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Apathy in Parkinson's Disease: A Behavioral Intervention Study

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Apathy in Parkinson's Disease: A Behavioral Intervention Study

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Abstract

Apathy, a symptom reflecting motivational and self-initiation impairment, is one of the most common neuropsychiatric symptoms in Parkinson's disease (PD), with an average estimated prevalence of 40-45%. Elevated apathy has been associated with a host of negative associates and consequences, including cognitive impairment, poor daily functioning, poor treatment compliance and illness outcome, reduced quality of life, and increased caregiver burden and distress. While some studies have evaluated pharmacologic approaches to the treatment of apathy, few studies have evaluated non-pharmacologic approaches and we have identified no studies that have evaluated the efficacy of non-pharmacologic treatments of apathy in Parkinson's patients despite the need for such research. The purpose of the present study was to develop and gather pilot data on the acceptability, feasibility, and estimated efficacy of a primarily telephone-based, 6-week activity scheduling and monitoring intervention that incorporates an external cueing component to target disease-related self-generational deficits, on reducing levels of apathy in non-demented, highly apathetic PD patients. The project included three phases: (1) development of protocol materials, (2) determine ease of training paraprofessional interventionists, and (3) to assess feasibility, acceptability, and estimated effect of treatment in a one-arm uncontrolled trial. Patient apathy, depression, and quality of life significantly improved post-treatment and improvements in apathy and depression were maintained at one-month follow-up. While enrollment proved challenging, feasibility, acceptability, and efficacy data were strong and promising. Larger, randomized controlled trials are needed to investigate the efficacy of the presented intervention.

Introduction

Parkinson's Disease (PD) is a chronic and degenerative neurological disorder that affects 600,000 to 1 million people in the United States alone. While motor dysfunction is most apparent in PD, psychiatric symptoms have been reported to occur in as many as 90% of PD patients. Apathy, a symptom reflecting motivational and self-initiation impairment, is one of the most common neuropsychiatric symptoms in PD and other disorders involving frontal-subcortical circuitry, with an average estimated prevalence of 40-45%. Elevated apathy has been associated with a host of negative consequences, including cognitive impairment, poor daily functioning, poor treatment compliance and illness outcome, reduced quality of life, and increased caregiver burden and distress. While some studies have evaluated pharmacologic approaches to the treatment of apathy, very few studies have evaluated non-pharmacologic approaches. Further, no studies have evaluated the efficacy of non-pharmacologic treatments of apathy in Parkinson's patients despite the need for such research.

The present study sought to develop and gather pilot data on the acceptability, feasibility, and estimated effect of a 6-week, primarily telephone delivered, activity scheduling program, that incorporated an external cueing component, on patient apathy and other important outcomes in a sample of non-demented, apathetic PD patients and their caregivers. Specifically, the intervention aimed to reduce elevated levels of apathy, improve patient depressive symptoms, daily functioning, and quality of life, and improve burden/distress in the caregivers/spouses of participating PD patients.

Parkinson's Disease

First described as the "shaking palsy" by James Parkinson in 1817 (Parkinson, 1817), Parkinson's Disease (PD) has since become prevalent worldwide, occurring in an estimated 600,000 to 1 million people in the United States alone with approximately 70,000 individuals developing PD each year (Mayeux, 2003). Most cases of PD present after the age of 50, with a mean age of onset at 55 to 60 years, and few cases, if any, appear after the age of 80 (Mackin, 2000; Stern, 1993). While initially characterized by its motor dysfunction, PD is now recognized as a disease in which psychiatric and cognitive complications are common. Although the exact cause of PD remains unknown, there are several theorized causes of the disorder including toxic exposures (environmental, occupational, or drug induced), oxidative stress, and genetics. Most cases of PD are considered idiopathic, or, of unknown cause.

Pathophysiology. PD is a chronic, progressive neurodegenerative disorder marked by slow degeneration of dopamine producing neurons primarily in the pars compacta of the substantia nigra. The depletion of dopamine interferes largely with the nigrostriatal pathway of the basal ganglia, a system largely implicated in the production of movement and coordinated muscle control (Gibb, 1992; Tisch, Silberstein, Limousin-Dowsy, and Jahanshahi, 2004). The nigrostriatal pathway is one of the major dopaminergic pathways in the brain and transmits dopamine from the substantia nigra (i.e., "nigro-") to the striatum (i.e., "-striatal"). It is the disruption of this circuit that results in the cardinal motor features of PD (i.e., tremor, rigidity, and bradykinesia). It is estimated that PD patients have lost at least 60-70% of their dopamine-producing cells by the time motor symptoms appear (Fearnley and Lees, 1991).

There is also evidence of disruption to other dopaminergic circuits (e.g., mesolimbic and mesocortical pathways) and other brain regions (e.g. locus ceoruleus, ventral tegmental area,

amygdala, raphe nuclei), resulting in noradrenergic, serotonergic, and cholinergic abnormalities of the basal ganglia (Lang and Lozano, 1998; Mackin, 2000). The mesolimbic dopamine pathway, often referred to as the "reward pathway," transmits dopamine from the ventral tegmental area (VTA) of the midbrain (i.e., "meso-") to the nucleus accumbens, ventral striatum, septal area, amygdala, hippocampus of the limbic system (i.e., "-limbic"), and is involved in pleasurable feelings of reward (i.e., hedonia), reward learning, and motivation (Tisch et al., 2004). Decreased dopamine in the mesolimbic pathway may contribute to psychiatric symptoms of depression and apathy (Lieberman, 2006; Fibiger, 1984). Decreased dopamine in the mesocortical pathway, a third major dopamine pathway that transmits dopamine from the VTA (i.e., "meso-") to the PFC (i.e., "-cortical"), underlies the executive dysfunction (e.g., set-shifting and verbal fluency) that is common among PD patients, as well as impairments in working memory, learning, and attention (e.g., Rinne et al., 2000; Floresco and Magyar, 2006).

Motor symptoms. The classic triad of motor signs in PD include resting tremor, rigidity, and bradykinesia/akinesia (Lang and Lozano, 1998). Resting tremor is the most common and identifiable sign of disease, with approximately 70% to 75% of cases reporting tremor as their initial complaint (Stern, 1993). The tremor is referred to as a *resting* tremor because it occurs when the limbs are at rest and subsides when movement is initiated voluntarily. Rigidity, or cogwheeling, refers to muscle stiffness that occurs and can result in muscle pain or discomfort. Bradykinesia refers to the slowness of voluntary movement (e.g., standing up, walking, and sitting down) that occurs as a result of delayed transmission signals from the brain to the muscles. Parkinson's gait, characterized by a shortened stride and shuffling steps, is another common feature. Other primary motor symptoms include postural instability, or poor balance, and coordination impairment. In later stages of the disease, akinesia (lack of voluntary movement),

festination (more severe and abnormal gait pattern), hypophonia (decreased speech volume), dysarthria (speech impairment), chewing and swallowing difficulties, as well as drooling can occur (Mackin, 2000).

Symptom progression varies by individual but typically progresses over a period of 10 to 20 years (Langston, 1990). Progression can be divided into three states: early, nonfluctuating, and fluctuating (Manyam, 1997). Patients in the early stage of disease generally show unilateral symptoms (i.e., on one side of the body) and may be monosymptomatic or have multiple mild symptoms that need minimal medication management or none at all. In the nonfluctuating stage, symptoms increase in severity but respond well to medication. Symptoms may respond to first-line dopamine replacement therapy (i.e., single drug treatment, such as Levodopa or a dopamine agonist) or to a combination of medications. Once patients have reached the fluctuating stage of disease, medication is less effective and symptom control fluctuates. Motor fluctuations may include the "wearing-off effect," in which dopamine replacement medication lasts for a decreasing amount of time, or the "on-off phenomenon," in which the patient cycles between experiencing complete improvement of symptoms that may last for hours to experiencing no therapeutic effect of the medication. When patients are "On" they feel more control over their movement; whereas, when patients are "Off" they experience the motor and non-motor symptoms of the disease (Stocchi, Jenner, and Obeso, 2010). The frequency of fluctuations varies by individual, but can occur several times per day.

Neuropsychiatric symptoms. While motor dysfunction is typically the most apparent in PD, the disease is often conceptualized as a neuropsychiatric disease because of the high prevalence of cognitive and psychiatric complications. Cognitive decline affects up to 90% of patients (Pirozzolo, Hansch, Mortimer, Webster, and Kuskowski, 1982). In contrast, dementia

(i.e. severe cognitive impairment that affects daily living) is less frequent, affecting approximately 25% of patients, as most symptoms are subtle and do not interfere significantly with everyday activities (Mayeux et al., 1990; Stocchi and Brusa, 2000). The greatest area of cognitive difficulty for PD patients involves executive functions, mental operations involved in adapting to novel situations, problem solving, planning, generating new concepts and elaborating cognitive and behavioral responses to environmental situations (Stocchi and Brusa, 2000). Other characteristic cognitive changes in PD include impairment in attention, abstraction and reasoning, visuospatial abilities, and memory (Stocchi and Brusa, 2000).

Psychiatric symptoms have been reported to occur in as many as 90% of PD patients (Starkstein, Mayberg, Leiguarda, Preziosi, and Robinson, 1992b). Apathy, depression, and anxiety are the most prevalent psychiatric symptoms in PD, but sleep disturbance and medication-induced hallucinations also occur at high rates (Aarsland et al., 2009; Jankovic J, 2008). These hallucinations are generally visual and benign in nature (Mackin, 2000). Psychiatric symptoms have a significant negative impact on daily functioning, quality of life, cognitive functioning and caregiver burden and distress (Aarsland et al., 2007; Karlsen et al., 2000; Shrag, Jahanshahi, and Quinn, 2000; Chen, 2004; Keranen et al., 2003), with some research suggesting that the negative impact of psychiatric symptoms is even greater than the impact of motor symptom severity (e.g., GPDS, 2002). Moreover, a multitude of studies have demonstrated that elevations in apathy, specifically, are associated with a host of negative consequences, from impaired cognitive and daily functioning to decreased treatment compliance and responsiveness to decreased quality of life in patients and caregivers (van Reekum, Stuss, and Ostrander, 2005; Onyike et al., 2007; de Vugt et al., 2003; Yeager and Hyer, 2008; Isella et al., 2002; Aarsland et al., 1997, 1999a; Levy et al., 1998).

Apathy

Apathy is characterized by diminished *motivation* and *initiative* in three domains- goal-directed behavior, thought, and emotion (Marin, 1991). It is one of the most common psychiatric symptoms in patients with neurologic disease (van Reekum, et al., 2005; Chase, 2010) and is associated with disruption of the brain's frontal-striatal circuitry. Patients with lesions to, or diseases affecting, the frontal and/or subcortical brain structures show high rates of apathy. Apathy, referred to as a "negative symptom" in the schizophrenia literature, affects about half of patients diagnosed with schizophrenia, and is associated with reduced frontal lobe volume and reduced functional outcome in this population (Kiang, Christensen, Remington, and Kapur, 2003; Roth et al., 2004; Fearden et al., 2009). Some of the most alarming rates of apathy have been reported in patients with progressive supranuclear palsy and frontotemporal dementia, with reported prevalences of 91% in progressive supranuclear palsy and 90% in frontotemporal dementia (Levy, 1998). Interestingly, these patients rarely have depression alone, and much more often present with apathy in the absence of depression than apathy in the presence of depression. The overall average point prevalence of apathy is 61.4% in traumatic brain injury (van Reekum et al., 2005), 57.5% in Huntington's disease (Levy, 1998; Paulsen et al., 2001), 55% in Alzheimer's disease (van Reekum et al., 2005), 40 and 45% in PD (Isella et al., 2002; Starkstein et al., 1992a), and 33.8% in vascular dementia (van Reekum et al., 2005).

Apathy is not depression. While apathy may exist as a symptom of depression, in many cases (e.g., neurologic diseases such as Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, and PD) apathy can occur without depression or, when they are both present within a particular patient, they may be clinically and anatomically independent and dissimilar in their correlations to other signs and symptoms (Levy and Czernecki, 2006). Various

methods have been employed to examine the discriminability of apathy and depression as independent clinical phenomena. Such investigations include the evaluation of the rates and relationships between apathy and depression in different diagnostic groups (i.e., PD, Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, and Huntington's disease; e.g., Marin, Firinciogullari, and Biedrzycki, 1994, Levy et al., 1998), the exploration of the differential relationship of apathy and depression with other clinical variables (i.e., stage of disease, cognitive impairment, and functional impairment; e.g., Landes, Sperry, and Strauss, 2005), the evaluation of their independent associations with cognitive functioning (e.g., Butterfield et al, 2010; Isella et al., 2002; Kuzis et al., 1999), and examination of the differential effects of treatment on apathy and depression (e.g., Padala, Burke, Bhatia, and Petty, 2007; Weitzner, Kanfer, and Booth-Jones, 2005). While certain symptoms may be *shared* among apathy and depression (i.e., diminished interest, psychomotor retardation, fatigue/hypersomnia, lack of insight), several researchers have suggested that certain symptoms are *unique* to apathy (i.e., blunted affect, indifference, low social engagement, diminished initiation, poor persistence) and certain symptoms are *unique* to depression (i.e., dysphoria, suicidal ideation, self-criticism, feelings of guilt, pessimism, hopelessness, sleep disturbance) (Marin, Firinciogullari, and Biedrzycki, 1993, Marin 1990, Landes, Sperry, Strauss, and Geldmacher, 2001).

Defining and measuring apathy. The definition of apathy has undergone numerous revisions over recent years. The study of apathy as a neuropsychiatric construct in neurological disorders began in 1990 (Marin, 1990; Burns, Folstein, Brandt, and Folstein, 1990; Robinson and Starkstein, 1990). While the term apathy (derived from the Greek term *pathos*, meaning passions) is conventionally described as the absence or lack of emotion, feeling, interest, or concern (Marin, 1990, 1991), Marin considered this description as lacking due to its failure to address a

variety of other features present in the apathetic patient. Marin (1991) proposed to define apathy as a distinct psychiatric syndrome characterized by *motivational impairment*, which he described as "a deficit in the direction, intensity and persistence of goal-directed behavior." Marin proposed that the clinical expression of apathy can be classified into three domains: (1) reduced goal-directed behavior (i.e., lack of productivity, effort, initiative, or perseverance; compliance or dependence on others to structure activity; diminished socialization or recreation), (2) reduced goal-directed cognition (i.e., lack of interests or lack of interest in learning new things or in having new experiences; lack of plans or goals; lack of concern about one's personal problems; lack of value attributed to goal-related domains), and (3) reduced emotional concomitants of goal-directed behaviors (i.e., flattened affect; reduced emotional intensity; lack of emotional responsiveness to positive or negative events) (Marin, 1991). His conceptualization of apathy as a disorder of drive and motivation slightly differs from other conceptualizations of apathy as more of a disorder of feeling and/or emotion expression (Starkstein and Leentjens, 2008). In fact, opinions differ on whether or not the criteria for apathy should include an emotional dimension.

More recently, the definition has evolved to highlight that initiation, or the lack of it, is key to the definition, whether that lack of initiation is in relation to behavioral action, cognitive action, or emotional action (Stuss, van Reekum, and Murphy, 2000; van Reekum et al., 2005; Levy and Czernecki, 2006). Stuss et al. (2000) defined apathy as "an absence of responsiveness to stimuli as demonstrated by a lack of self-initiated action." Levy and Czernecki (2006) viewed apathy as "a quantitative reduction of self-generated voluntary and purposeful behaviors" as compared to previous behavior, despite an unchanging environment or physical constraints.

In addition to experiencing *symptoms* of apathy, several neuropsychiatric disorders seem to produce a *syndrome* of apathy, in which a pattern of apathy symptoms from each domain are

present but this motivational impairment is not secondary to cognitive or intellectual impairment (i.e., dementia), emotional distress (i.e., major depression), or diminished level of consciousness (i.e, delirium or drowsiness) (Marin, 1990, 1991). Due to the fact that the many patients experience apathy in the presence of depression or dementia, Starkstein (2000) adapted diagnostic criteria for the diagnosis of apathy syndrome that allowed for the diagnosis of apathy even in the presence of depression or dementia, assuming that the symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning.

Discussion continues regarding a consensus as to the appropriate gold standard for clinical diagnosis of apathy. Some suggest that apathy is underrepresented in psychiatric classification systems, like the ICD-10 and DSM-IV. After all, apathy is not referenced in the ICD-10 (World Health Organization, 1993) and is only mentioned specifically in relation to four disorders of the DSM-IV (American Psychological Association, 1994), with no inclusion of the term "apathy" in the DSM-IV glossary. Discussion regarding differential diagnosis and whether apathy should appear as a stand-alone disorder in the DSM-V has begun (Stephenson, 2005). If not included as a stand-alone disorder, potential improvements of the status of apathy, including clarifying the definition, adding apathy to the glossary of the DSM, or creating a reference to help direct clinicians to the range of disorders commonly associated with apathy, are being considered by DSM-IV Editor (Stephenson, 2005).

The majority of clinical research studies thus far have defined apathy by using self-, relative- and clinician-rating scales that examine the presence, frequency, and severity of apathy symptoms. Psychometric support exists for a number of such instruments and cut-off scores have been established for several to indicate the presence of clinically significant apathy. Such cut-off scores have been determined based on either the presence of a bimodal distribution or the

identification of scores that indicate apathy levels of 1 ½ – 2 standard deviations above the mean of healthy elderly controls. For instance, the *Apathy Evaluation Scale (AES)*, developed by Marin and colleagues in 1991, was one of the first instruments created to assess apathy in neurologic populations and continues to be widely used due to its strong psychometric support (Marin and Wilkozs, 2005). The *AES* consists of 18 items, scored on a four-point Likert scale, that assess emotional, cognitive, and behavioral symptoms of apathy. It has been validated for the assessment of apathy in patients with PD, Alzheimer's disease and other dementias, stroke, and major depression (Pluck and Brown, 2002; Marin, Biedrzycki, and Firinciogullari, 1991) and has demonstrated adequate reliability and validity for use in PD (Pluck and Brown, 2002; Starkstein et al., 1992a). The cut-off score of 38 on the self-rating scale, a score indicative of apathy levels of 1 ½ standard deviations above the mean for healthy elderly controls, has been established to indicate significantly elevated apathy (Marin et al., 1994). The *AES* was later modified and abridged to the 14-item *Apathy Scale* (*AS)* (Starkstein et al., 1992a). Similar instruments include the *Frontal Systems Behavior Scale (FrSBe*; Grace and Malloy, 2001), formerly known as the *Frontal Lobe Personality Scale (FLOPS*; Grace, Stout, and Malloy, 1999) and the *Lille Apathy Rating Scale (LARS;* Sockeel et al., 2006). Shorter screening instruments include the apathy item (item 7) of the *Neuropsychiatric Inventory (NPI*; Cummings et al., 1994), which assesses the frequency and severity of apathy; the *Apathy Inventory (AI;* Robert and colleagues, 2002), a three item apathy scale that measures the frequency and severity of emotional blunting, lack of initiative, and lack of interest; and item 4 (assessing apathy) on Part I of the *Unified Parkinson's Disease Rating Scale (UPDRS)*. For the purposes of the present study, the assessment of apathy will focus on apathy symptom severity based on number and severity of apathy symptoms using the *AES*, and a cut-off score will be utilized to identify patients with elevated apathy.

Pathogenesis of apathy. Understanding the neural basis of apathy requires an understanding of motivation circuitry, including the neuroanatomical regions and neurochemical pathways involved. Core neural structures underlying motivation, or self-generated voluntary goal-directed behavior, include the ventral tegmental area (VTA), nucleus accumbens (NA), striatum (i.e., caudate and putamen), ventral pallidum (VP), medial dorsal nucleus of the thalamus (MD), and the anterior cingulate (AC) of the prefrontal cortex (PFC). Some of these functionally connected regions, specifically the AC, NA, VP, and MD, have been referred to as the cortico-striatal-pallidal-thalamic circuit (Kalivas, Churchill, and Klitenick, 1993; Marin, 1996) and damage to regions along this pathway has been strongly associated with disorders of motivation (i.e., apathy, abulia, akinetic mutism) (Marin, 2005).

The VTA, NA, and VP have been referred to as the "core circuit" of motivation (Kalivas et al., 1993; Marin, 1996), although some consider the AC as part of the "core circuit" due to its interconnection with the other components and its important role in motivational aspects of decision-making (Marin, 1996). The medial portions receive input from the amygdala, hippocampus, and AC, therefore modulating information in the "core circuit" and influencing response selection based on current environmental stimuli, previously reinforcing stimuli, and the organism's drive state (Marin and Wilkosz, 2005; Marin, 1996). The lateral portions of the "core circuit" project via the MD to the motor cortex, basal ganglia, pedunculopontine nucleus, reticulospinal tract, and AC. The translation of motivation into action depends on the information flow through this "core circuit" and damage to the circuit results in impairment to the initiation and maintenance of goal-directed behavior and locomotor action (Kalivas et al., 1993; Pierce and Kalivas, 1997).

These structures communicate largely by way of dopamine, a neurotransmitter that travels through the brain via the dopaminergic pathways (i.e., nigrostriatal, mesolimbic, and mesocortical) described previously. Dopamine is centrally involved in motivation and reward processing as well as in the personality characteristic of novelty/sensation seeking (Marin and Wilkosz, 2005). Interference to the structures of this motivational circuit, whether from localized damage (e.g., frontal lobe, amygdalar, hippocampal, or basal ganglia lesions) or disease (e.g., PD, Alzheimer's disease, or Huntington's disease), often results in the presence of apathy or more severe motivational impairment (i.e., athymhormia, abulia, akinetic mutism).

Levy and Dubois (2006) maintain that apathy can stem from different neuroanatomical mechanisms. Emotional apathy appears to be related to lesions of the orbital-medial PFC or related basal ganglia subregions; cognitive apathy appears to be related to lesions of the dorsolateral PFC and related basal ganglia subregions; and apathy that reflects a problem with "auto-activation" appears to be related to lesions to the associative and limbic regions of the internal globus pallidus.

Negative consequences of apathy. Apathy has been associated with a host of negative consequences for a variety of patients and their caregivers, from impairments in cognition and daily functioning to poor illness outcome and increased likelihood for institutionalization to increased caregiver distress. Several studies have shown an association between apathy and cognitive impairment (Starkstein et al., 1992a; Levy, 1998; Aarsland et al., 1999b; Kuzis et al., 1999; Isella et al., 2002; Pluck and Brown, 2002; Feil, Razani, Boone, and Lesser, 2003; Starkstein, Ingram, Garau, and Mizrahi, 2005; Butterfield et al., 2010). In a sample of Alzheimer's disease patients, those with apathy had significantly more severe cognitive deficits than those without apathy (Starkstein et al., 2005). In a sample of PD patients, apathy predicted

impairments in executive functioning and memory over and above that of depression (Butterfield et al., 2010). Findings from several studies (e.g., Isella et al., 2002; Pluck and Brown, 2002) suggest that apathy is more strongly associated with cognitive impairment than is depression, and many authors encourage careful examination of symptoms in order to identify the presence of dysphoria (e.g., sad mood, guilt, pessimism) versus apathy (e.g., decreased initiation, decreased persistence) (Boyle and Malloy, 2004).

Some studies suggest that apathy may, in fact, be a predictor of dementia. In a sample of apathetic and non-apathetic Alzheimer's disease patients, patients in the apathetic group showed a significantly faster rate of cognitive decline than those in the non-apathetic group over time (Doody et al., 1995). One longitudinal study (Copeland et al., 2003) showed that individuals with MCI who exhibited the symptom of "passivity" (i.e., apathy) had higher rates of conversion to dementia over a three year time period. Another longitudinal study (Starkstein et al., 2006) found that, in patients with mild and moderate dementia, apathy was associated with faster declines in cognitive ability and daily functioning. A recent study demonstrated that MCI patients with apathy showed significantly higher rates of conversion to dementia (60%) than MCI patients classified as either depressed (7.9%) or depressed and apathetic (19%) (Vicini Chilovi et al., 2009). Even when controlling for age, functional status, and cognitive status, the presence of apathy in MCI patients was a positive risk factor for conversion to dementia, whereas depression was not. Results of these studies suggest that apathy may be a marker of conversion from MCI to dementia. Onyike et al. (2007) suggests that apathy in elderly individuals may be considered a "predementia phenotype," stating that "dementia may begin with apathy."

In terms of the negative association between apathy and functional abilities, Starkstein and colleagues (1993) found that patients in a stroke inpatient unit with apathy and depression were more functionally impaired than patients with apathy alone, but that apathetic patients without depression were more functionally impaired than those with depression alone and were more functionally impaired than those with neither apathy nor depression. In another study (Resnick et al., 1998), apathy level upon admission into a geriatric inpatient rehabilitation unit (i.e., reasons for admission included hip fracture, stroke, etc.) was the second strongest independent predictor of daily functioning at discharge. Apathetic Alzheimer's disease patients scored lower on activities of daily living than non-apathetic Alzheimer's disease patients, regardless of whether these patients had comorbid depression (Starkstein et al., 2001). Hamilton et al. (2003) observed that apathy independently predicted functional disability in patients with Huntington's disease. Further, high apathy has been predictive of poor daily functioning and poor quality of life in normal elderly (Cahn et al., 2000), dementia populations (Norton et al., 2001; Samus et al., 2005), PD (Pluck and Brown, 2002; Weintraub, Moberg, Duda, Katz, and Stern, 2004), and patients with subcortical infarcts (Reyes et al., 2009), and has been predictive of poor adaptive, social, and occupational functioning in patients diagnosed with schizophrenia (Velligan, Ritch, Sui, DiCocco, and Huntzinger, 2002).

Elevated apathy can also result in poorer treatment compliance, social and community participation, and even illness outcome. Resnick et al. (1998) found that geriatric patients in an inpatient rehabilitation unit participated less in rehabilitation when apathy was high, while those with low levels of apathy participated in rehabilitation more frequently. In a sample of TBI patients, those with elevated apathy showed unsatisfactory integration into home and community activities (Cattelani et al., 2008). Mayo and colleagues (2009) found that even minor apathy was

strongly and negatively associated with recovery of social and community participation post-stroke, and apathy had a significant negative effect on physical function and general health over the first twelve months post stroke (Mayo, Fellows, Scott, Cameron, and Wood-Dauphinee, 2009). In a sample of schizophrenic patients, apathy was independently related to poor functional outcome, poor treatment compliance, and low treatment benefit (Kiang, Christensen, Remington, and Kapur, 2003). Tattan and Creed (2001) observed that apathy also was more common in schizophrenic patients who were noncompliant with their medication than in those who demonstrated medication compliance.

Studies have shown that caregiver distress is associated with ratings of patient apathy at all levels of disease severity (Kaufer et al., 1998; Boyle and Malloy, 2004; Aarsland et al., 2007). When patients display a reduction in goal-directed behavior and initiative, spouses and caregivers often carry the burden of assuming responsibilities of the patient or constantly having to prompt the patients to engage in necessary activities. This might include the caregiver having to remind the patient of the day's agenda, having to prompt the patient to take his/her medications, pay bills, get dressed, or do necessary household chores. In addition, caregivers may feel somewhat isolated if the patient is failing to initiate conversation, is generally less interested in social interaction. Spouses may become discouraged that they have become the sole member of the household to plan and initiate couples activities, such as vacations or day trips. Caregivers sometimes become frustrated with the patient and may misinterpret the patient's lack of initiative as laziness or contempt. Hence, apathy can contribute to caregiver stress whether or not it is of concern to the patient him/herself.

Treating apathy. Due to the many negative impacts of apathy for patients and caregivers, identifying effective treatments to attenuate apathy is of increasing interest. There are

no medications approved for the specific treatment of apathy (Chase, 2010). Surprisingly few studies have conducted methodologically sound randomized controlled trials (RCT) to investigate the efficacy of pharmacologic or behavioral treatments on reducing apathy. Of the few that have been conducted, most have assessed apathy secondarily rather than as a primary outcome variable. Behavioral strategies are often preferred by individuals preferring to defer pharmacologic treatment. In addition, some studies suggest that behavioral strategies provide an added benefit when combined with pharmacologic treatment in patients with anxiety or mood disorders (Pampallona, Bollini, Tibaldi, Kupelnick, and Munizza, 2004; Mavissakalian, 1990). To date, many more treatment studies have focused on the use of medications as compared to the use of behavioral strategies on reducing elevated apathy in patients. Notably, most pharmacologic treatment studies have targeted dementia populations with dopaminergic agents or acetylcholinesterase inhibitors or schizophrenic patients with atypical antipsychotics (Chase, 2010).

Pharmacologic Treatments. Apathy and amotivation have been associated with neurochemical abnormalities, most notably deficient dopamine signaling (Guimaraes, Levy, Teixeria, Beato, and Caramelli, 2008). Dopamine has been considered the principle neurotransmitter of goal-directed behavior and motivation (Duffy and Kant, 1997). It has been suggested that the reduction of dopamine seen with advancing age might explain the increase in passivity and amotivation that is seen in healthy elderly individuals (Shulman, 2000). In addition, PD patients score lower on novelty-seeking than age-matched and disability-matched controls, attributed to the known disease-related dopamine deficiency (Menza, Forman, Goldstein, and Golde, 1990; Menza, Golbe, Cody, and Forman, 1993). For this reason, several studies have attempted to treat apathy using medications that enhance the neurotransmission of dopamine and

other catecholamines (i.e., epinephrine, norepinephrine), which all derive from the same precursors and are part of a shared synthesis pathway.

Methylphenidate is considered one of the most promising pharmacologic agents for future research on the treatment of apathy (van Reekum et al., 2005) and many studies have evaluated its effect on apathy in patients with PD, demented elderly, and major depressive disorder (Padala et al., 2007; Keenan et al., 2005; Chatterjee and Fahn, 2002; Jansen et al., 2001). Methylphenidate is a dopamine reuptake inhibitor that blocks the dopamine transporter and stimulates the release of dopamine and norepinephrine into the synapse, resulting in an overall increase of dopamine in the synapse (Volkow et al., 1998, 2001). The results of one small RCT (n = 13), one open-label study, and three case reports suggest that methylphenidate is effective in improving apathy in neurodegenerative diseases (Drijgers, Aalten, Winogrodzka, Verhey, and Leentjens, 2009). Other catecholamine agonists, including levodopa (L-Dopa), dopamine agonists, amantadine, and selegiline, have also demonstrated a positive effect on apathy in select cases of PD, traumatic brain injury, stroke, and depression (Roth, Flashman, and McAllister, 2007; Marin, Fogel, Hawkins, Duffy, and Krupp, 1995; Czernecki et al., 2002; van Reekum et al., 1995; Kraus and Maki, 1997; Newburn and Newburn, 2005). Atypical antipsychotics (e.g., resperidone, olanzapine, clozapine), which target the dopamine system, have also proven effective in reducing the negative symptoms of schizophrenia, which resemble the symptoms of apathy (van Reekum et al., 2005). According to a review of apathy treatment studies (van Reekum et al., 2005), five out of six RCTs (with a total N of 3,182 patients) showed a decrease in negative symptoms as a result of atypical antipsychotic medication.

In addition, cholinergic and serotonergic pathways also play a modulatory role in motivation (Shulman et al., 2000) and may effectively reduce apathy in certain cases. A recent

review, conducted by Drijgers and colleagues (2009), examined several pharmacologic treatment studies conducted in neurodegenerative disease populations (e.g., Alzheimer's disease, PD, Lewy body dementia, frontotemporal dementia, vascular dementia). These authors concluded that, given that the majority of these studies lacked sufficient information to calculate effect sizes or to determine the clinical relevance of the effects, the overall efficacy of cholinesterase inhibitors to treat apathy is inconclusive and firm conclusions can not be drawn.

Non-pharmacologic Treatments. There is increasing interest in the identification of non-pharmacologic treatments, as many patients wish to avoid dependence on an increased number of daily medications. Non-pharmacologic interventions have also shown an added benefit when used in conjunction with medical treatment (Pampallona et al., 2004; Mavissakalian, 1990). Such interventions provide tools and strategies to be used by patients and their spouses or caregivers to increase patient independence, patient/caregiver well-being and quality of life, and to reduce caregiver burden. Surprisingly few studies have investigated non-pharmacologic methods of treating elevated apathy, and all of the existing behavioral studies have been conducted with dementia patients. We are unaware of any studies that have yet investigated non-pharmacologic treatment approaches to reducing apathy in PD patients. Activity therapy, cognitive-communication therapy, emotion-oriented care, multisensory stimulation, and psychomotor therapy are behavioral approaches that have been investigated for the treatment of apathy in demented patients with neurodegenerative disease (i.e., mostly Alzheimer's disease) (Roth, Flashman, and McAllister, 2007). These will be outlined here.

Politis et al. (2004) conducted a RCT that investigated the impact of a 4-week activity-based intervention on apathy in mixed dementia patients (i.e., diagnosed using the DSM-IV) living in long-term care. Thirty-six patients were randomized to either a kit-based activity

therapy group or a time-and-attention control group. Activity therapy consisted of mental stimulation activities that were provided in a standardized, structured manner. Sessions lasted thirty minutes and occurred at a frequency of three times per week. At each session, patients chose from a selection of kit-based activities (i.e., geography, fun foods, farm animals, vegetables, and musical instruments). Each activity contained questions related to the activity topic. Each question served as a prompt for reflection and discussion. Many questions were similar to trivia questions and required the participant to discuss past experiences as they related to the topic. Participants of the control group spent the same amount of time in sessions. Rather than a structured interaction, however, these sessions were unstructured and consisted of participant-led discussions on the participant's discussion topic (i.e., past history, interests) or activity (i.e., puzzles, artwork, reading) of choice.

Results of the study revealed a statistically significant reduction in apathy, as rated using the *NPI,* along with improved quality of life and a reduced need for cueing in non-study activities for individuals in both groups two weeks post-treatment. However, there was no significant difference between groups. These results suggest that an activity-based mental stimulation intervention improves dementia patients' level of apathy, quality of life, and need for cueing, but not any more benefit than one-on-one attention. The improvement in both groups may be explained by seemingly similar quality of engagement with activities and with the interventionist.

Chapman et al. (2004) evaluated the effect of an 8-week cognitive-communication therapy on apathy in patients with mild to moderate Alzheimer's disease. Fifty-four participants were included in the study and were assigned to one of two groups: cognitive-communication therapy plus donepezil or donepezil alone. The therapy consisted of twelve hours of therapy over

a period of eight weeks and incorporated participant-led discussions, conversations about the patient's life history, psychoeducation about Alzheimer's disease, and homework assignments. Results revealed a trend for decreased apathy, as measured using the *NPI*, in the combined treatment group versus the medication-only group even after a twelve month follow-up.

Other studies have investigated the effect of validation/integrated emotion-oriented care on apathy in dementia patients (Verkaik, van Weert, and Francke, 2005; Finnema et al, 1998, 2000; Droes et al., 1999; Schrijnemaekers, van Rossum E, van Heusden MJT, and Widdershoven, 2002). This type of care seeks to restore feelings of self-worth and reduce levels of stress by validating the patient's emotional ties to his/her previous life experiences (APA, 1997). It may also incorporate other methods of emotion-oriented care, such as supportive psychotherapy or gentle care, which aims to provide an atmosphere of safety, comfort, and closeness for the patients (Verkaik et al., 2005; Buijssen, 1991). Results of a review (Verkaik et al., 2005), which evaluated the effect of validation/integrated emotion-oriented care on apathy in patients with dementia and included one multi-site RCT of 146 patients with a "usual care" control group, revealed no significant effect of this treatment on apathy.

Kragt et al. (1997) examined the effect of multisensory stimulation (MSS), or Snoezelen, therapy on apathy in sixteen dementia patients. MSS was initially developed as a leisure center that provided sensory stimulation in a number of modalities (i.e., auditory, visual, and tactile) to patients with severe learning disabilities. The treatment has been tried in dementia populations in an effort to counter the lack of stimulation that often occurs with these patients due to their severe cognitive impairment and their inability to engage in many tasks. In this study, patients were placed in a controlled environment in which auditory, visual, and/or tactile sensory stimulation was provided. MSS therapy was compared to a usual care control condition. Results

revealed reduced apathy over a three-day evaluation period. Baker et al. (2003) evaluated the effect of MSS on behavior, mood, and cognition in a multi-national RCT of 136 dementia patients assigned to a MSS therapy or an activity group. Each patient participated in eight thirty-minute sessions over a period of four weeks. Results suggested that MSS and activity therapies had little effect on behavior, mood, or cognition immediately post-treatment or at follow-up. Apathy, as measured by five items of the Behaviour Rating Scale of the Clifton Assessment Procedures for the Elderly (Pattie and Gilleard, 1979) did improve somewhat but only in patients with more severe dementia who were assigned to MSS therapy.

In another RCT design, Hopman-Rock et al. (1999) evaluated the effect of Psychomotor therapy versus a control condition on apathy in 92 elderly patients with cognitive impairment. Psychomotor therapy consisted of 15 sessions over a period of approximately 8 weeks and involved participation in a variety of physical activities, sports, and games, as well as relaxation training. No significant change in apathy was observed.

There is limited evidence available from which to determine whether non-pharmacologic treatments may be effective for attenuating apathy in patients with dementia, although some studies have shown promising results. No studies, however, have investigated such treatments in PD patients despite that rates of elevated apathy are significantly greater in even non-demented PD patients as compared to age-matched controls (Zgaljardic et al., 2007; Onyike et al., 2007) and despite its negative consequences on patients and caregivers (van Reekum et al., 2005; Onyike et al., 2007).

Apathy in PD

PD is a classic example of a subcortical disorder in which apathy is a well-recognized feature (Isella et al., 2002; Pluck and Brown, 2002; Aarsland et al., 1999b; Starkstein et al., 1993;

Marsden and Parkes, 1977). "Clinical" apathy (i.e., identified by a cut-off score established from a bimodal distribution of apathy or indicating a level that is 1 ½ standard deviations above the mean of healthy elderly controls) has been identified in approximately 40% to 45% of PD patients (Isella et al., 2002; Starkstein et al., 1992a), compared to 6.8% in healthy older adults (Onyike et al., 2007), with apathetic syndromes (i.e., not secondary to depression, delirium, or dementia) present in about 12% of PD patients (Starkstein et al., 1992a).

The origin of apathy in PD is unclear, however, there exist several hypotheses. First, apathy appears to be a result of neurological disturbance rather than a result of psychosocial limitations of physical disability. Apathy does not correlate with severity of disease. In addition, Pluck and Brown (2002) demonstrated that, while PD and osteoarthritis are similarly chronic, progressive conditions that cause considerable disability, "clinical" apathy (as determined by a previously established cut-off score of 38 on the AES; Marin et al., 1994) was found in 37.8% of PD patients, but no evidence of "clinical" apathy (i.e., 0%) was present in osteoarthritic patients.

Apathy may be a result of disruption to any one or more of the many pathways and regions affected in PD, including dopaminergic, cholinergic, noradrenergic, or serotoninergic pathways, or the affect of cortical lesions in associative cortices (Levy and Czernecki, 2006). It is hypothesized that the hallmark dopamine depletion of PD may contribute (Levy and Dubois, 2006). Czernecki et al. (2002) demonstrated that apathy fluctuated between "off" and "on" states in PD patients, suggesting that apathy is at least partly dependent on dopamine. In other words, the reduction of dopamine in the dopaminergic pathways (e.g., mesocortical, mesolimbic) may ultimately interrupt normal reward processing, goal-directed behavior, and initiation. However, apathy is present in PD even in relatively early stages of the disease, when the dopamine mesocortico/limbic pathways are relatively spared (Levy and Czernecki, 2006). In addition, tasks

assessing reward sensitivity and changes in reward contingencies have been found to not be impaired in PD patients even when tested in the "off" state (Levy and Czernecki, 2006). Further, apathy can be unresponsive to dopaminergic treatment and remains an important problem in many PD patients receiving dopaminergic treatment (Sockeel et al., 2006).

Another hypothesis to explain apathy in PD suggests that apathy (along with several other signs of the disease) may result from the inability of the basal ganglia to adequately identify and separate relevant signals to be sent to the prefrontal cortex (Filion and Tremblay, 1991; Tremblay, Filion, and Bedard, 1989; Tremblay and Filion, 1989). In other words, the signal to noise ratio is diminished and relevant signals are clouded. Levy and Czernecki (2006) suggest that this may contribute to apathy by making it difficult for output structures (i.e., prefrontal cortex) to disambiguate the relevant signal, causing problems in decision making and resulting in aborted or delayed responses.

The negative consequences of apathy that have been presented in this paper extend to non-demented PD patients. Several studies have shown an association between apathy and cognitive impairment in non-demented PD patients, even when controlling for the influence of depression (Starkstein et al., 1992a; Aarsland et al., 1999; Isella et al., 2002; Pluck and Brown, 2002; Butterfield et al., 2010). In PD, apathy has been reported to impede the treatment of motor disability, lead to increased disability, poor daily functioning (i.e., ADLs), and a diminished quality of life (Pluck and Brown, 2002; Weintraub et al., 2004; Barbas, 2006). Authors have urged the pursuit of treatment for apathy for non-demented PD patients as quality of life in this population and their carers may be stabilized or enhanced with early detection and treatment of elevated apathy (Zgaljardic et al., 2007).

A Proposed Intervention for Apathy in PD

Given that apathy reflects amotivation evidenced by a decrease in goal-directed behavior, and considering the positive of behavioral activation therapies for improving activity level and mood in depression as well as the positive results of activity engagement therapies in some studies on decreasing apathy in dementia patients, we hypothesize that a treatment aimed at increasing goal-setting and activity identification and engagement, such as those components utilized in Behavior Activation Therapy (BAT; Lewinsohn, 1975), will benefit the apathetic patient and their spouses or caregivers. Activity planning, scheduling, and monitoring provides an external structure that is favorable for PD patients, while facilitating self-management skills and patient independence. To provide added external support, we propose to incorporate an external cueing component to the intervention, which will consist of regular reminder call prompts. Further, this intervention will exist as a primarily telephone-based intervention in an effort to reduce cost while addressing several common barriers to treatment that are important to consider when working with patients diagnosed with PD. Telephone treatment delivery reduces travel and waiting time, allows for more flexible scheduling, makes treatment available to individuals with transportation problems and those who live far from the treatment center, and may improve rates of participation and adherence (Simon, Ludman, Tutty, Operskalski, and Von Korff, 2004).

Treatment Rationale.

Behavioral Activation Therapy and Activity Scheduling. Behavioral Activation Therapy (BAT) is a treatment initially developed as a treatment for depression (Lewinsohn, 1975) and emerged following a component analysis of Cognitive-Behavioral Therapy (CBT; Jacobsen et al., 1997) in which researchers concluded that the cognitive aspect of CBT added little to the

treatment of depression relative to the behavioral component. Depression, from a behavioral perspective, is maintained by environmental circumstances that reinforce and perpetuate depressive behavior, and by a lack of environmental circumstances to reinforce healthy behavior. Therefore, the goal of BAT for treating depression is to eliminate factors that reinforce depressed behavior and to increase activities that positively reinforce engagement in healthy behaviors. It involves an assessment of factors that may be maintaining depressive behavior, assessment of current activity engagement, construction of an activity hierarchy to plan pleasurable activities for the coming weeks, and regular monitoring of engagement in these planned activities. Interventionists, family members (if involved), and the depressed individual themselves are to provide positive reinforcement when pleasurable activities are engaged in.

Lejuez, Hopko, and Hopko (2001) developed a Brief Behavioral Activation Treatment for Depression (BATD). BATD begins with a baseline evaluation of depressive symptoms, baseline daily monitoring of occurring activity engagement, and a functional evaluation of whether one's environment is supportive of healthy versus depressive behavior. This is followed by guided identification of potential activities, selection of 15 target activities that range from easy to difficult, and graded monitoring of activity engagement. Finally, subjects are to schedule rewards for themselves for achieving weekly goals. This gives the subject something to look forward to and provides a source of motivation for engaging in activities and for completing the monitoring logs. This proposed study utilized the general structure as well as specific elements of *BATD* to target apathy in non-demented PD patients. Specific BAT-derived elements included in our treatment protocol included (1) baseline assessment of the target outcome variable (i.e., apathy) and level of activity engagement, (2) weekly evaluation and monitoring of activities, (3)

identifying activities, (4) creating an activity hierarchy, (5) charting progress using existing activity logs, and (6) planning rewards for meeting goals.

Goal Setting and Self-Regulation. As Locke and Latham (1991, 2002) and others have avowed, goal setting is a cornerstone of motivation and has a considerable impact on directing and organizing behavior. Goals can stimulate goal-directed behavior and cognition by enhancing effort and persistence, providing direction, and motivating strategy development due to the identification of discrepancy between the present state and the ideal/goal state (Bandura, 1991; Locke and Latham, 1991, 2002). The most important features of effective goal setting include goal specificity, goal difficulty, goal commitment, and feedback (Bandura, 1991; Bandura and Cervone, 1983; Locke and Latham, 1991, 2002). People with specific goals demonstrate greater on-task attention and strategic planning (e.g., who, what, when, where, why?). Such specificity also increases the likelihood of goal attainment. Effective goals must also be difficult but, importantly, attainable. Goals that are too easy fail to motivate the individual. Goals that are considered unattainable due to practical inability to attain (e.g., physical or cognitive inability), however, are discouraging. These goals are less likely to result in the feeling of competence; hence, the individual is less likely to put forth effort toward an unattainable goal. Further, individuals are more likely to be motivated by goals to which they are committed. Individuals often feel committed to goals that are self-set, as opposed to goals that are assigned to them. However, individuals can become committed even to goals that are assigned to them. Finally, the provision of feedback is essential in maintaining motivation. Individuals who receive feedback on their performance show more effortful performance than those that do not receive feedback (Bandura, 1991; Bandura and Cervone, 1983). Without such feedback, we are unable to

determine how well or how poorly we are performing and are unable to determine whether changes need to be made or new strategies adopted.

Another factor of goal setting that enhances motivation is the use of implementation intentions. Implementation intentions are plans that help individuals to (a) initiate, or get started toward, goal attainment, and (b) prepare themselves for potential set-backs that may interfere with goal attainment (Gollwitzer and Sheeran, 2006). They are effective in initiative goal striving and in enhancing persistence in the face of interference (Gollwitzer and Sheeran, 2006). Planning when, where, and how one will begin working toward a goal can trigger the desired behavior when that time and place are present. For example, one individual may have the goal of incorporating exercise into their daily routine. To help them to initiate engagement toward this goal, they may decide that they will begin exercising on Monday morning at 8am. Identifying a specific time and location increases the likelihood that the behavior will, in fact, be triggered. Ideally, when 8am on Monday morning comes around, the individual is triggered to perform the planned behavior. Determining a routine (e.g., "I will go for a 1 mile walk every weekday morning at 8am") also makes it more likely that these conscious intentions will become more automatic over time, which makes the goal less vulnerable to distraction (Franken, 2007).

Implementation intentions also prepare one for potential interferences, or set-backs. It is advantageous for an individual to contemplate potential interferences and plan their response to that interference ahead of time using an if-then frame. For example, "In an effort to prevent distraction from my goal, *if* I receive a phone call within 15 minutes prior to my scheduled walk, *then* I will not answer the phone call."

Self-generational deficits and the use of external cueing in PD. Internally-regulated self-generation is a well-studied, key feature of PD that manifests in several domains. These

deficits are a direct result of the disruption to the basal ganglia that occurs in the development and advancement of PD; the basal ganglia plays an important role in internally guided self-generation (Marsden, 1982). The common motor impairments of bradykinesia (slowness of movement) and akinesia (inability or delay in initiating movement) are especially evident when patients attempt to self-initiate behavior (vs. acting in response to an external cue). Interestingly, these impairments in self-initiation are remedied by external cues.

External sensory cues (e.g., visual, auditory, and cutaneous) have been used repeatedly in the rehabilitation of motor deficits, such as gait, in PD (Rubinstein, Giladi, and Hausdorf, 2002; Lim et al., 2005; Nieuwboer, Rochester, and Jones, 2008). Both single training sessions and extended training (i.e., 3-6 weeks) using external cueing have resulted in improved gait (i.e., walking speed, step length), balance, and transfers (Hausdorff et al., 2007; Morris, Iansek, Matyas, and Summers, 1996; Rochester et al., 2010; Nieuwboer et al., 2007; Mak and Hui-Chan, 2008; Sidaway, Anderson, Danielson, Martin, and Smith, 2006). Spatial cues, such as the presence of lines placed perpendicular to the walking path, have resulted in increased stride length and gait velocity in PD patients (Martin, 1967). The provision of auditory cues, such as the use of a metronome, has improved gait velocity and cadence (Thaut et al., 1996). Cutaneous cues, provided using electrical stimulation on the hand or earlobe, have shown to improve the timing and kinematics (i.e., force production, velocity of movement) of gait initiation in PD patients (Burleigh-Jacobs, Horak, Nutt, and Obeso, 1997). External cues have even been shown to improve the initiation and structure of eye movements in PD patients (Winograd-Gurvich et al., 2004).

In addition to aiding motor performance, several studies have demonstrated that many cognitive performance deficits in PD can be remedied by the use of external cues. It is well-

known that PD patients (and others with lesions to the basal ganglia) display a cognitive inertia that is demonstrated by deficits in executive cognitive tasks that involve self-generation, such as those involving set-shifting, planning, or the self-generation of cognitive strategies, rules, or verbal fluency (Levy, 2007). Several studies have demonstrated that PD patients perform poorly on tasks when cues are absent, but that performance improves with the use of external cues (e.g., Buytenhuijs et al., 1994; Brown and Marsden, 1988; Taylor, Saint-Cyr, and Lang, 1986, 1990; Breen, 1993). For instance, Brown and Marsden (1988) demonstrated that PD patients performed poorly on executive functioning tasks in which the patients had to rely on their own internal cues or strategies and on tasks that required self-directed task specific planning, but demonstrated intact performance when external cueing or external stimulus control was provided. Control subjects, however, performed equally well on the task regardless of whether external cues were provided or not. Similar, PD patients show impairment on tasks of attention that require internal control, but perform well when external control is provided (Brown and Marsden, 1990).

On memory tasks, PD patients perform more poorly than age-matched, healthy control subjects on free recall, however, their performance improves to normal on recognition tasks (e.g., Weiermann, Stephan, Kaelin-Lang, and Meier, 2010; Breen, 1993). In other words, while PD patients have difficulty retrieving items that were previously encoded, they are able to retrieve these items when they are provided with an external cue. Buytenhuijs and colleagues (1994) investigated the differential influence of explicit versus implicit cues on memory performance in PD patients. The authors used the California Verbal Learning Test (Delis, Kramer, Kaplan, and Ober, 1987), a verbal memory test comprised of a list of several words from four semantic categories. Subjects were not made explicitly aware of the semantic organization of the items; therefore, the semantic relationship of the items was considered an implicit cue that must be

generated by the subject to help them in recalling the items learned. Subjects that recalled items in the order that the experimenter read them were said to be guided by explicit cues external to the subject. In this study, PD subjects recalled items in a serial fashion, reflecting a more externally imposed strategy, whereas control subjects recalled items in semantic clusters, a result of an internally generated strategy. A follow-up study demonstrated that when PD patients are made aware of semantic clustering- in other words, when semantic clustering is externally provided as an explicit strategy- their memory recall improves (van Spaendonck et al., 1996). This suggests that PD patients use this recall strategy when prompted but do not initiate the use of the strategy on their own. Kritikos et al. (1995) has suggested that explicit cues improve performance in PD patients by replacing internally generated cues that are defective as a result of basal ganglia disruption.

In summary, several studies have demonstrated that the use of external cues can compensate for the reduction in self-generation ability in PD patients resulting from disruption to the basal ganglia and frontal-subcortical circuitry. The present intervention was designed to address this hallmark self-initiation deficit (1) by supplying external sources of cueing and (2) by increasing engagement in pleasurable activities through providing increased structure and planning. The intervention was designed to reduce reliance on spouses or caregivers and to increase independence in the PD patient.

Purpose of the Proposed Study

The purpose of the present study was to develop and gather pilot data on the acceptability, feasibility, and estimated effectiveness of a 6-week activity scheduling and monitoring intervention, that incorporated an external cueing component to target disease-related self-generational deficits, on reducing levels of apathy in non-demented, highly apathetic PD

patients. Secondly, this study sought to investigate whether this intervention improved patient depression, daily functioning, and quality of life, and whether it effectively improved burden, distress, relationship satisfaction and quality of life in patients' caregivers/spouses.

To our knowledge, clinical trials investigating the effect of non-pharmacologic interventions on motivational deficits have not been conducted with non-demented PD patients despite the known negative effects of apathy on patients and their caregivers. Given that non-demented PD patients are still largely cognitively intact and may be at a point in their disease where maintaining their independence remains important to them, a non-pharmacologic treatment that improves existing apathy while decreasing reliance on their spouse or caregiver may be a treatment of choice for these individuals. As suggested by Zgaljardic et al. (2007), quality of life in this population may be stabilized or enhanced with early detection and treatment of elevated apathy.

Due to the time and expense that goes into conducting full RCTs, it is prudent for researchers to first conduct preparatory studies that assess whether a new treatment protocol holds promise for effective change. While internal validity of this study would be stronger with the addition of a randomized attention control group and larger sample size, a relatively recent shift in the approach to intervention research emphasizes a stage model that highlights the importance of feasibility and early phase studies in developing a foundation for future efficacy and effectiveness trials with new interventions in new populations (see Waskow, 1984; Onken, Blaine, and Battjes, 1997; Rounsaville and Carroll, 2001; van Teijlingen and Hundley, 2001; Kazdin, 2003; Robey, 2004). Completing a Phase One study within a three-stage model of intervention (Rounsaville and Carroll, 2001) not only helps the researcher to understand recruitment and retention challenges, acceptability of the program by the patient population

recruited, and the feasibility of implementing a larger randomized controlled trial before putting resources into such a study, but also has the potential to convince funding bodies that a larger study is feasible and worth funding (van Teijlingen and Hundley, 2001). Collection of pilot data will also allow us to estimate effect sizes of the intervention.

Given that this study is a pre-experimental design, treatment implementation/fidelity methods were enacted as recommended by Lichstein's Treatment Implementation model (Burgio et al., 2001) in order to ensure that the treatment was *delivered* adequately by interventions, *received* by participants as intended, and *enacted* by participants in their day-to-day lives as intended. Select strategies were implemented to improve these factors, such as the development of a treatment manual and use of an adherence checklist to guide uniform protocol delivery, didactic instruction and role plays during training and monitoring of new interventionists to ensure competency of treatment delivery, use of a planning meeting with the participant and the provision of a participant workbook to help with adequate treatment receipt, documentation of weekly activity engagement by both participants and interventionists to verify treatment receipt and enactment, and encouragement of participants' performance of skills as well as the provision of feedback during weekly phone contacts to improve treatment enactment.

Specific Aims. The current study had three specific aims:

Aim 1: Develop the Parkinson's Active Living (PAL) program protocol and materials to promote uniform treatment delivery. The structure and elements from an existing behavioral treatment, the *Brief Behavioral Activation Treatment for Depression* (Lejuez et al., 2001), were used as a foundation from which a manual for use by PAL interventionists was developed that outlines the PAL protocol. A workbook was be created for use by PD participants in the program that provides psychoeducation on apathy in PD, a description of the six week program, and

forms for their use in identifying activities and monitoring activity engagement over the course of the program.

Aim 2: Determine feasibility or ease of training new interventionists. Competency of program delivery was determined by interventionists' protocol adherence during role plays and during implementation of the protocol with patient participants. Adherence was calculated as a percentage using protocol adherence checklists created by the P.I..

Aim 3: Conduct a single-group study to obtain preliminary data feasibility of the PAL protocol for this population, to identify any additional logistical problems which might occur using the proposed methods, and to determine a within-subject effect by evaluating effect sizes. A one-arm, uncontrolled exploratory trial was conducted. Feasibility was investigated by calculation of attrition rates. Acceptability was investigated by examining satisfaction ratings provided by PD participants. Effect of treatment was determined by comparing pre-intervention and post-intervention ratings of our primary (i.e., apathy) and secondary (i.e., patient depression, patient quality of life, patient daily functioning, spousal burden) outcome variables. Correlations were also examined to determine correlates to response to treatment. The methods and results for each of the three aims will be described separately and in detail below.

Aim 1: Development of Parkinson's Active Living (PAL) Protocol and Materials

Method

In order to promote uniform treatment delivery, two documents were developed to facilitate treatment delivery of the PAL program: (1) a manual for use by interventionists, or Program Coaches, that outlines the treatment protocol and (2) a workbook for use by PD participants in the program.

The manual was modeled after the *Brief Behavioral Activation Treatment for Depression (BATD)*, developed by Lejuez, Hopko, and Hopko (2001) for the treatment of depression. Lejuez et al. (2001) provided several forms for activity and reward planning and monitoring that were adapted for use with PD patients within the current program. These forms were used to guide goal-setting and to provide an external structure for PD participants. Of note, this intervention was developed with the consideration of key features unique to PD patients, including an added external cueing component (i.e., automated phone call reminders to engage in planned activities several times weekly) to target the disease specific self-generation/self-initiation deficits, optional involvement of the spouse/caregiver during the training session to provide caregivers with psychoeducation about motivational deficits as well as tools and strategies to supplement and reinforce the individual treatment sessions, and the provision of material in both verbal and written form to facilitate learning and memory retention. This intervention was developed as a primarily telephone-based intervention to overcome potential barriers to treatment.

The PAL Program Coach Manual and the PAL Participant Workbook were developed by the P.I. with the help of two research assistants. The manual and workbook were reviewed by graduate students and research assistants in the P.I.'s clinical neuropsychology research lab. Once revisions were made based on this feedback, a focus group was organized consisting of PD patients and spouses. Participants were mailed a copy of the participant workbook prior to the meeting for their review.

The focus group was led by two research assistants, one who served as the primary moderator and one who served as an assistant to the moderator. Both were familiar with the program protocol and had been involved in the development of the manual and participant workbook. Research assistants were selected to serve as focus group moderators, rather than the

P.I., in order to increase the possibility of open, uncensored feedback from focus group participants. *Designing and Conducting Focus Group Interviews* (Krueger, 2002) was used to provide a basic structure, participant rules for the focus group, and guidance for the moderators. Following recommendations from Kruger (2002), the focus group consisted of six individuals (four PD patients and two spouses/caregivers of PD patients). Participants were seated at a conference table to enhance communication amongst participants. The meeting was initiated with a standard introduction that included a welcome and introduction of moderator and assistant, overview of the topic (e.g., purpose of the meeting, explanation of what the results will be used for, explanation of why participants of the group were selected), explanation of ground rules (e.g., no right/wrong answers, listen respectfully despite disagreement, talk to each other when appropriate). Participants were asked a list of questions, including general open-ended questions and pointed questions. Notes were taken by the assistant to the moderator throughout the meeting to record participant opinions and feedback to guide revisions.

Results

The focus group meeting lasted one and a half hours. Results of the meeting showed that participants expected the program to be feasible within a PD population, clear to understand and follow, and attainable. The patient workbook was judged to be readable and appropriate. Voluntary participation was deemed adequate. Suggested changes included reducing the number of goals to five, allowing flexible use of the *iPing* system (mild concerns that it may be obnoxious, although most participants did not express concern over this system), using the term "program" rather than "intervention", explaining the term "apathy" to avoid negative connotation, and emphasizing the difference between initiating an activity and persisting to complete an activity during psychoeducation at the Planning Session. Feedback resulted in minor changes to

the protocol, the manual, and the participant workbook. The final PAL Program Coach Manual and PAL Participant Workbook are may be available by contacting the author. A brief outline of each is provided below.

PAL Program Coach manual.

***Section 1: Copy of the Participant Workbook*.** A copy of the PAL Participant Workbook is provided in this section.

***Section 2: Instructions for each session*.** This section provides step-by-step instruction for the initial Planning Session and the six telephone sessions and includes a list of goals for the session, materials needed, and a script for Program Coaches to follow.

Section 3: How to set-up iPing. This section provides a description of the online *iPing* reminder call system as well as instructions for how to set up reminder calls for each participant. Computer screen-shots are provided for ease of training and use.

***Section 4: Important readings*.** This section includes relevant articles that may be of use for Program Coaches in helping them understand Parkinson's disease, apathy, and other relevant topics.

***Section 5: Extra forms*.** This section includes a copy of all forms used during the Planning Session for easy access for Program Coaches.

Participant Workbook.

Part 1: Introduction. This section provides a brief introduction to the PAL program, including a description of the program's purpose, a definition of apathy, a brief summary of the program, and a brief description of the role of their Program Coach.

Part 2: Program Rationale. This section provides more information on the definition and prevalence of apathy in Parkinson's disease, the potential influence of apathy on patients and

caregivers, the purpose of the program, and a theoretical rationale. The theoretical rationale includes an explanation of behavioral activation for the treatment of depression (Lejuez et al., 2001), goal-setting theory (Locke and Latham, 1991, 2002), implementation intentions (Gollwitzer and Sheeran, 2006), and PD self-generational deficits that can be aided through the use of external structure and cueing, in order to support the use of activity scheduling in the protocol.

Part 3: Program Overview. This section provides a brief overview of the program timeline and participants responsibilities.

Part 4: Step-by-Step Guide. This section provides a more detailed description of the timeline and participant responsibilities at each segment. Baseline evaluation, details of the Planning Session, and information on how to document activity accomplishments and how to report this information to the Program Coach are described.

Aim 2: Feasibility of Training Interventionists

Method

Four undergraduate research assistants were trained as interventionists to determine the ease at which this intervention could be learned and uniformly delivered by new interventionists (referred to as Program Coaches). Each interventionist attended three training sessions that included review of the program background, protocol, and materials and a series of role plays in which interventionists were able to display competence in proper treatment delivery. During the first training session, the P.I. guided trainees through a review of the program manual, forms, and assessment measures; they learned to administer baseline evaluations; and, received readings on apathy in PD, goal-setting theory, implementation intentions, and research on the benefits of external cueing in PD. The duration of the first session was approximately two hours. In the

second training session, trainees engaged in role plays. First, the P.I. modeled the role of the interventionist while the trainee acted as the study participant. The duration of the second session was approximately two hours. Next, trainees were encouraged to practice with each other, taking turns playing the role of interventionist and study participant. Finally, competence was assessed during a third session in a role play with the P.I., with the trainee acting as the interventionist and the P.I. acting as the client. The duration of the third session was approximately two hours.

Four newly trained interventionists were able to display an average of 97% adherence (94% for Planning Sessions, 100% for Phone Sessions) according to an adherence checklist (see Appendix) during a mock session role play with the P.I. at the end of training (see Table 1). They were able to demonstrate an understanding of goal-setting, the implementation intention process, and the use of activity scheduling and monitoring forms; show proficiency in the administration of the treatment protocol; and, demonstrate the ability to troubleshoot potential problems that participants or their caregivers may have during treatment participation.

Table 1

Summary of adherence ratings for newly trained interventionists during mock role play at the end of training

	Adherence during role play of Planning Session	Adherence during role play of Phone Session	Overall adherence score
Trainee 1	95%	100%	98%
Trainee 2	100%	100%	100%
Trainee 3	92%	100%	96%
Trainee 4	90%	100%	95%
Average adherence	**94%**	**100%**	**97%**

Due to initial difficulty identifying eligible participants in the Tampa Bay area where interventionists were trained and resided, slow recruitment speed, and brief time commitments of the trained interventionists, the P.I. ultimately served as the interventionist for 85% of the study participants. Three of the newly trained interventionists ran 1-2 participants each (15% of the total sample). To evaluate uniformity of treatment delivery through the duration of the study for this 15% of participants, these sessions were audio-taped and tapes were reviewed by the P.I. and assessed for adherence to the protocol using the training checklist. Adherence during these sessions ranged from 93% - 100%, with an average of 99% overall (96% for Planning Sessions and 100% for weekly phone sessions).

Aim 3: Phase One Exploratory Study

Method

Participants and procedure. 34 PD patients and 27 spouses/family members of PD patients were enrolled to participate in this study. Inclusion criteria included diagnosis of idiopathic PD, no history of other neurodegenerative disease, no current psychotic disturbance, AES $\geq$ 35, and MMSE $\geq$ 24. Individuals diagnosed with PD were initially recruited from the University of South Florida (USF) Parkinson's Disease Center of Excellence and from monthly PD support groups in the Tampa Bay area. Due to difficulty identifying eligible participants, recruitment was expanded to include the University of Florida's (UF) Center for Movement Disorders and Neurorestoration and PD support group meetings in Gainesville, The Villages, and Orlando.

To provide detail on recruitment method and challenges faced during the recruitment process, a detailed account of the recruitment process is provided here and presented in Figure 1.

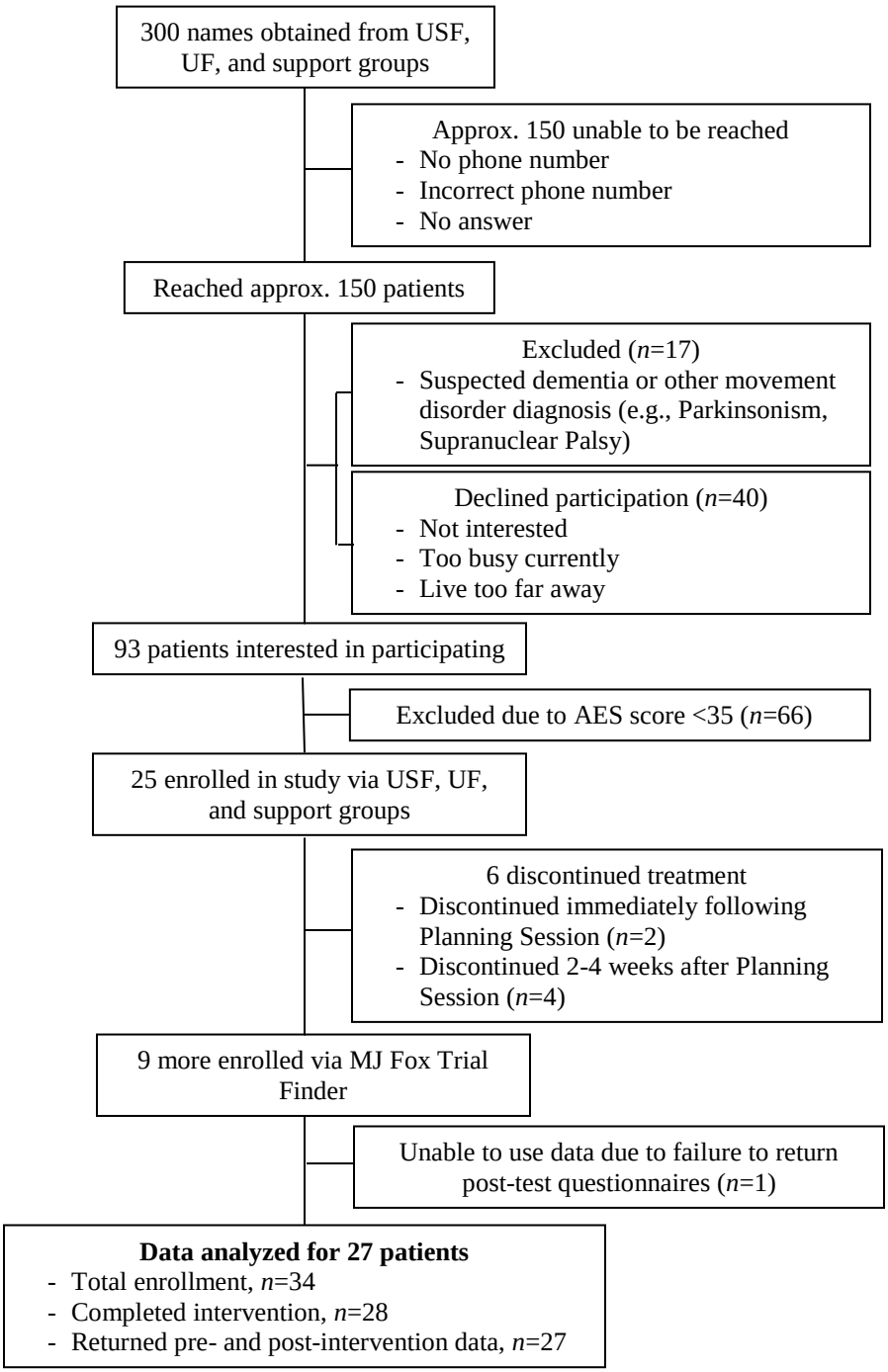

Figure 1. Recruitment diagram

Given that all calls were not recorded, the numbers here may underestimate exact values but provide an idea of the process. Review of available call logs revealed that of approximately 300 participant names received from the PD Center of Excellence at USF, patient databases at UF, and support groups, approximately 150 were able to be reached. Of these, 17 were excluded because of suspected dementia or other movement disorder diagnosis (e.g., Progressive Supranuclear Palsy, Lewy Body Dementia) and another 40 declined participation due to being busy, ill, living too far away, or not believing they were experiencing symptoms of apathy. Of the remaining 93 participants, 66 individuals were interested in participating but failed screening due to an AES score that was below the 35 point cut-off. Of these, 25 participants enrolled in our study and 19 completed all six weeks of the study.

Finally, a new resource intended to connect researchers with individuals diagnosed with Parkinson's disease who are interested in participating in research, the Michael J. Fox Trial Finder website, was discovered and utilized. This new resource proved to be the most efficient recruitment source. Hundreds of emails were sent out to PD patient members of the site whose city of residence was within 60 miles from Tampa, Gainesville, or Orlando. The exact number of responders from this recruitment method is unclear as they were directed to an online survey in the mass email. Nine individuals recruited from this method participated in our study within a 12 week period, one of whom did not return post-test questionnaires. Due to attrition (which is discussed in detail later), 27 PD patients and 23 spouses/family members were included in final analyses.

Each study participant was asked if they would like to identify a spouse or a close family member to serve as an *optional* informant. Informants were asked to complete questionnaires but were not required to attend the Planning Session. Informants who chose to attend the Planning

Session were involved in the psychoeducational portion of the session but were encouraged to be observers during goal setting rather than active participants. Responsibilities of the informants were limited to completing questionnaires at the three time points.

PD patients were asked to complete the *AES*, an 18-item self-report that assesses apathy severity, as a first phase of screening. A score of 35 or higher (reflecting a score of greater than 1.0 standard deviation above the mean for healthy elderly controls) was considered indicative of elevated apathy in the present study (Marin et al., 1994). Individuals with elevated levels of apathy underwent a second phase screening process. Patients who endorsed current hallucinatory disturbance or severe global cognitive deficit (i.e., MMSE-II < 24) were excluded from further participation.

Intervention procedure details are presented in the Program Coach manual. To summarize, participants attended one in-person session (Planning Session) lasting about 2 to 2 ½ hours. Participants were first consented and expectations of participation were discussed. They then completed baseline assessments to assess global cognitive functioning (i.e., MMSE), a verbal fluency evaluation (i.e., letter and category fluency), and an interview to assess apathy symptomatology (i.e., LARS). Patients were guided through discussion of life areas and asked whether they perceived a need for improvement in each life domain, such as relationships with family, friends, or romantic partner, spirituality, physical and emotional health, recreational enjoyment, education or career pursuits, household projects needing to be initiated or completed. Based on this discussion, five goals were selected to be targeted during the six week intervention period. Each activity was planned for specific days and times during the week. Participants left the Planning Session with a calendar for each week of the program that outlined when each activity was to be completed. At the end of each week, the Program Coach conducted a phone

session with each patient, during which participants reported the number of activity goals accomplished the previous week, discussed problems with attaining planned goals, and reviewed the goals planned for the upcoming week. Participants were allowed to make adjustments to their plan for the upcoming week if determined that their initial plan was no longer realistic or feasible. Phone sessions lasted 10 to 20 minutes.

Outcome measures were mailed to participants at three time points: pre-intervention, post-intervention, and at one-month follow-up. Pre-intervention baseline evaluations were completed up to one week prior to the Planning Session (first session, completed in-person). Post-intervention evaluations were completed within one week after participants completed the sixth and final week of the intervention. One month follow-up evaluations were completed one month after the sixth and final week of the intervention. Participants were told that the one-month follow-up questionnaire packet was optional to reduce perceived demand of participation. A timeline of activities is presented below (See Figure 2).

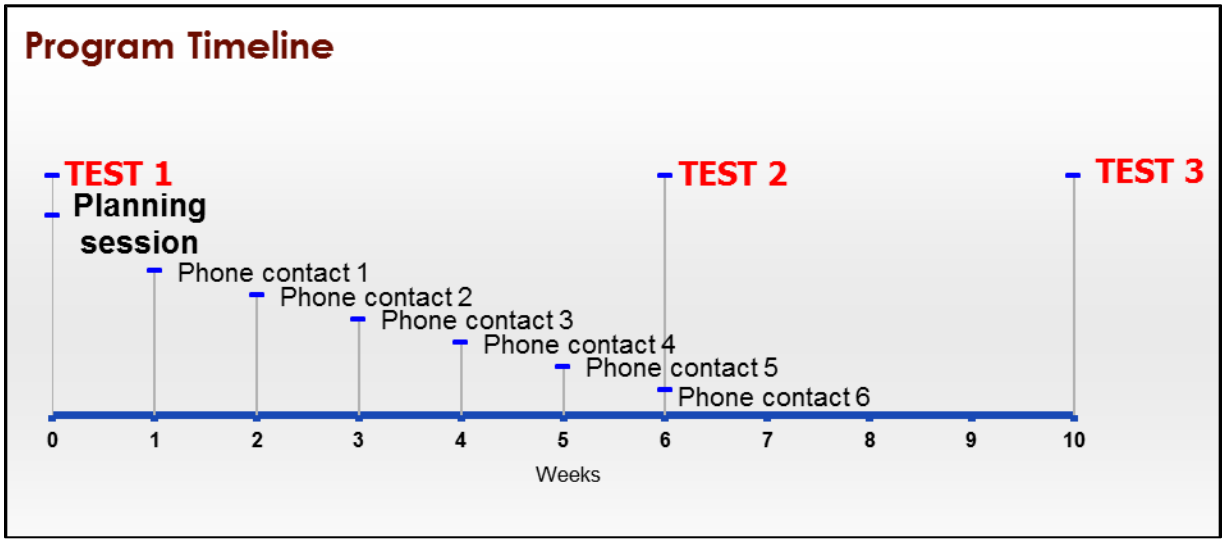

Figure 2. Program Timeline

Baseline Measures. PD *patients* were administered the following measures at baseline, at the beginning of their Planning Session:

Mini Mental State Exam – Second Edition: Standard Version (MMSE-II). The MMSE-II:SV (Folstein, Folstein, White & Messer, 2012) was administered to patient participants at baseline only as a screener for suspected dementia. The MMSE-II is a revised version of the original MMSE (Folstein, Folstein, & McHugh, 1975) with problematic items replaced and select tasks modified to adjust difficulty level. Overall difficulty level as well as structure and scoring of the original MMSE remain, allowing the MMSE-2 and MMSE scores to be comparable. Brief version items, totaling 30 points as in the original MMSE, were used in this study. Each item assesses one of the following domains: orientation to time, orientation to place, registration, attention, recall, naming, repetition, comprehension, reading, writing, and drawing. Patients scoring less than 24 (Folstein et al., 1975) were excluded from the study to avoid confounds of significant cognitive impairment, which may affect patients' ability to validly complete self-report measures. The MMSE-II has been found to be reliable and valid in assessing global cognitive status (Folstein et al., 2012).

Letter Fluency and Animal Naming. Letter Fluency and Animal Naming of the *Controlled Oral Word Association test (COWA;* Spreen & Strauss, 1991) were administered to patient participants who speak English as a first language at baseline only. They were administered to assess phonemic and category verbal fluency, indices of executive cognitive function, for the purpose of sample descriptives and to determine whether they impact response to treatment.

Lille Apathy Rating Scale (LARS). The LARS (Sockeel et al., 2006) was administered to patient participants at baseline only for the purpose of better understanding the types of apathy

that patients experience and evaluating whether these specifics impact response to treatment. The LARS is a 33-item structured interview that assesses apathy in nine domains: reduction in everyday productivity, lack of interest, lack of initiative, extinction of novelty seeking and motivation, blunting of emotional responses, lack of concern, poor social life, and social awareness. The interview is based on the conceptual principles proposed by Marin et al (1991) and Stuss et al. (2000). Items 1-3 are coded on a five-point Likert scale and remaining items are coded as binary (yes/no) responses. A global apathy score as well as nine domain scores can be calculated. In a PD sample, the LARS was reported to have good concurrent validity (r = 0.75 - 0.87), split- half reliability (r = 0.73-0.80), and inter-rater reliable were strong (r = 0.98), and sensitivity and specificity were high (0.89 and 0.92, respectively) (Sockeel et al., 2006; Zahodne et al., 2009).

Outcome Measures. The following self-report measures were completed by *patients* at baseline, post-intervention, and at one-month follow-up.

Primary Measure.

Apathy Evaluation Scale (AES). The AES-S (Marin, 1991) is an 18-item self-rating scale that was developed to assess apathetic symptoms within behavioral, cognitive, and emotional domains and was selected as the primary outcome measure for this study. A sample of healthy control participants scored an average of 28.1 points (SD = 6.4) on the self-rating form of this test. Traditionally, 38 has been used as a cut-off score to represent clinically significant apathy given that this score reflects apathy 1 ½ SD above the mean of healthy elderly controls. We used a cut-off of 35 points, reflecting a score greater than 1.0 SD above the mean in order to include a wider sample of patients endorsing problems in this domain. The AES has been used in a number of clinical groups, including PD, and has been found to have good construct and internal

consistency validity (α = 0.86) (Marin et al., 1991). In a sample of PD patients, convergence between self-rated and clinician-rated apathy was strong (r = 0.74) as was test-retest reliability (α = 0.85) (Pluck and Brown, 2002). Sensitivity to change has not been formally evaluated but some evidence of it exists from its use in a studies of the impact of methylphenidate and of deep brain stimulation on apathy (Leentjens et al., 2008).

Secondary Measures.

Geriatric Depression Scale (GDS). The *GDS* (Yesavage et al., 1983) is a 30-item self-report instrument designed to identify depression in elderly individuals. The scale excludes somatic symptoms of depression that are common in the elderly. Respondents must select "yes" or "no" in response to each item, reflecting how they have felt over the past week. A normative sample of healthy elderly individuals scored a mean of 5.75 (SD = 4.34) on the GDS (Yesavage et al., 1983). Scores classify patients in the ranges of normal (score of 0 – 10), mild depression (score of 11 – 19), or severe depression (score of 20 – 30). In a PD population, the test has well-established internal consistency (α = 0.92, split-half r = 0.91) and good discriminability between depressed and non-depressed PD patients (i.e., sensitivity, positive and negative predictive values = 0.79 – 0.85 for cut-off score of 13/14) (Ertan, Ertan, Kiziltan, and Uyguçgil, 2005).

Unified Parkinson's Disease Rating Scale (UPDRS, Part II). The Activities of Daily Living section of the *UPDRS* (Part II) (Fahn and Elton, 1987) was administered to assess self-reported daily functioning. This section of the *UPDRS* contains 13 items assessing different areas of daily functioning (i.e., speech, salivation, swallowing, handwriting, cutting food, dressing, hygiene, turning in bed, falling, freezing, walking, tremor, sensory complaints) using a five point Likert scale (i.e., 0-4), with higher scores indicating greater impairment.

Parkinson's Disease Quality of Life Scale (PDQ-39). The PDQ-39 (Peto et. al, 1995) was used to assess overall and eight disease-specific quality of life domains: Activities of Daily Living (ADLs), Communication, Social, Cognition, Emotion, Stigma, Discomfort, and Mobility. The PDQ-39 was developed specifically for use with PD patients. This scale includes 39 items on a 5 point Likert scale ("Never" to "Always"). Dimension scores are converted into a scale from 0 (perfect health as assessed) to 100 (worse health as assessed). Studies have demonstrated that the PDQ-39 has strong global reliability and variable subscale reliability (internal consistency: Global PDQ, $\alpha = 0.94$; 4/8 subscales, $\alpha = 0.43$-0.93; temporal stability of scales, $r = 0.76$-0.90). Convergent validity between the PDQ-39 and PDQL was strong particularly for summary indices ($r = -0.91$; subscales, $r = -0.31$-0.81) and group comparisons support content validity (Marinus, Ramaker, van Hilten, & Stiggelbout, 2002).

The following measures were completed by *patients* post-intervention only:

Client Satisfaction Questionnaire (CSQ-8). The CSQ-8 (Larsen, Attkisson, Hargreaves, & Nguyen, 1979) was administered post-intervention only and used with author permission. The CSQ-8 is an eight item scale assessing general satisfaction with services provided, such as whether the participant's needs were met, whether the participant would recommend the services to others, and overall satisfaction. Response options differ item by item but each assesses satisfaction using a 4-item Likert anchored scale with item scores ranging from 1 to 4. Higher scores represent higher satisfaction. Examples include "How satisfied are you with the amount of help you have received?" (for which the response options are 1 = "Quite dissatisfied", 2 = "Indifferent or mildly dissatisfied", 3 = "Mostly satisfied", 4 = "Very satisfied", and "Have the services you received helped you to deal more effectively with your problems?" (for which the response options are 1 = "No, they seemed to make things worse", 2 = "No, they didn't help", 3

= “Yes, they helped somewhat”, 4 = “Yes, they helped a great deal”. In order to better understand satisfaction as rated by this measure, we used a “school room” transformation method suggested by Attkisson and Greenfield (2009) that consists of summing the eight item scores and multiplying by 3.125 resulting in scores ranging from 25 to 100. Reported internal consistency of the CSQ-8 is strong (α = .92 - .93), construct validity appears adequate (i.e., clients who discontinue treatments were significantly less satisfied than those who do not, $r = 0.37$; satisfaction significantly correlated moderately with global improvement on a symptom checklist, SCL-90, $r = 0.53$) (Larsen et al., 1979; Attkisson & Zwick, 1982).

Participant Satisfaction Questionnaire (PSQ). The PSQ was administered at post-intervention only. The PSQ was created by the researchers conducting this study in order to evaluate satisfaction with *specific* aspects of this program, such as courtesy of program staff, convenience of scheduling, location and parking, tailoring of goals, helpfulness of the program, usability of materials, satisfaction with *iPing* automated phone calls, whether participants would recommend the program, whether participants would pay for the service, and overall satisfaction. Items are on a 5-point Likert scale with scores ranging from 1 (“strongly disagree”) to 5 (“strongly agree”) and with a separate option of “no opinion”. Higher scores represent greater satisfaction.

The following measures were completed by *informants* at baseline, post-intervention, and at one-month follow-up:

Zarit Burden Inventory. The Zarit Burden Inventory (Zarit, Reever, & Bach-Peterson, 1980) is a 29-item questionnaire used to assess caregiver burden in terms of personal and role strain. Items assess frequency of strain on a 5-point Likert scale from “Never” to “Nearly Always”. Higher scores represent higher burden. It has good internal consistency reliability (α

= .92) and is highly correlated with caregiver depression and behavior problems in the patient ($p < 0.001$) (Hérbert, Bravo, Préville, 2000).

Statistical Analyses. Means, standard deviations, and frequencies were calculated to determine sample characteristics. *Uniformity* of treatment delivery was investigated by calculation of percentages. *Feasibility* was investigated by calculation of attrition rates. *Acceptability* was investigated by calculation means, standard deviations, and frequencies of satisfaction ratings provided by PD participants.

As a primary outcome analysis, matched pairs t-tests were used to evaluate whether a significant difference was present between pre-intervention and post-intervention apathy scores (i.e., AES). To evaluate whether a significant difference was present between pre-intervention and post-intervention secondary outcome variables (i.e., patient depression, QoL, basic daily functioning, and carer burden/stress) from pre-test to post-test, further dependent paired t-test analyses were conducted. For exploratory purposes, another set of matched pairs t-tests were used to evaluate whether changes identified at post-test were maintained at one-month follow-up.

Lastly, to investigate whether certain baseline variables (e.g., level of patient's baseline cognitive function, degree of baseline functional impairment) were associated with response to treatment (i.e., defined as AES score at Time 2 minus AES score at Time 1), several correlations were examined. The results of these correlations provide some insight into what variables may guide inclusion/exclusion criteria in future uses of this intervention.

Results

Patient demographics. Patient demographic information is summarized in Table 2. PD participants ranged in age from 44 to 86 years (mean = 66, SD = 10.7), were majority male (n = 22, 81.5%) and Caucasian (n = 23; 85%), and ranged in disease duration from <1 to 23 years. All

patients had elevated apathy as determined by an inclusion cut-off score of 35 on the AES, representing a score greater than 1.0 SD above the mean of healthy elderly controls.

Table 2

Summary of sample demographics

n = 27	*n*	Range	Mean (SD)
Age	27	44 - 86	66 (10.7)
Disease duration (yrs)	24	<1 - 23	10.1 (6.2)
MMSE-II	27	24 - 30	28.1 (1.5)
Baseline Apathy	27	35 - 55	42.1 (41.0)

	n	%
Gender		
Male	22	81.5 %
Female	5	18.5 %
Ethnicity		
White	23	85 %
Hispanic	4	15 %

Treatment delivery. An adherence checklist was used as a guide during all sessions to ensure uniform treatment delivery (see Appendix). Sessions administered by newly trained undergraduate interventionists were audio-taped and tapes were reviewed by the P.I. and assessed for adherence to the protocol using the training checklist. As reported above, adherence during the sessions administered by new trained interventionists ranged from 93% - 100%, with an average of 99% overall (96% for Planning Sessions and 100% for weekly phone sessions). No major deviations of the protocol occurred. Sessions administered by the P.I.were not recorded; therefore, adherence ratings of these sessions were unable to be evaluated.

Feasibility. Treatment feasibility was assessed by investigating attrition rates and reasons for discontinuation of treatment. Of 34 participants who were initially enrolled and completed the initial Planning Session, two individuals attended the Planning Session but discontinued participation before completing Week 1, before beginning treatment. Reasons for their discontinuation included mistakenly thinking compensation would be provided for participating, feeling satisfied with their current level activity, and/or disinterest in the scheduling aspect of the study. Therefore, of the 32 who continued beyond the first meeting, 28 completed all six weeks of the study (12.5% attrition). In addition, post-intervention data was not received from one of the subjects who completed the intervention. Analyses reported include the 27 individuals who completed the 6-week program and for whom we received pre-intervention and post-intervention data.

Table 3 displays information of the four individuals who initiated treatment but discontinued treatment early.

Table 3

Summary of patients who discontinued treatment

Subject	Gender	Age	MMSE	Disease Duration	Baseline AES	Duration of participation	Reason for discontinuation
1	M	78	26	3.1 yrs	47	2 weeks	- goals were not stimulating him - wife was pushing him to accomplish the planned goals
2	M	54	29	14.8 yrs	42	3 weeks	- difficulty sticking to a schedule
3	F	75	28	2.1 yrs	42	4 weeks	- medical complications prevented her from keeping up with goals - did not want to

							disappoint PC by not fulfilling her obligation
4	M	70	30	3.3 yrs	38	3 weeks	- too busy with work and family visitors to keep track of goals - did not feel he could commit to accomplishing all goals

Acceptability. Acceptability of the study was measured by examining compliance and participant satisfaction ratings and related comments submitted by participants after completing Week 6. Compliance was measured by examining percentages of goal attainment. For most patients (and as is described in the PAL manual), two goals were planned for Week 1, three goals for Week 2, four goals for Week 3, and five goals for Weeks 4 to 6. Examples of goals selected by participants include walking a quarter mile three times weekly, practicing vocal exercises for 10 minutes seven days per week, call son/daughter once per week, have lunch with a friend once weekly, work on specified household project once weekly. While most participants were engaging in five goals by Week 4, different goals required more or less engagements (e.g., some required initiation in the planned activity only once during the week while others required engagement seven times during the week). We evaluated compliance in three ways: (1) examining means, medians, modes, and quartiles of the raw number of goals completed in full (e.g., a participant who planned to exercise three times during the week only gets a point for completing the goal in full if s/he engaged in exercise three times; if s/he exercised only twice, the goal was not considered completed in full), (2) examining means, medians, modes, and quartiles of the raw number of activity engagements accomplished, and (3) examining the percentage of activity engagements accomplished relative to the number of activity engagements planned (i.e., number times participant engaged in an activity on the schedule ÷ number of total

engagements in activities planned for that week). This information is displayed in Tables 4, 5, and 6.

Table 4

Descriptives of raw number of goals completed in full, by week

Week	Mean (SD)	Median	Mode	Quartiles			Range
				1	2	3	
1	1.5 (.7)	2	2	1	2	2	0-2
2	2.3 (.8)	2	3	2	2	3	0-3
3	3.1 (1.0)	3	4	2.5	3	4	0-4
4	3.6 (1.0)	4	4	3	4	4	2-5
5	3.2 (1.4)	3	2	2	3	4	1-5
6	3.7 (.9)	4	4	3	4	4	1-5

Table 5

Descriptives of raw number of activity engagements accomplished, by week

Week	Mean (SD)	Median	Mode	Quartiles			Range
				1	2	3	
1	5.5 (3.6)	4	2	2.25	4	8.5	1-13
2	7.6 (4.6)	7	4	4	7	10	1-17
3	10.2 (4.7)	9	6	6.5	9	12	4-24
4	11.2 (6.2)	10	6	6.5	10	14.5	3-26
5	11.0 (6.2)	9	9	6.25	9	15.75	2-25
6	11.5 (5.9)	10	7	7	10	13.75	4-29

Table 6

Descriptives of percent activities engaged relative to number of activities planned, by week

Week	Mean (SD)	Median	Mode	Quartiles			Range
				1	2	3	
1	93.8% (30.5)	100%	100%	82%	100%	100%	33.3-200%
2	95.7% (29.7)	100%	100%	80%	100%	100%	28.6-175%
3	96.7% (23.8)	100%	100%	83%	100%	111%	37.5-150%
4	91.1% (31.2)	92.3%	100%	76%	92%	100%	17.7-162.3%
5	87.6% (34.2)	88.7%	multiple	63%	89%	115%	25-155.6%
6	92.3% (23.9)	89.4%	100%	76%	89%	103%	36.4-135.7%

As displayed, several participants exceeded the frequency of activity engagements at times by performing a planned activity more times during their week than they had planned, resulting in a percentage above 100 (e.g., a participant who planned to ride their bike 4 times but rode their bike 5 times instead would receive a percentage score of 125%). An examination of median scores demonstrate that at least 50% of participants were accomplishing at least 100% of planned activities during Weeks 1, 2, and 3, at least 92% during Week 4, and at least 89% during Weeks 5 and 6. An examination of quartiles demonstrate that 25% of participants were accomplishing at least 100% of planned activities during Weeks 1, 2, and 3, and that 25% of participants were exceeding their planned activity goals during Weeks 3, 5, and 6.

Patient participants of the program completed two satisfaction surveys upon completing their six-week program. Results of the CSQ-8, a measure of general satisfaction with the program, are presented in Table 7. Possible scores on this measure range from 25 to 100. In sum, obtained scores ranged from 71.9 to 100, with the most frequent score being 100, representing the highest level of satisfaction. 50% of scores (i.e., median) were at or above 87.5.

Table 7

Summary of CSQ Scores

Mean (SD)	86.9 (10.4)
Median	87.5
Mode	100.0
Range	71.9 – 100.0
Quartile 1	76.6
Quartile 2 (median)	87.5
Quartile 3	96.9

Results of participant satisfaction as rated on the PSQ, a measure assessing satisfaction with *specific* aspects of this program, are presented in Tables 8 – 28. Overall, the majority of participants were satisfied with the overall program, indicated that the program helped them to deal more effectively with their problems, and would recommend the program to others. For instance, 88.5% of patients answered "strongly agree" and 3.8% answered "agree" to the statement "I was satisfied with the treatment provided by my program coach". No patients reported disagreement with this statement.

While satisfaction with the program was overall very high, there were more mixed opinions of the *iPing* automated reminder call service and mixed opinions on whether participants would pay for the service themselves. To the item "I was satisfied with the automated *iPing* phone call reminders ", 60% of participants indicated "agree" or "strongly agree", while 16% endorsed "disagree" or "strongly disagree". 8% answered with "neither agree nor disagree" and 16% reported "no opinion". To the item "If I had to, I would pay for this type of services myself", 25% of patients endorsed "agree" or "strongly agree", while 30% of patients endorsed "disagree" or "strongly disagree". 30% answered with "neither agree nor disagree" and 15% reported "no opinion". 88% of patients agreed or strongly agreed that the materials were easy to read and understand, while no patients expressed disagreeing with this.

Specific comments received from participants after completing the program are presented in Table 29.

Table 8

My privacy was respected during the program.

Response	Frequency	Percent
Strongly agree	21	84.0
Agree	2	8.0
Neither agree or disagree	1	4.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	1	4.0

Table 9

My program coach was courteous.

Response	Frequency	Percent
Strongly agree	25	96.2
Agree	0	0.0
Neither agree or disagree	0	0.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	1	3.8

Table 10

All other staff members were courteous.

Response	Frequency	Percent
Strongly agree	10	40.0
Agree	0	0.0
Neither agree or disagree	0	0.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	15	60.0

Table 11

The program coach scheduled appointments at convenient times.

Response	Frequency	Percent
Strongly agree	21	80.8
Agree	3	11.5
Neither agree or disagree	1	3.8
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	1	3.8

Table 12

I was satisfied with the treatment provided by my program coach.

Response	Frequency	Percent
Strongly agree	23	88.5
Agree	1	3.8
Neither agree or disagree	0	0.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	2	7.7

Table 13

My first visit for the planning session was scheduled quickly.

Response	Frequency	Percent
Strongly agree	25	96.2
Agree	0	0.0
Neither agree or disagree	1	3.8
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	0	0.0

Table 14

It was easy to schedule phone calls after my initial planning session.

Response	Frequency	Percent
Strongly agree	18	69.2
Agree	6	23.1
Neither agree or disagree	0	0.0
Disagree	1	3.8
Strongly disagree	0	0.0
No opinion	1	3.8

Table 15

I was seen promptly when I arrived for the planning session.

Response	Frequency	Percent
Strongly agree	22	84.6
Agree	0	0.0
Neither agree or disagree	0	0.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	4	15.4

Table 16

The location of our first session was convenient for me.

Response	Frequency	Percent
Strongly agree	20	76.9
Agree	4	15.4
Neither agree or disagree	1	3.8
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	1	3.8

Table 17

I was satisfied with the services provided by my program coach.

Response	Frequency	Percent
Strongly agree	26	84.6
Agree	1	3.8
Neither agree or disagree	1	3.8
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	2	7.7

Table 18

Parking was convenient for me.

Response	Frequency	Percent
Strongly agree	16	61.5
Agree	0	0.0
Neither agree or disagree	1	3.8
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	9	34.6

Table 19

My program coach understood my goals and tailored them to me.

Response	Frequency	Percent
Strongly agree	21	80.8
Agree	1	3.8
Neither agree or disagree	0	0.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	4	15.4

Table 20

The instructions my program coach gave me were helpful.

Response	Frequency	Percent
Strongly agree	23	88.5
Agree	1	3.8
Neither agree or disagree	1	3.8
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	1	3.8

Table 21

The materials provided were easy for me to read and understand.

Response	Frequency	Percent
Strongly agree	21	84.0
Agree	1	4.0
Neither agree or disagree	1	4.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	2	8.0

Table 22

I was satisfied with the automated iPing phone call reminders.

Response	Frequency	Percent
Strongly agree	10	40.0
Agree	5	20.0
Neither agree or disagree	2	8.0
Disagree	2	8.0
Strongly disagree	2	8.0
No opinion	4	16.0

Table 23

I knew what was expected of me week to week.

Response	Frequency	Percent
Strongly agree	22	88.0
Agree	1	4.0
Neither agree or disagree	0	0.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	2	8.0

Table 24

I was satisfied with the overall quality of my program.

Response	Frequency	Percent
Strongly agree	14	53.8
Agree	5	19.2
Neither agree or disagree	5	19.2
Disagree	0	0.0
Strongly disagree	1	3.8
No opinion	1	3.8

Table 25

I would recommend this program to other Parkinson's patients.

Response	Frequency	Percent
Strongly agree	20	76.9
Agree	1	3.8
Neither agree or disagree	4	15.4
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	1	3.8

Table 26

I would return to this facility if I wanted to participate in other research studies.

Response	Frequency	Percent
Strongly agree	13	65.0
Agree	2	10.0
Neither agree or disagree	0	0.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	5	25.0

Table 27

If I had to, I would pay for this type of services myself.

Response	Frequency	Percent
Strongly agree	3	15.0
Agree	2	10.0
Neither agree or disagree	6	30.0
Disagree	3	15.0
Strongly disagree	3	15.0
No opinion	3	15.0

Table 28

Overall, I was satisfied with my experience with the Parkinson's Active Living program.

Response	Frequency	Percent
Strongly agree	15	75.0
Agree	0	0.0
Neither agree or disagree	3	15.0
Disagree	0	0.0
Strongly disagree	0	0.0
No opinion	2	10.0

Table 29

Post-Intervention Patient Comments

• *iPing* was very helpful and easy to use.
• Canceled *iPing* calls after the 4th week. The calls were starting to grate on me.
• Feedback from Coach was helpful overall and gave me an incentive to be more productive. *iPing* was helpful even. Most important in terms of helpfulness, though, was the Coach calling me each week.
• I found that having a list of tasks and calls to remind me a great help to me to get going and get things done. *iPing* really helped and it is was really gets me up and doing the activities.
• I noticed that if the weekly calendar is not in front of me, I forget to do my activities.
• I was not expecting any great changes in my apathy or enthusiasm but was wrong. I did lose the slow, apathetic fog that had been plaguing me. Feeling like my "old self" felt familiar and good. I didn't like *iPing* because it didn't work properly- did not register "yes", kept calling back, repeated questions. Frustrating! Setting goals and thinking about them during the week was helpful for me. The Program Coach's weekly calls were important because it showed I wasn't just forgotten about or treated like a number. And, pleasing the Program Coach helps!
• *iPing* phone calls help. I'd like to use this myself from now on. Weekly calls also kept me on track.
• My kids loved my increased contact with them!
• My Coach was very nice and extremely easy to talk to!
• Setting the goals and making a plan motivated me to get more done. It's what I used to do and I had gotten away from it. Having my Coach call each week also helped a lot because I wanted to please her by accomplishing what I'd set forth to do. *iPing* was not too important to me because I had it all in my own calendar.
• This program was the nudge I needed to get moving. I wouldn't have accomplished as much without this program. *iPing* was helpful at the beginning but then after 3-4 weeks I set my own alarms.
• This program changed my life!

Intervention Outcomes.

Diagnostics. The primary outcome variable was apathy severity. Secondary outcome variables included patients' self-rated depression, quality of life, and daily functioning, and informants' self-rated carer burden. Examination of boxplots confirmed that data points of interest and change scores fell within acceptable limits (+/- 3 standard deviations from the mean) for analysis. Scores were normally distributed for most variables (Shapiro-Wilk test of normality, $p < .05$), with the exception of pre-intervention patient-rated apathy and post-intervention patient

depression. Patient rated apathy was normally distributed as assessed by Kolmogorov-Smirnov test of normality ($p > .05$), however, examination of normality using the Shapiro-Wilk test, a more rigorous test and often recommended with small samples sizes, showed deviation from normality ($p < .05$). Investigation into the distribution of pre-intervention apathy scores revealed that these variables were slightly positively skewed. Matched pairs/dependent t-tests are fairly robust to deviations from normality, however, to be conservative a square root transformation was applied to the data and analyses were run in two ways- using the original variable and using the transformed variable. No difference was observed in the results of the two approaches, therefore, all reported analyses were run on the original dataset. Mauchly's Test of Sphericity when evaluating change across three time points indicated that the assumption of sphericity had not been violated ($\chi^2(2) = 2.148$, $p = .342$).

Primary outcome variable. Matched pairs t-tests, conducted to determine whether apathy severity scores as assessed by the self-report Apathy Evaluation Scale (AES), revealed that apathy was significantly different from pre-intervention (42.1 ± 6.0) to post-intervention (36.1 ± 8.3) with a large effect ($t(26) = -4.002$, $p < .0005$; $d = 0.77$) with pre-intervention AES scores significantly higher than post-intervention AES scores . In terms of clinically significant change, mean apathy score pre-intervention was 2.2 SD above the mean of healthy elderly controls whereas post-intervention apathy levels were at 1.3 SD above the mean of healthy elderly controls. This demonstrates a drop of nearly 0.9 SD.

A look at change in pre-intervention to post-intervention apathy level at the individual participant level revealed that five participants (19%) showed a ≥ 2 SD decrease, nine participants (33%) showed a 1 to 2 SD decrease, and three participants (11%) showed a 0.5 to 1 SD decrease in apathy from pre- to post-intervention. Ten participants (37%) went from having

elevated apathy (AES ≥ 35) to having apathy levels within a normal range (AES < 35). Apathy scores increased by 1-2 SD in two patients from pre- to post-intervention.

Secondary outcome variables. We were also interested in investigating whether the intervention may have had an impact on secondary variables, including patients' self-rated depression, quality of life, and daily functioning, and informants' self-rated carer burden. Patient's self-rated depression significantly decreased from pre-intervention (13.61 ± 7.04) to post-intervention (10.78 ± 6.54), demonstrating a medium to large effect ($t(22) = -3.380$, $p < .01$, $d = .70$). In terms of clinical significance, the mean depression score pre-intervention (13.61) was qualitatively in the mildly depressed range and post-intervention (10.78) was qualitatively within normal limits as scores of 0-10 on the GDS represent depressive symptomatology in the normal range, scores of 11 or greater indicate the presence of at least mild depression (Yesavage et al., 1983). A look at change in pre-intervention to post-intervention depression at the individual participant level revealed that three participants (11%) showed a ≥ 2 SD decrease, six participants (22%) showed a 1 to 2 SD decrease, and three participants (11%) showed a 0.5 to 1 SD decrease in depression from pre- to post-intervention. Four participants (15%) went from having elevated depression (GDS ≥ 11) to having depression levels within a normal range (GDS < 11). Depression scores increased by 1 SD in one patients from pre- to post-intervention.

Patient's self-rated quality of life significantly improved from pre-intervention (30.82 ± 15.18) to post-intervention (25.51 ± 13.51), demonstrating a medium effect ($t(23) = -2.458$, $p < .05$, $d = .50$). No significant change was observed in patients' self-reported basic daily functioning from pre-intervention (15.42 ± 6.48) to post-intervention (14.79 ± 5.91) ($t(23) = -1.17$, $p = .254$; $d = .24$). No significant change was observed in informants' self-reported carer

burden from pre-intervention (23.85 ± 17.92) to post-intervention (23.21 ± 17.82) ($t(19) = -0.401$, $p = .693$; $d = .09$).

One-month Follow-Up. Given that a significant change was present from pre-intervention to post-intervention in patient apathy, depression, and quality of life, matched pairs t-tests were conducted comparing post-intervention scores to one-month follow-up scores to examine whether these changes were maintained at follow-up. The decrease in apathy from pre-intervention to post-intervention was maintained at one-month follow-up (36.9 ± 7.0) as reflected by a significant difference between pre-intervention (42.2 ± 6.0) and one-month follow-up (37.0 ± 7.4) apathy scores ($t(19) = -4.264$, $p < .0005$; $d = .95$) and no significant change from post-treatment (35.1 ± 7.5) to one-month follow-up (37.0 ± 7.4) ($t(19) = 1.213$, $p = 0.24$; $d = .27$).

The decrease in depression from pre-intervention to post-intervention was also maintained at one-month follow-up as reflected by a significant difference between pre-intervention (13.61 ± 7.04) and one-month follow-up (10.2 ± 6.5) depression scores ($t(17) = -4.002$, $p < .005$; $d = .94$) and no significant change from post-treatment (10.78 ± 6.54) to one-month follow-up (10.2 ± 6.5) ($t(15) = -.265$, $p = 0.80$; $d = .07$).

The improvement in quality of life from pre-intervention to post-intervention was not maintained at one-month follow-up. There was no significant difference between pre-intervention (30.82 ± 15.18) and one-month follow-up (27.0 ± 14.8) in quality of life scores ($t(17) = -0.975$, $p = .343$; $d = .23$), nor was there a significant change from post-treatment (25.51 ± 13.51) to one-month follow-up (27.0 ± 14.8) ($t(18) = 0.681$, $p = 0.51$; $d = .16$).

Associations with Change. To investigate whether certain baseline variables were associated with response to treatment (i.e., defined as AES score at Time 2 minus AES score at Time 1), several correlations were examined (see Table 30).

Table 30

Correlations between baseline variables and response to treatment

	MMSE-II	Disease duration	GDS	AES	LARS: Novelty Seeking	LARS: Self-Awareness	COWA[a]	Animal Naming[a]
Response to treatment	-.165^{ns}	.048^{ns}	-.160^{ns}	-.287^{ns}	**.415**^{t} (*n*=20)	**.410**^{t} (*n*=20)	**-.483*** (*n*=17)	.085^{ns}

MMSE-II: Mini Mental Status Examination-II; GDS: Geriatric Depression Scale; AES: Apathy Evaluation Scale-Self; LARS: Lille Apathy Rating Scale; COWA: California Oral Word Association test

[a] *Verbal fluency scores are reported for participants who speak English as a first language*

* *p<0.05* ***p<0.01* ^{t} *trend, p=.07* ^{ns} *not significant, p>0.05*

Investigation of correlation coefficients revealed no significant correlation between response to treatment and baseline global cognitive function (MMSE-II total score), category fluency, duration of disease, or baseline apathy or depression scores. However, response to treatment was significantly and negatively associated with baseline phonemic fluency, a measure related to frontal executive functioning (COWA scaled score corrected for age and education), reflecting that higher executive functioning was related to greater change in apathy from pre-test to post-test. A small to moderate positive trend was present in the correlation between response to treatment and apathy related to novelty seeking (LARS Novelty Seeking subscale) and self-awareness (LARS Self-Awareness subscale) in that patients who endorsed greater motivation behavior toward novelty seeking and those who endorsed greater motivation behavior toward self-evaluation/self-awareness showed a greater decrease in apathy from pre-intervention to post-intervention.

Discussion

The purpose of the present study was to develop and gather pilot data on the acceptability, feasibility, and effectiveness of a primarily telephone-based, 6-week activity scheduling and monitoring intervention that incorporates an external cueing component to target disease-related self-generational deficits, on reducing levels of apathy in non-demented, highly apathetic PD patients. Specific aims of this study included (1) developing the PAL program protocol and materials, including a guide, or manual, for interventionists to use to administer the PAL program and a participant workbook for patient participants; (2) determining feasibility or ease of training new interventionists as determined by rates of protocol adherence during protocol administration following training; and (3) obtaining pilot data on the feasibility of implementing the treatment protocol and retaining participants through the duration of the program in a population of non-demented PD patients, on the acceptability or perceived satisfaction of the program, and to determine a within-subject effect on primary (i.e., patient apathy) and secondary (i.e., patient depression, quality of life, daily functioning, and spousal burden) variables by evaluating effect sizes.

We hypothesized that a behavioral intervention aimed at increasing activity identification, goal-setting, and activity engagement that incorporated an external cueing structure would benefit the apathetic PD patient and their spouses by improving patient apathy, depression, quality of life, daily functioning, and spousal burden. The *Brief Behavioral Activation Treatment for Depression (BATD;* Lejuez et al., 2001) served as the foundation from which the PAL program was developed in that its structure was replicated and several forms

from the BATD manual were either adapted for easier use with PD patients or used without adaptation. The PAL program was delivered primarily as a telephone-based intervention as it required one in-person Planning Session with the remaining six sessions occurring by telephone. It was designed with important factors for behavior change in older adults in mind, including attention to the provision of social support, consideration of self-efficacy, program tailoring, goal-setting, weekly performance feedback, and positive reinforcement (Cress et al., 2005), as well as applying our knowledge of the benefit of external structure and cueing for PD patients specifically. The program was designed as an individually tailored program in which activities reflecting the participants' preferences and capabilities were selected by participants after brainstorming ideas with their Program Coach, was flexible week to week to prevent threats to self-efficacy, and incorporated goal-setting with weekly guidance and reinforcement through telephone check-ins with their Program Coach. Spouses were not involved in an effort to facilitate self-management and patient independence; patients were encouraged to self-identify goals during the Planning Session and spouses were not required to be actively involved in the study outside of optionally completing questionnaires at three time points.

Feasibility of Interventionist Training

Following the development of the PAL protocol, administration manual, and participant workbook, four new undergraduate or post-baccalaureate student interventionists were trained to determine ease of training and fidelity of treatment implementation by new interventionists following training sessions. Prior studies have shown success in using "paraprofessionals" to deliver psychosocial interventions to promote self-management of behavior (Sacco, Malone, Morrison, Friedman, & Wells, 2009; Sacco, Morrison, & Malone, 2004; Christensen & Jacobson, 1994). Training included three training sessions, during which trainees reviewed the

PAL treatment manual, forms, and assessment measures; learned to administer baseline evaluations; received readings on apathy in PD, goal-setting theory and the use of implementation intentions (i.e., how to design goals that increase the likelihood of goal attainment), and research on the benefits of external cueing in PD; and engaged in role plays. Interventionists were encouraged to use the training checklist and manual during sessions to ensure uniformity of treatment. Ease of training was confirmed by rating four newly trained paraprofessional interventionists, or Program Coaches, on adherence to the protocol during administration. Overall, newly trained interventionists were able to display 97% adherence (94% for Planning Sessions, 100% for Phone Sessions) during a mock session role play with the P.I. at the end of training and 99% adherence (96% for Planning Sessions, 100% for Phone Sessions) when working with patient participants.

While the number of newly trained interventionists is small, this data provides promise for training paraprofessional interventionists with ease through the provision of psychoeducation and role plays and for competency in terms of uniformity of administration to be able to be demonstrated rather quickly, within three separate training sessions totaling approximately six hours. In addition, newly trained interventionists had not been previously trained in psychotherapy; rather, they were undergraduate research assistants with an interest in pursuing graduate school in clinical psychology. Since the P.I. of the present study, a doctoral candidate with therapy experience, served as the Program Coach for the majority of participants in this exploratory study, we cannot speak to whether or not acceptability of this program by this patient population would have been different had the newly trained interventionists served as Program Coaches for all participants in this study.

Feasibility of Enrollment

It was expected that recruitment would be slow due to several anticipated barriers, including targeting a population of individuals who are not only experiencing difficulties in motor functioning but also specific difficulties with motivation and initiative, requiring a minimum of a six week time commitment by participants, expecting active involvement in the intervention over six weeks by requiring participants to document accomplishment of planned activities and to attend weekly phone sessions, and the lack of compensation for participating. However, recruitment proved to be even slower than expected. Efforts were made early on to minimize enrollment difficulty by choosing to design the protocol to be primarily delivered as a telephone intervention with exception of the first session occurring in-person. Prior studies have shown telephone delivery of behavioral interventions to be successful in offering cost-effective mental health services (e.g., McBride & Rimer, 1999; Sacco et al., 2004, 2008; Eakin, Lawler, Vandelanotte, & Owen, 2007). Efforts were also made to minimize the number of exclusion criteria in order to cast a wider net during recruitment, including reducing the typical AES cut-off from 38 to 35 points. Additionally, recruitment began in the Tampa Bay region but was extended to include the Orlando, Gainesville, The Villages, and surrounding areas.

A large number of individuals who expressed interest in participating failed to qualify due to an AES score falling below the cut-off score of 35. Interestingly, several individuals who were referred to our study from UF based on having a "high apathy" score on the Apathy Scale (AS; Starkstein et al, 1992a), another measure commonly used to assess apathy in PD patients, during their UF clinic or research visit did not qualify for our study when they completed our AES as a screening measure. Other institutions with a focus in PD research, such as the University of Florida, have used the AS to assess apathy symptoms in their clinics and in their

PD research. The AS, which was abridged from the AES (which we used), consists of 14 items on a four point Likert scale (0-3; "Not at all" to "A lot"), has been recommended for use with PD patients (Leentjens et al., 2008), and also has good psychometric support (Starkstein et al., 1992a; Ferencz et al., 2010). Sensitivity and specificity was determined for the AS by comparing scores to whether a neurologist classified patients as apathetic or nonapathetic (66% sensitivity, 100% specificity; Starkstein et al., 1992a), however, specificity and sensitivity of the AES has not been determined. Since neither measure has been evaluated for sensitivity or specificity against a "gold standard", it is difficult to predict how use of the AS versus the AES would affect recruitment. A task force of apathy researchers was recently created to identify criteria for diagnosing apathy, which has since been published (Robert et al., 2009) and could be used at this point to evaluate the sensitivity and specificity of both the AES and AS.

Ultimately, the Michael J. Fox Trial Finder, a rather new service that connects PD researchers to PD patients, proved to be a very efficient method for recruitment. In order to register a study onto the site, researchers must submit proof of approval from a university's Institutional Review Board (IRB), which staff of the Trial Finder review. Once approved, researchers can browse through individuals whose basic demographic and disease criteria match study inclusion criteria and may contact participants through a two-way anonymous messaging to inform them of the study. Unfortunately, the service was officially launched in April of 2012 and the researchers of this study were not aware of this service until several months into the study. Currently, just under 20,000 individuals across the United States have registered as PD patients or PD caregivers who are interested in participating in research. The site was recently launched in the UK, Ireland, and Canada as well. This resource will do wonders to increase the ease of conducting future research in PD.

Feasibility of Retention

Treatment feasibility was assessed by investigating retention through attrition rates and participants' reported reasons for discontinuing treatment. Two individuals who attended the Planning Session discontinued participation before engaging in Week 1 activities (i.e., before initiating treatment) due to mistakenly thinking compensation would be provided for participating, feeling satisfied with their current level activity, and/or disinterest in the scheduled structure of the study. 82% of those who enrolled completed the program and 87.5% of participants who began treatment following the Planning Session persisted through all six weeks of the program. We are unaware of data that reports rates of adherence to similar behavioral interventions with Parkinson's patients, however, one study reported adherence rates of 79% for PD patients participating in a home-based exercise program. Those who were older, reported higher disease severity, and who endorsed extreme depression or anxiety reported even lower adherence to exercise (47%) (Pickering, Fitton, Ballinger, Fazakarley & Ashburn, 2013). Ongoing social support, provided by the Program Coach during the PAL program, also likely contributed to adherence. Ravenek and Schneider (2009) demonstrated that social support and perceived control both played an important role in PD patients' willingness to adhere to participation in an exercise program. More generally, therapeutic alliance research has shown that a positive therapeutic relationship has served as a contributing mechanism of change in outcome research for various psychotherapies (Lambert & Barley, 2002).

Review of participants' reported reasons for discontinuing treatment reveals that barriers to continued participation in this program may include concern over not being able to achieve 100% of activity goals and disappointing their Program Coach, disinterest in having to follow a schedule of planned activities, feeling satisfied with level of baseline activity, feeling as if the

selected goals are not stimulating enough, interference of unexpected medical complications, and the negative involvement of a spouse or caregiver.

While some of these barriers, such as new onset of medical complications, cannot be prevented, recognition of others may be useful during recruitment and during interactions with participants early on and over the course of their participation. For instance, ensuring that individuals are aware that they will be expected to follow a schedule of activities and that participants join if and only if they recognize a problem with their level of activity may increase retention. Further, Program Coaches should emphasize that participants do their best rather than attempting to achieve 100% of the plan and should be highly attentive to goal difficulty and feasibility when helping participants select goals. As past research has demonstrated in the field of workplace motivation, effective goals must also be somewhat challenging but, importantly, attainable (Bandura, 1991; Bandura and Cervone, 1983; Locke and Latham, 1991, 2002). Goals that are too easy fail to motivate the individual and goals that are impractical in attainment are discouraging. The Program Coach is essential in ensuring that participants feel a sense of competence by gauging aspects of goal challenge week to week, foreseeing problems with this before they arise, and adjusting the plan before a participant becomes too discouraged or too bored.

Acceptability

In order to better understand how the intervention program was accepted by participants, we investigated compliance and satisfaction ratings. For most patients, two goals were planned for Week 1, three goals for Week 2, four goals for Week 3, and five goals for Weeks 4 to 6, although this standard procedure was adjusted slightly to tailor to individual participant needs. To reiterate, each goal specified an activity to target per week and each goal varied in its

frequency of planned engagement and in its duration. For instance, a participant may have selected during the first week to engage in Tai Chi exercise only once during the week but to engage in that same Tai Chi exercise daily (i.e., seven times) during Week 5. At the end of the week, the goal was only deemed completed in full if and only if the participant engaged in that planned activity the number of times planned. Therefore, we evaluated goal compliance by examining descriptives of the number of goals participants were able to complete in full each week, descriptives of the number of individual activity engagements accomplished each week, and percentages of activity engagements accomplished relative to the number of activity engagements planned.

A summary of statistics related to goal achievement were presented in Tables 4 – 6. Examination of this data may help in the future implementation of the program by helping Program Coaches to set expectations for clients and to recognize times at which goal attainment commonly becomes difficult. A look at quartile data revealed that the majority of patients had no difficulty meeting all planned goals in full during Weeks 1 (i.e., two goals), 2 (i.e., three goals), and 3 (i.e., four goals). They achieved greatest compliance during the first three weeks, engaging in over 94% of planned activities on average, with a median of 100% of planned activities achieved. Compliance dropped slightly after this point, but participants were still engaging in over 88% of planned activities on average during the final three weeks, with medians of 89% - 92%.

The majority of participants were unable to accomplish more than four goals in full despite the fact that five goals were planned for participants in Weeks 4 to 6. In fact, less than 25% were able to accomplish all five goals during Weeks 4 and 5 and less than 15% of participants were able to accomplish all five goals during Week 6. This suggests that setting

more than four goals may increase challenge. While this raises questions as to whether setting four goals is too arduous, that determination must be made client to client by the Program Coach's estimate, however, we expect that setting more than four goals may generally help to increase challenge, which is an essential element in increasing motivation according to goal-setting theory (Locke & Latham, 1990). At the very least, and considering that one of the common reasons given for early discontinuation of treatment in this study was participants' concern that they could not achieve the goals set, we believe it is important for Program Coaches to warn participants that it may become more challenging after Week 3 to achieve all goals set but to encourage participants to do their best even if unable to achieve all goals planned.

In terms of participants' satisfaction with the program, the majority of participants were satisfied with the program overall, indicated that the program materials were easy to read and understand, that it helped them to deal more effectively with their problems, and that they would recommend the program to others. One participant reported that the program helped her to lose the "slow, apathetic fog that had been plaguing [her]" and that "feeling like [her] old self felt familiar and good." One participants specifically reported that the program "changed [his] life". Some participants requested blank copies of the weekly calendars to use independently after participation in the study was complete.

While reports of satisfaction with the program were generally very high, there were mixed opinions on two things. Firstly, participants gave mixed reviews of the *iPing* automated reminder call service. 60% of participants endorsed satisfaction with the *iPing* reminder calls while 16% endorsed dissatisfaction with this service. Additionally, use of the *iPing* system was also one of the most demanding aspects for the Program Coach to manage as setting up the calls was somewhat time consuming and required weekly attention, particularly if goals were adjusted

during the program. The system was not only unreliable at times for participants (i.e., sending multiple reminders of the same goal, not sending calls when scheduled), but it was unreliable at times for Program Coaches during initial set-up as well in that the service was out of order on two occasions, lasting up to three weeks at one point in time. As this study did not investigate mechanisms of change, the importance of this component of the intervention is unknown.

Secondly, participants were mixed on whether they would pay for the PAL service themselves. 25% of patients indicated that they would pay for the services provided in the PAL program themselves while 30% of patients indicated that they would not. A survey of PD patients inquiring how much money they would pay for this service would be useful, particularly for follow-up studies and if this program is to be distributed or made available for consumers in the future.

Outcomes

Primary outcome analyses revealed a large effect of the treatment on apathy severity from pre- to post-intervention and the change in scores was clinically significant as represented by a nearly 0.9 standard deviation drop in apathy score. 19% showed a ≥ 2 SD decrease and 33% of participants showed a 1 to 2 SD decrease in apathy score from pre- to post-intervention. 37% of participants went from having significantly elevated apathy (AES ≥ 35) to having apathy levels within a normal range (AES < 35), demonstrating that several participants who were experiencing significantly and clinically elevated apathy were no longer experiencing unusual elevations post-intervention. This reduction in apathy was maintained at one-month follow-up. Given that this was not a controlled study, we cannot determine the mechanism of change or say with confidence that the changes observed were due to the intervention itself. We also cannot determine how these changes were maintained as we did not gather data on whether participants

continued to practice skills or whether they utilized materials (e.g., weekly checklists, weekly calendars, *iPing*). These concerns are discussed in detail below under "Limitations".

Secondary outcome analyses revealed a medium to large effect of treatment on patient depression and a medium effect on patient quality of life. A look at changes in individual scores shows that the changes in depression were not as dramatic as those in apathy in that only 15% of participants showed a change from having elevated depression (GDS ≥ 11) to having depression levels within a normal range (GDS < 11). However, 33% of participants showed a greater than 1 SD drop in depression score, which is generally considered to reflect clinically significant change. Change at one-month follow-up was also maintained for depression but not for quality of life ratings. The effect of treatment on patients' self-reported basic daily functioning, as measured by independence in basic activities of daily living, was small and present (d = .24) although non-signficant. The effect of treatment on carer burden was non-significant (d = .09).

While we are unaware of any studies that have evaluated the impact of behavioral activation alone on depression or apathy in PD, our findings that increasing activity engagement was related to decreases in apathy and depression over time is not too surprising given the success of recent trials evaluating the effect of modified cognitive behavioral treatment (CBT) on depression in PD using in-person and telephone delivery. Dobkin and colleagues (2007) showed that modified CBT improved depression in depressed PD patients in a single-arm, uncontrolled trial. A follow-up investigation using a randomized controlled trial (RCT) design further supported the effectiveness of CBT on depression in depressed PD patients (Dobkin et al., 2011a). This group also recently found that telephone delivery of CBT on depression in PD (Dobkin et al., 2011b) reduced depression in PD patients. They will likely follow-up this study with an RCT.

Given the high prevalence of apathy and depression in PD, these results show promise that improving motivation and mood by means of a behavioral approach, rather than a pharmacological approach, is possible in PD. Notably, a number of participants in this study were on medications that have shown to improve apathy and mood; therefore, it is not clear whether this behavioral intervention would be effective had patients been required to discontinue pharmacologic treatments.

Predictors of Response to Treatment

To investigate whether certain baseline variables were associated with response to treatment, several correlations were examined. Investigations revealed that individuals with better verbal phonemic fluency were more likely to show a greater reduction in apathy from pre- to post-intervention. This information is interesting as it suggests that the utility of the PAL program may depend, in part, on the integrity frontal executive functioning. Verbal phonemic fluency is dependent upon left inferior frontal cortex and subcortical structures generally (Costafreda et al., 2006; Hirshorn & Thompson-Hill, 2006; Schlosser et al., 1998) and with reduced caudate grey matter volume in PD (Ellfolk et al., 2013) and is related to executive functioning, slow speed of processing, and apathy. Interestingly, a recent study similarly showed that higher executive functioning, as assessed using a task of frontal cognitive flexibility and set-shifting (Trail Making Test), was a significant predictor of response to CBT for depression in PD patients (Dobkin et al., 2012). We only assessed one aspect of executive functioning, however, it would be interesting to investigate the relationship of treatment response with other aspects of executive functioning. The term executive functioning is a broad label for cognitive functions associated with frontal-subcortical circuits, including one's ability to be cognitively flexible, generate new concepts, elaborate cognitive and behavioral responses to environmental situations,

adapt to novel situations, set-shift, problem solve, plan and organize, inhibit oneself, process information quickly, and to retrieve information freely from memory without cues. Involvement in the program required several aspects of executive functioning, including brainstorming of goals, willingness to engage in new activities, ability to make changes to one's day-to-day activity engagement, ability to flexibly adjust goals week to week when necessary, and willingness to push beyond one's comfort level. Some supports were provided, of course, to account for the executive difficulties common in PD, such as the provision of a Coach as a guide during brainstorming and throughout the program, a structured calendar of activities, and *iPing* reminder calls.

Response to treatment in our study was not related to global cognitive functioning. It is possible that this finding may have differed had we evaluated global cognitive functioning using a measure that better assess executive functions, such as the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) or the Parkinson's Disease – Cognitive Rating Scale (PD-CRS; Pagonabarrage et al., 2008). The measure of global cognitive functioning that we used, the standard score of the MMSE-II, is not heavily reliant on executive skills.

In addition, a positive trend suggests individuals who describe themselves as having greater motivation behavior toward novelty seeking and those who describe themselves as having greater motivation behavior toward self-evaluation/self-awareness (as measured by the LARS) may be more likely to find a greater benefit from this intervention. In other words, individuals who show greater interest in seeking new experiences are more likely to benefit from this program as are individuals who are comfortable with and able to evaluate whether they are doing well or poorly and to make adjustments to their behavior based on their self-evaluation. This raises questions such as what other personality variables (for instance, openness to

experience, conscientiousness, and extraversion), may also be associated with response to treatment. Some of the individuals that discontinued our program reported that the reason for their early discontinuation had to do with disliking the scheduling aspect of the program. Perhaps individuals with greater desire for flexibility, such as those who might score as those who might score as a "judging" (versus "perception") lifestyle type on the Myers-Briggs Type Indicator (MBTI; Myers, Briggs, McCaulley, Quenk, & Hammer, 1998), would be more likely to refuse to participate, discontinue early, be noncompliant, or benefit from the program overall.

Study Limitations

While the present study shows promise for the potential beneficial impact of the PAL program on improving apathy, depression, and quality of life in patients with PD, the findings should be interpreted with caution due to several limitations to the design and methodology that compromise the internal validity of our results and challenge the implications of our findings. Internal validity refers to the extent to which a cause and effect relationship can be determined within a study. A study that is considered to have good internal validity is able to demonstrate that the proposed "cause" precedes the "effect", that the proposed "cause" and "effect" are correlated, and, importantly, that alternative explanations (i.e., possible third variable "causes") are controlled for and ruled out (Shadish, Cook, and Campbell, 2002). The lack of a randomized time and attention control group in this study prevents us from being able to draw firm conclusions about the reasons underlying observed change in apathy, depression, and quality of life. We are unable to determine whether the change occurred as a result of the intervention itself or as a result of alternative threats, such as attrition bias, experimenter bias, or participant effects.

Attrition bias is a type of selection bias cause by attrition. Given that our analyses were run on only those subjects who participated throughout the full six weeks of the study, it is

possible that participants who were feeling a benefit of the program were more likely to stay enrolled in the study for the duration while those who did not feel an improvement in their motivation, mood, or quality of life may have been the ones to drop out, therefore increasing the perceived effect of treatment.

Experimenter bias refers to the potential for researchers to inadvertently influence the behavior of the participants in a way that facilitates the experimenter's desired outcome. Since the P.I. was the primary interventionist in the study and was keenly aware of the hypotheses being tested, was involved in all aspects of the study (recruitment, protocol administration, and analysis), and all parties were aware of the treatment received by each participant, the possibility of experimenter bias is a limitation. Importantly, efforts were made to minimize this where possible, including use of specific inclusion criteria to minimize experimenter bias in selection of participants, standardization of administration procedures through the use of an administration manual and adherence checklist, the use of research assistants for the majority of data entry, and double-checking of all data by a second rater to verify accurate data entry.

In addition, participant effects or demand characteristics may threaten validity in that some participants explicitly stated a desire to satisfy their Program Coach. The fact that we found significant changes on select measures and not on all measures suggests this may not have been the case. Efforts were made to minimize this by informing participants of the importance of data accuracy over pleasing their coach and encouraging all participants during all phone sessions to report honestly. Given that the accountability to an outside person's evaluation likely serves as an important motivator for participants to improve their activity level, inclusion of a control group in a single-blind study would help control for the influence of participant effects.

Given that the current study was conducted on a selective population, specifically, individuals diagnosed with PD who were not suspected of severe cognitive impairment based on a score ≥ 24 on the MMSE-II, we cannot speak to the utility of the PAL program with other populations, such as its generalizability to PD patients with severe cognitive impairment, other patients with neurodegenerative disease (e.g., Huntington's disease, Progressive Supranuclear Palsy, Alzheimer's disease), or to healthy elderly individuals experiencing apathy. Within our sample, exclusion criteria were minimized in order to increase generalizability within a non-demented PD population specifically. In addition, minority groups were underrepresented in this sample and the sample was primarily male, making generalizability to underrepresented groups unclear. Further, individuals who volunteered in the study may be qualitatively different than those who did not. We suspect that those who chose to participate have at least some interest and motivation toward self-improvement, toward satisfying a spouse who may have urged them to participate, or to contribute to research in PD.

While the sample size of our study is equivalent to and even larger than similar intervention studies that have been conducted in PD (e.g., Dobkin et al., 2007), power analysis suggest that our sample would have been too small to detect anything less than a medium effect of treatment at post-intervention and a large effect of treatment at one-month follow-up due to attrition of responders at the one-month follow-up time point. A larger sample size would not allow detection of smaller effects on dependent variables of interest, but would also allow us to do further exploratory analyses. For instance, it would be interesting to investigate whether differences existed in response to treatment between individuals with apathy but no depression and individuals with apathy plus depression, males versus females, mildly elevated baseline apathy (1 – 1.5 SD above the mean) versus extremely elevated apathy (>2 SD above the mean),

and whether the type of activity (e.g., physical exercise, social involvement, cognitive/learning activity) or number of activities selected by participants may have determined their response to treatment or satisfaction with the program.

Future Research

There are several ways in which future research can help to clarify the benefit of the present intervention on this and other populations of interest. Firstly, pursuit of a single-blind randomized controlled trial (RCT), which includes randomized assignment to a PAL treatment versus an attention control group and possibly an additional usual care or psychoeducation only control condition, would be ideal as it would provide control over several factors that pose threats to the internal validity of the present study. An RCT would afford investigation of whether improvements in patient apathy, depression, and quality of life that were observed in this study are explained by components of the PAL intervention itself or to alternative explanations discussed.

A larger sample size would be helpful in allowing examination of whether other patient or caregiver variables are impacted by this intervention, such as frontal executive functioning or other cognitive functions in patient participants, mood in spouses or caregiver, and relationship satisfaction in both patients and spouses. A larger sample size would also provide increased power to examine differences in sample characteristics and other correlates that may moderate or mediate response to change, such as baseline apathy and depression levels, current executive functioning abilities of all types (e.g., fluency, set-shifting, problem solving, planning and organization, decision making), disease variables (e.g., disease duration, stage of disease, comorbidities, medication status), motivation to change, and differences in personality

characteristics (e.g., rigidity, flexibility, desire for structure, conscientiousness, agreeableness, openness to experience).

Because the present program includes multiple components (e.g., brainstorming life areas needing improvement, the act of goal-setting, use of strategies during goal setting such as the SMART acronym and implementation intentions, the use of automated *iPing* calls, weekly contact with a Program Coach who provided praise and encouragement, identification and attainment of a reward when all goals were met at the end of a week) and activities ranged in difficulty, type (e.g., physical activity vs. increasing learning vs. increasing social contact vs. increasing engagement in household projects), and frequency across participants, we were unable to determine which of these many factors, individually or in combination, were responsible for observed change in dependent variables, if any. Future investigations of mechanisms of change can help distinguish between the influence and necessity of these different factors, which can contribute to the inclusion of factors that are key to effecting change and to the exclusion of factors deemed less essential.

Further, we do not know whether level of training within the field of psychology for Program Coaches may have also influenced the acceptability and/or effect of the intervention, although paraprofessionals, including undergraduate student interventionists, have been used to implement self-management interventions with good success (Sacco et al., 2009; Sacco et al., 2004; Christensen & Jacobson, 1994). Given that training of PAL Program Coaches proved to be rather quick and adherence by newly trained interventionists was strong, we suspect that training of paraprofessionals would be successful. However, we also expect that the rapport built between the patient participant and the Program Coach is also important. The therapeutic relationship or presence of therapist support has often been reported as an important element of both program

participation in PD patients (Pickering et al., 2013) as well as response to intervention in psychotherapy in various populations (Lambert & Barley, 2002), and it is likely that the therapeutic relationship is also important for response to treatment in this program as well.

Interestingly, we received about five requests to participate from individuals who lived out of state or overseas. We did not include participants who were unable to attend one in-person session, however, we are interested in whether this program could be administered via Skype if materials are provided to participants to review during an online face-to-face session. Some studies have shown successful treatment outcomes with PD patients using treatments delivered online. For instance, Constantinescu and colleagues (2011) showed successful delivery and receipt of vocal training for the treatment of hypokinetic dysarthria in PD patients using online delivery. Online delivery of cognitive-behavioral therapy through emailing has been effective for individuals (not with PD) diagnosed with depression, generalized anxiety disorder, and social anxiety disorder (e.g., Andersson, 2009; Andersson et al., 2012).

Given that some patients expressed dissatisfaction with the *iPing* automated reminder system, we suggest that follow-up studies consider using alternatives to this system that are more reliable and easier for the interventionists to manage. Identification and use of a text messaging service may be most ideal as many individuals in our study owned and regularly used a cell phone. We also recommend studies to include follow-ups beyond one month in order to evaluate whether observed changes persist longer term. Finally, it would also be useful to gather survey data on how much individuals would be willing to pay for this type of service. This kind of data might provide more compelling support for the pursuit of future research to grant funding agencies.

Investigations into whether other populations may benefit from this study is also warranted. Apathy is also common in a number of other neurodegenerative diseases, including Alzheimer's disease, Huntington's disease, and Progressive Supranuclear Palsy. Due to the need to be able to understand how to use the weekly calendar and checklist, we expect that individuals with dementia would have great difficulty following this program on their own. However, it may be the case that caregivers of patients could be trained to implement the program with their loved one. In this case, caregivers would provide prompting to their loved one when it is time to engage in a scheduled activity. Whether this program would be feasible and acceptable in a caregiver population of patients with dementia, such as in Alzheimer's dementia, Parkinson's disease dementia, vascular dementia, or other, has yet to be determined.

Implications for Clinical Practice

The present study provides great promise for the use and potential benefit of the PAL program on improving motivation, mood, and perceived quality of life in non-demented PD patients. Given that apathy is one of the most common neuropsychiatric symptoms in PD and other disorders involving frontal-subcortical circuitry, occurring in an estimated 40-45% of PD patients (Isella et al., 2002; Starkstein et al., 1992a) and that apathy has been associated with a wide variety of undesirable factors, including cognitive impairment, poor daily functioning, poor treatment compliance and illness outcome, reduced quality of life, and increased caregiver burden and distress (e.g., Isella et al., 2002; Pluck and Brown, 2002; Copeland et al., 2003; Starkstein et al., 2006; Vicini Chilovi et al., 2009; Starkstein et al., 1993, Resnick et al., 1998, Pluck and Brown, 2002, Weintraub, et al., 2004, Velligan et al., 2002, Mayo et al., 2009), treatments targeting apathy are particularly important. Behavioral interventions provide a non-pharmacologic alternative for patients who are frequently on a number of medications already

and wish to avoid risking side effect encounters by adding additional medications to their regimen.

Further, a wealth of research has shown that physical and mental activity engagement are strong protective factors for warding off severe cognitive impairment (e.g., Fratiglioni, Paillard-Borg, & Winblad, 2003; Verghese et al., 2003, 2006; Wilson et al., 2002) and that increased physical activity engagement prevents physical deterioration and the onset of other health problems in the general population (e.g., Murray & Lopez, 1997; Lopez, Mathers, Ezzati, Jamison, & Murray, 2006; Warburton, Nicol, & Breedin, 2006). These findings have also been demonstrated in PD populations (e.g., Tanaka et al., 2008; Speelman et al., 2011). PD patients are faced with having difficulties with self-generation, making activity initiation even more difficult relative to a normal elderly population. They are physically more sedentary than controls and this worsens as their disease progresses (van Nimwegan et al., 2011). Given that the use of external cues have been demonstrated to help counter the self-generation difficulties that PD patients experience in a variety of domains, including gait initiation (e.g., Rubinstein et al., 2002; Thaut et al., 1996; Burleigh-Jacobs et al., 1997), ocular movements (Winograd-Gurvich et al., 2004), and persistence and cognitive processing (e.g., Buytenhuijs et al., 1994; Brown and Marsden, 1988), we expect that the structured aspect of the PAL program with the use of a calendar, weekly telephone sessions with a supportive Program Coach, and automated *iPing* calls were helpful for increasing and maintaining activity and productivity in this population.

The PAL program would be an excellent addition to PD support groups. Several support groups are implementing music and exercise programs. The PAL program could be used during support group meetings as a method to increase engagement in a number of target activities, including physical exercise to improve strength and physical health, vocal exercise to improve

vocal strength given that hypophonia is a common symptom in PD, cognitive activity to target improvement in cognitive health, and social engagement to improve mood, cognitive functioning, and quality of life overall. While we did not implement the program as a group activity, we expect that the program might be successful in small groups. It is also possible that PD support group members could serve as peer coaches to contact each other weekly once individual goals are established at the beginning. Psychotherapists and mental health counselors may find the program useful for PD patients, or other patients struggling with apathy, in individual therapy sessions.

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Appendix: Program Coach Adherence Checklist

TREATMENT ADHERENCE SCALE
Planning Session

Date:
Coach:
Rater:

RATING KEY:
Y = Yes; Coach did not deviate from protocol
N = No; Coach deviated from protocol (comment should be noted)
CR = Cannot Rate / Not Applicable (comment should be noted)

PLANNNG SESSION:
Duration: _____

Rating	Item
	INFORMED CONSENT:
Y N CR	1. Did the Program Coach (PC) adequately review informed consent?
Y N CR	2. Did the PC ensure that the participant understands the timeline of the study (i.e., 6-week intervention, 3 questionnaires over 12 weeks, weekly phone contact with PC, automated reminder calls)?
Y N CR	3. Did the PC ensure that the participant understands his/her responsibilities (i.e., completing questionnaires at appropriate time points, monitoring activities daily)?
	Comments: _____
	_____
	VERIFICATION OF CONTACT:
Y N CR	4. Did the PC verify the phone number of the participant and verify the contact number for *iPing* contacts?
Y N CR	5. Did the PC inform the participant that *iPing* would call from a 1-866 number?

	Comments: _____ _____
	SCHEDULING:
Y N CR	6. Did the PC schedule upcoming *iPing* phone contacts?
	Comments: _____ _____
	QUESTIONNAIRE COLLECTION:
Y N CR	7. Did the PC collect the questionnaire AND check for missing data?
	Comments: _____ _____
	BACKGROUND/RATIONALE: Did the PC adequately explain the reason for conducting this study by addressing the following points?
Y N CR	8. PC stated that apathy in PD is common.
Y N CR	9. PC explained why apathy is relevant to PD patients.
Y N CR	10. PC provided at least three examples of apathy in PD.
Y N CR	11. PC provided at least three examples of the negative consequences of apathy.
Y N CR	12. PC stated that apathy can affect the spouse/caregiver.
Y N CR	13. PC stated purpose of this study.
Y N CR	14. PC stated that this participant is in the study because they scored high on a measure of apathy.
	*Comments:*_____ _____

	REVIEW OF THE MANUAL:
	Unit 1
Y N CR	15. PC stated that Unit 1 introduces the program and reiterates that they will work together through this program to increase activity and goal attainment.
	Comments: _____
	_____
	Unit 2
Y N CR	16. PC stated that Unit 2 provides a rationale for the study, including more depth into the theories and strategies that served as the foundation for this study, in case the participant wishes to read this at home.
	Comments: _____
	_____
	Unit 3
Y N CR	17. PC stated the requirements of the participant and spouse as participants in the study.
Y N CR	18. PC reviewed the timeline.
	Comments: _____
	_____
	Unit 4
Y N CR	19. PC stated the purpose of the baseline evaluation.
Y N CR	20. PC provided participant with dated questionnaire packets.
Y N CR	21. PC guided the participant in brainstorming activity ideas using the Life Areas Assessment.
Y N CR	22. PC guided participant in the selection of six target goals.
Y N CR	23. PC verified that the selected goals range in level of difficulty (two easy, two moderate, two difficult).
Y N CR	24. PC verified aloud that these goals are S-M-A-R-T goals.

Y	N	CR	25. PC correctly transferred target goals to the Master Activity Log
Y	N	CR	26. PC sufficiently planned the upcoming 6 weeks, incorporating the goal hierarchy and titrating engagement across the 6 weeks, using the Master Activity Log.
Y	N	CR	27. PC presented implementation intention question #1 and obtained a response from the participant.
Y	N	CR	28. PC presented implementation intention question #2 and obtained a response from the participant.
Y	N	CR	29. PC reviewed the 6-week plan with the participant and spouse
Y	N	CR	30. PC presented the Weekly Behavioral Checklist for Week One (with first week's goal, frequency, and duration listed) and gave a clear explanation of how to use it by circling Y or N and using tick-marks for achieved goals.
Y	N	CR	31. PC guided participant through the identification of rewards and verified that the participant knows how to use the reward checkboxes
Y	N	CR	32. PC reminded participant to have this form with them during all future telephone contacts.
Y	N	CR	33. PC explained the *iPing* system, including (i) rationale, (ii) schedule of *iPing* calls, and (iii) call will come from a 1-866 number.
			Comments: _____ _____
			REVIEW:
Y	N	CR	34. PC verified that participant knows which activities s/he is targeting this week.
Y	N	CR	35. PC verified that participant has planned a day and time to initiate the first activity (implementation question #1).
Y	N	CR	36. PC verified that participant has determined a time of day when s/he will record his/her activity accomplishments for each day (e.g., before bed, after dinner, after taking evening medications) (implementation question #2).
Y	N	CR	37. PC verified that participant knows how to record activity accomplishments by circling "Y," "N," and marking when activity goals have been met for the week.
Y	N	CR	38. PC verified that participant knows what s/he is supposed to do after placing a tick-mark, or check-mark, in the "activity completed" column (Answer: Reward!).

Y N CR	39. PC reminded the participant that s/he will receive automated reminder calls a few times this week from a 1-866 number, to answer this call, and to answer "Yes" when asked if the call has been received.
Y N CR	40. PC reminded the participant when the next scheduled telephone contact will occur.
	Comments: _____ _____

TREATMENT ADHERENCE SCALE
Phone Sessions

Date:
Coach:
Rater:

RATING KEY:
Y = Yes; Coach did not deviate from protocol
N = No; Coach deviated from protocol (comment should be noted)
CR = Cannot Rate / Not Applicable (comment should be noted)

PHONE SESSIONS:
Duration: _____

Rating	Item
	GREETING:
Y N CR	1. PC greeted the participant by introducing him/herself in a friendly manner.
	Comments: _____
	_____
	REVIEW OF THE PREVIOUS WEEK:
Y N CR	2. (If applicable) PC asked if the needed questionnaires have been mailed.
Y N CR	3. PC recapped the number of goals targeted for the previous week AND named each of these goals.
Y N CR	4. PC recorded the number of accomplished goals in the "Do" column AND verified that these are the number of goals reached to completion (i.e., target frequency and duration).
Y N CR	5. PC used praise to reinforce the participant for accomplished goals, and asked about and encouraged seeking the planned reward.
Y N CR	6. PC asked for an explanation on why unachieved goals were not accomplished AND asked if the goal may be unrealistic.
Y N CR	7. PC commented on whether these goals should be adjusted and made appropriate adjustments (if applicable).
	Comments: _____
	_____

	PLANNING FOR THE WEEK AHEAD:
Y N CR	8. PC prompted the participant to pull out a blank Behavior Checklist and label it appropriately.
Y N CR	9. PC clearly and accurately (including any changes) stated what the planned goals are for the upcoming week, including frequency and duration information.
Y N CR	10. PC verified that the participant understand his/her responsibilities for this week.
Y N CR	11. PC asked the participant if s/he has any questions.
Y N CR	12. PC reminded the participant that s/he will continue to receive automated reminder calls from a 1-866 number, to answer this call, and to answer "Yes" when asked if the call has been received.
Y N CR	13. (If applicable) Did the PC inform the participant that s/he will need to complete the appropriate questionnaire packet this week AND state the date by which it must be mailed.
	Comments: _____
	_____
	CONCLUDE:
Y N CR	14. PC reminded the participant of the date and time of the next scheduled phone contact.
	Comments: _____
	_____