise intervention could also be helpful in improving quality of life among persons with PD. Both CBT and exercise have yielded positive effects on quality of life in non-PD individuals with anxiety disorders, with specific effects on aspects of QoL related to physical function and mental health (Herring, Johnson, & O'Connor, 2016; Hofmann, Wu, & Boettcher, 2014). These two domains seem particularly relevant areas of interest for anxious individuals with PD. Lastly, preliminary findings in Study Two suggested that treatment of anxiety may reduce fear of falling in PD. Exercise interventions could further explore this relation by examining the effects of resistance and balance training, for example, on fear of falling and anxiety. For individuals with persistent fear of falling despite improved balance, CBT could be added to exercise training to directly target the psychological fear. In PD, fear of falling has been shown to predict recurrent falls (Mak & Pang, 2009), and to affect quality of life to a greater extent than falls (Grimbergen, Schrag, Mazibrada, Borm, & Bloem, 2013), further emphasizing the need to address this symptom in intervention studies.

Overall, these future avenues of research emphasize the need for treatment trials of CBT and exercise for anxiety and associated symptoms in PD, with the goal of establishing several evidence-based treatment options. This approach will allow us to best match an individual to a specific treatment strategy and optimize treatment response. For example, individuals who respond best to behavioral strategies may benefit from exercise interventions for mood as a first treatment approach, whereas CBT may be most

helpful for individuals who present with inflexible cognitive schemas, to assist them in shifting thought patterns and facilitating subsequent engagement in behavioral treatment components (e.g., exposures). To that end, it will be crucial for future PD intervention trials to examine predictors of treatment response.

Conclusion

In sum, this set of studies critically adds to the PD literature in its primary focus on anxiety and evaluation of potential treatment options. Studies One and Two included an investigation of its relation to cognition in early disease stages, and a utility and feasibility study to examine the potential of CBT for anxiety in PD, using a rigorous single-case, multiple-baseline experimental design. In Study Three, we reviewed the literature on exercise interventions in PD and provided systematic rationale for the targeted use of exercise interventions to improve anxiety, as well as cognition and sleep, in this population. Anxiety in PD continues to receive less attention in clinical and research settings even compared to other non-motor symptoms, despite its high prevalence, negative impact on quality of life, and comorbidity with other non-motor symptoms (Gallagher & Schrag, 2012; Hanna & Cronin-Golomb, 2012). Our findings help to describe anxiety as it relates to cognition in mild to moderate PD, and also provide preliminary evidence for the use of CBT, delivered either in person or via secure videoconferencing, as a feasible treatment strategy to reduce anxiety and comorbid depressive symptoms in PD. In addition, aerobic and resistance exercise interventions offer a promising alternative treatment strategy, known to benefit physical functioning in

PD (Goodwin et al., 2008), but with the potential to also improve mood, cognition, and sleep in this population, especially for individuals who fail to respond to CBT or who do not have access to CBT.

With improved recognition of anxiety in PD, we can hope to intervene early in the disease course and improve daily functioning and quality of life. We hope our work will provide the impetus for future research focused on anxiety in PD to better understand its unique clinical presentation, distinct from depression and apathy, and to develop tailored, evidence-based treatments for this symptom, such as CBT and exercise. Future work should also aim to explore strategies for dissemination of such treatments with new technologies, in order to increase access to mental healthcare for individuals with PD and alleviate the negative effects of anxiety and associated non-motor symptoms across all stages of the disease.

LIST OF ABBREVIATED JOURNAL TITLES

Acta Neurol Scand	Acta Neurologica Scandinavica
Acta Neurol Scand Suppl	Acta Neurologica Scandinavica. Supplementum
Acta Neuropathol	Acta Neuropathologica
Age Ageing	Age and Ageing
Aging Ment Health	Aging & Mental Health
Alzheimer Dis Assoc Disord	Alzheimer Disease and Associated Disorders
Am J Geriatr Psychiatry	The American Journal of Geriatric Psychiatry
Am J Phys Med Rehabil	American Journal of Physical Medicine & Rehabilitation
Am J Prev Med	American Journal of Preventitive Medicine
Am J Psychiatry	The American Journal of Psychiatry
Ann Behav Med	Annals of Behavioral Medicine
Annu Rev Neurosci	Annual Review of Neuroscience
Arch Clin Neuropsychol	Archives of Clinical Neuropsychology
Arch Gen Psychiatry	Archives of General Psychiatry
Arch Gerontol Geriatr	Archives of Gerontology and Geriatrics
Arch Intern Med	Archives of Internal Medicine
Arch Neurol	Archives of Neurology
Arch Phys Med Rehabil	Archives of Physical Medicine and Rehabilitation
Arthritis Care Res (Hoboken)	Arthritis Care & Research
Behav Brain Res	Behavioural Brain Research
Behav Neurol	Behavioural Neurology
Behav Neurosci	Behavioral Neuroscience
Behav Res Ther	Behaviour Research and Therapy
Behav Ther	Behavior Therapy
Biol Psychiatry	Biological Psychiatry
Br J Psychiatry	The British Journal of Psychiatry
Br J Sports Med	British Journal of Sports Medicine
Br Med Bull	British Medical Bulletin
Brain Behav Immun	Brain, Behavior, and Immunity
Brain Cogn	Brain and Cognition
Brain Res	Brain Research
Brain Res Rev	Brain Research Reviews
Cell Tissue Res	Cell and Tissue Research
Cereb Cortex	Cerebral Cortex
Clin Case Stud	Clinical Case Studies
Clin Neuropharmacol	Clinical Neuropharmacology
Clin Psychol Rev	Clinical Psychology Review

Clin Psychol Sci Prac	Clinical Psychology: Science and Practice
Clin Rehabil	Clinical Rehabilitation
CNS Neurol Disord Drug Targets	CNS & Neurological Disorders Drug Targets
CNS Spectr	CNS Spectrums
Cochrane Database Syst Rev	The Cochrane Database of Systematic Reviews
Cogn Behav Neurol	Cognitive and Behavioral Neurology
Cogn Behav Pract	Cognitive and Behavioral Practice
Cognit Ther Res	Cognitive Therapy and Research
Complement Ther Med	Complementary Therapies in Medicine
Compr Physiol	Comprehensive Physiology
Contemp Clin Trials	Contemporary Clinical Trials
Curr Med Chem	Current Medicinal Chemistry
Curr Neurol Neurosci Rep	Current Neurology and Neuroscience Reports
Curr Opin Neurobiol	Current Opinion in Neurobiology
Curr Treat Options Neurol	Current Treatment Options in Neurology
Dement Geriatr Cogn Dis Extra	Dementia and Geriatric Cognitive Disorders Extra
Depress Anxiety	Depression and Anxiety
Drugs Aging	Drugs & Aging
Eur Arch Psychiatry Clin Neurosci	European Archives of Psychiatry and Clinical Neuroscience
Eur J Cardiothorac Surg	European Journal of Cardio-Thoracic Surgery
Eur J Neurol	European Journal of Neurology
Eur J Neurosci	The European Journal of Neuroscience
Eur J Pain	European Journal of Pain (London, England)
Eur J Phys Rehabil Med	European Journal of Physical and Rehabilitation Medicine
Eur Neurol	European Neurology
Eval Program Plann	Evaluation and Program Planning
Exp Neurol	Experimental Neurology
Expert Rev Neurother	Expert Review of Neurotherapeutics
Front Hum Neurosci	Frontiers in Human Neuroscience
Front Med (Lausanne)	Frontiers in Medicine
Front Neurol	Frontiers in Neurology
Gait Posture	Gait & Posture
Geriatr Gerontol Int	Geriatrics & Gerontology International
Geriatr Psychol Neuropsychiatr Vieil	Gériatrie et psychologie neuropsychiatrie du vieillissement
Hum Brain Mapp	Human Brain Mapping
Int J Geriatr Psychiatry	International Journal of Geriatric Psychiatry

Int J Neurosci	The International Journal of Neuroscience
Int J Sports Med	International Journal of Sports Medicine
Int Psychogeriatr	International Psychogeriatrics
J Affect Disord	Journal of Affective Disorders
J Aging Phys Act	Journal of Aging and Physical Activity
J Aging Res	Journal of Aging Research
J Am Geriatr Soc	Journal of the American Geriatrics Society
J Anxiety Disord	Journal of Anxiety Disorders
J Behav Med	Journal of Behavioral Medicine
J Clin Exp Neuropsychol	Journal of Clinical and Experimental Neuropsychology
J Clin Neurosci	Journal of Clinical Neuroscience
J Clin Psychiatry	The Journal of Clinical Psychiatry
J Clin Psychol Med Settings	Journal of Clinical Psychology in Medical Settings
J Clin Sleep Med	Journal of Clinical Sleep Medicine
J Consult Clin Psychol	Journal of Consulting and Clinical Psychology
J Geriatr Psychiatry Neurol	Journal of Geriatric Psychiatry and Neurology
J Gerontol	Journal of Gerontology
J Gerontol A Biol Sci Med Sci	The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences
J Gerontol B Psychol Sci Soc Sci	The Journals of Gerontology. Series B, Psychological Sciences and Social Sciences
J Health Psychol	Journal of Health Psychology
J Int Neuropsychol Soc	Journal of the International Neuropsychological Society
J Mov Disord	Journal of Movement Disorders
J Neurol	Journal of Neurology
J Neurol Neurosurg Psychiatry	Journal of Neurology, Neurosurgery, and Psychiatry
J Neurol Phys Ther	Journal of Neurologic Physical Therapy
J Neurol Sci	Journal of the Neurological Sciences
J Neuropsychiatry Clin Neurosci	The Journal of Neuropsychiatry and Clinical Neurosciences
J Neuropsychol	Journal of Neuropsychology
J Neurosci	The Journal of Neuroscience
J Nucl Med	Journal of Nuclear Medicine
J Parkinsons Dis	Journal of Parkinson's Disease
J Psychiatr Res	Journal of Psychiatric Research
J Psychopharmacol	Journal of Psychopharmacology
J Psychosom Res	Journal of Psychosomatic Research
J R Soc Med	Journal of the Royal Society of Medicine

J Sport Exerc Psychol	Journal of Sport & Exercise Psychology
J Yoga Phys Ther	Journal of Yoga & Physical Therapy
JAMA	JAMA: Journal of the American Medical Association
JAMA Neurol	JAMA Neurology
Lancet Neurol	The Lancet. Neurology
Mayo Clin Proc	Mayo Clinic Proceedings
Mov Disord	Movement Disorders
N Engl J Med	The New England Journal of Medicine
Nat Rev Neurosci	Nature Reviews. Neuroscience
Nat Sci Sleep	Nature and Science of Sleep
Neurobiol Aging	Neurobiology of Aging
Neurobiol Dis	Neurobiology of Disease
Neurodegener Dis	Neurodegenerative Diseases
Neurol Sci	Neurological Sciences
Neuromolecular Med	Neuromolecular Medicine
Neuropathol Appl Neurobiol	Neuropathology and Applied Neurobiology
Neuropsychiatr Dis Treat	Neuropsychiatric Disease and Treatment
Neuropsychiatry Neuropsychol Behav Neurol	Neuropsychiatry, Neuropsychology, and Behavioral Neurology
Neuropsychol Rev	Neuropsychology Review
Neurorehabil Neural Repair	Neurorehabilitation and Neural Repair
Neurosci Biobehav Rev	Neuroscience and Biobehavioral Reviews
Neurosci Lett	Neuroscience Letters
Neuroscientist	The Neuroscientist
News Physiol Sci	News in Physiological Sciences
Nurs Health Sci	Nursing & Health Sciences
Nurs Res	Nursing Research
Parkinsonism Relat Disord	Parkinsonism & Related Disorders
Parkinsons Dis	Parkinson's Disease
Pathol Biol (Paris)	Pathologie-Biologie
Pharmacogenomics J	The Pharmacogenomics Journal
Phys Ther	Physical Therapy
Physiol Behav	Physiology & Behavior
PLoS One	Public Library of Science One
Postgrad Med J	Postgraduate Medical Journal
Proc Natl Acad Sci U S A	Proceedings of the National Academy of Sciences of the United States of America
Prog Brain Res	Progress in Brain Research
Prog Neurobiol	Progress in Neurobiology
Prog Neuropsychopharmacol Biol Psychiatry	Progress in Neuropsychopharmacology & Biological Psychiatry
Psychiatry Investig	Psychiatry Investigation
Psychiatry Res	Psychiatry Research

Psychol Aging	Psychology and Aging
Psychol Assess	Psychological Assessment
Psychol Sci	Psychological Science
Psychosom Med	Psychosomatic Medicine
Qual Life Res	Quality of Life Research
Rev Bras Fisioter	Revista Brasileira de Fisioterapia
Rev Neurosci	Reviews in the Neurosciences
Scand J Med Sci Sports	Scandinavian Journal of Medicine & Science in Sports
Sleep Med	Sleep Medicine
Sleep Med Rev	Sleep Medicine Reviews
Sports Med	Sports Medicine
Ther Adv Neurol Disord	Therapeutic Advances in Neurological Disorders
Transl Neurodegener	Translational Neurodegeneration
Trends Neurosci	Trends in Neurosciences
Trends Pharmacol Sci	Trends in Pharmacological Sciences

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