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Title: Effect of Mental Imagery Training on Brain Plasticity and Motor Function in Individuals With Parkinson's Disease

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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2017-1)

Protocol Title: **Effect of Mental Imagery Training on Brain Plasticity and Motor Function in Individuals with Parkinson's Disease: A functional MRI investigation**

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Version Date: 3-31-2022

(*If applicable*) Clinicaltrials.gov Registration #: NCT03623386

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. Read the following instructions before proceeding: 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

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SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

Parkinson's disease (PD) is the fastest growing neurological disorder and affects over six million individuals globally. With increasing life expectancy, this number is estimated to double by 2040 (Dorsey and Bloem, 2018). The impaired ability to sustain a steady motor performance is a major cause of morbidity in patients with PD. This is characterized by a rapid progressive decline in the speed, amplitude, and force of movements during continuous tasks (e.g., walking, writing) (Chee et al., 2009; Kang et al., 2011; Ling et al., 2012). The effectiveness of standard therapies including dopaminergic treatment and deep brain stimulation is variable (Espay et al., 2011; Baraduc et al., 2013). There is an urgent need for novel therapies in PD with minimal adverse effects for better symptom control. Functional magnetic resonance imaging (fMRI)-based neurofeedback has been successful in symptomatic treatment of various neuropsychiatric conditions (e.g., anxiety, addiction) (Hartwell et al., 2013; Scheinost et al., 2013a; Young et al., 2014). Neurofeedback enables individuals to obtain voluntary control over their brain activity. With practice, individuals can learn to regulate behavior that is associated with this brain activity. This project will examine the effect of fMRI-based neurofeedback on brain plasticity and motor performance in patients with PD.

Neuroimaging studies typically implicate the dysfunction of motor cortical-striatal circuits as the neural underpinning of the difficulty with sustained motor performance in patients with PD (Berardelli et al., 2001). Specifically, deficient recruitment of the dorsomedial frontal cortex (dmFC) during sequential movements has been shown (Jahanshahi et al., 1995; Samuel et al., 1997; Catalan et al., 1999; Sabatini et al., 2000; Nakamura et al., 2001; Yu et al., 2007). Yet, the role of dysfunction in limbic circuits pertaining to the internal drive behind movement has been under-investigated in PD. The insula is a limbic region affected by the pathological process in PD (Braak et al., 2006). It processes viscero- and somatosensory signals and integrates them with the emotional and motivational context (Craig 2002, 2003, 2009; Critchley et al., 2004, 2013; Critchley 2005; Critchley and Harrison, 2013; Dijkerman et al., 2007; Garfinkel et al., 2015; Kenzie et al., 2016; Kurth et al., 2010; Strigo et al., 2016). This information about the body is relayed to the dmFC and used to initiate new or modify ongoing movements (Farrer and Frith, 2002; Paulus et al., 2009; Zapparoli et al., 2017). The insula then evaluates the outcome of the movement to reinforce adaptive movements in the future (Brass and Haggard, 2010). An appropriate level of insula interaction with the dmFC seems necessary to initiate and continue movement. Indeed, using resting-state fMRI, we demonstrated significantly reduced functional connectivity of the insula in patients with PD compared with controls (Tinaz et al., 2016a). We propose that fMRI-based neurofeedback can enhance the insula-dmFC functional connectivity, thus, improve sustained motor performance in patients with PD. To test our hypotheses, we will enroll subjects with PD and randomize them to two groups: PD-neurofeedback and matched PD-control.

Aim 1: **To examine whether subjects with PD can learn to increase the right insula-dmFC functional connectivity with neurofeedback-guided motor imagery using fMRI**.

The PD-neurofeedback group will perform motor imagery of complex whole body movements (e.g., walking, jogging) in the scanner and focus on the kinesthetic aspects of motor imagery (i.e., body sensations evoked by the imagined movements). This task was chosen based on our preliminary data showing the involvement of the insula (sensation) and dmFC (movement) during kinesthetic motor imagery. Subjects will receive intermittent neurofeedback on their performance. The neurofeedback signal will be computed based on the functional connectivity strength between the subject's right insula and dmFC. The matched PD-control group will perform visual imagery (e.g., shapes, colors) in the scanner and will not receive neurofeedback. Subjects in both groups will also continue their respective imagery training at home. *Hypothesis: The PD-neurofeedback group, but not the PD-control group, will*

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learn to increase the right insula-dmFC functional connectivity strength.

Aim 2: **To examine the effects of neurofeedback-guided motor imagery training on intrinsic functional connectivity of brain networks**.

We will obtain resting-state fMRI scans from the PD-neurofeedback and PD-control groups at baseline and post-training to examine the changes in intrinsic functional connectivity of the right insula and dmFC with the whole brain. *Hypothesis: Post-training, the intrinsic functional connectivity a) between the right insula and dmFC and b) of the right insula and dmFC with the whole brain, specifically with the motor cortical-striatal regions, will be significantly stronger in the PD-neurofeedback compared with the PD-control group.*

Aim 3: To examine the effects of neurofeedback-guided motor imagery training on motor function.

We will measure the severity of motor dysfunction using clinical rating scales and administer standard motor function tests (e.g., timed up and go, five times sitting-to-standing) to measure movement speed and vigor in PD-neurofeedback and PD-control groups. These measurements will be performed at baseline and post-training. *Hypothesis: There will be significant improvement in motor function in the PD-neurofeedback compared with the PD-control group post-training.*

This project has potential for direct clinical significance for patients with PD: 1) Interventions such as deep brain stimulation exert their effect by altering the abnormal activity of targeted brain circuits underlying PD pathology. FMRI-based neurofeedback training offers an unprecedented opportunity to have a similar effect noninvasively. 2) The mental strategies that were successfully and reliably used during neurofeedback could be practiced off-line. Therefore, neurofeedback has the potential to be implemented as a personalized treatment modality. 3) It could also be incorporated into rehabilitation and exercise programs as an adjunct treatment modality.

Rationale for Additional FMRI Experiments: 1) Our findings have shown that despite engaging different brain networks specific to imagery type (i.e., motor versus visual), subjects in both PD-neurofeedback and PD-control groups improved their motor function comparably (Tinaz et al., 2022). This suggests that there may be a "shared" brain network subserving both motor and visual imagery and mediating the motor response. To test this hypothesis further, we plan on using a hybrid mental imagery of everyday task performance in the scanner that will include both motor and visual features. The results of this experiment will also inform the choice of off-line imagery practice that can potentially yield most benefits. 2) It is also important to establish to what extent mental imagery of everyday task performance is equivalent to observation of the actual task performance in terms of brain networks. If the brain networks involved in these tasks overlap significantly, this will further support the use of mental imagery as a mental training tool.

Exploratory Aim 1: To examine the functional connectivity of brain networks associated with hybrid mental imagery.

We will recruit a new cohort of PD patients who will practice imagery of everyday task performance (e.g., preparing a meal, grocery shopping) in the MRI scanner. The imagery task will include motor and visual components. We will measure the functional connectivity of brain networks subserving hybrid mental imagery.

Exploratory Aim 2: To compare the functional connectivity of brain networks during imagining versus observing the performance of everyday tasks.

The same new PD cohort in Exploratory Aim 1 will also watch brief video footage of everyday task performance in the MRI scanner. We will compare the functional connectivity of brain networks

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involved in hybrid mental imagery of everyday task performance with those recruited during observation of the actual task performance.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities.

   2 years

3. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

1. Introduction

Patients with PD have great difficulty sustaining a steady motor performance. This is characterized by a rapid progressive decrement in the speed, amplitude, or force of movements, and impairs everyday motor functioning of patients with PD (e.g., gait, speech, handwriting). It has been shown that the decrement is most pronounced when patients with PD have to internally generate movement and improves when they are provided external cues for movement (Demirci et al., 1997; Morris et al., 2008; Tinaz et al., 2016b). For example, patients with PD can improve the progressive decline in their stride length while walking when provided with horizontal stripes on the floor (Morris et al., 2008). In a repetitive hand squeeze task using a hand clench dynamometer, we also demonstrated that patients with PD, while on dopaminergic medication, showed rapid decrement in muscle force compared with controls. This decrement was reversed when they were provided visual feedback on their performance (Tinaz et al., 2016b). These findings suggest that there is a problem with internal motivation of movement in patients with PD (Mazzoni et al., 2007).

Neuroimaging studies typically implicate the dysfunction of motor cortical-basal ganglia circuits as the neural underpinning of the difficulty with internally-generated movement in patients with PD (Berardelli et al., 2001). The dmFC regions, including the supplementary motor area (SMA), pre-SMA, and cingulate motor areas, are involved in intentional motor control. Numerous studies have shown deficient recruitment of these regions and the basal ganglia during internally-generated sequential movements in patients with PD (Jahanshahi et al., 1995; Samuel et al., 1997; Catalan et al., 1999; Sabatini et al., 2000; Nakamura et al., 2001; Yu et al., 2007). However, initiating and sustaining movements require an internally driven mechanism (i.e., “cues”) for not only motor, but also motivational and sensory preparedness (Chaudhuri et al, 2000). In addition to the motor cortical-basal ganglia circuits, the limbic circuits also play a role in the integration of these cues. Therefore, it is conceivable that the disrupted integration in both motor and limbic circuits in PD may lead to defective cue production for initiating and sustaining movements. Yet, the potential role of dysfunction in limbic circuits pertaining to the internal drive behind intentional movement has been under-investigated in PD. We propose that the standard cortical-basal ganglia circuit model of motor dysfunction in PD needs to be expanded to include the insula.

1.1. Insula is involved in body awareness and intentional movement.

The insula is a limbic region which is anatomically connected to many brain regions and demonstrates functional diversity (Nieuwenhuys 2012; Nomi et al., 2016; Uddin et al., 2014). It processes the viscerosensory and somatosensory afferent information from the brainstem, thalamus, and somatosensory cortex, and integrates it with the emotional and motivational context (Craig 2002, 2003, 2009; Critchley et al., 2004, 2013; Critchley 2005; Critchley and Harrison, 2013; Dijkerman et al., 2007; Garfinkel et al., 2015; Kenzie et al., 2016; Kurth et al., 2010; Strigo et al., 2016). This rich information

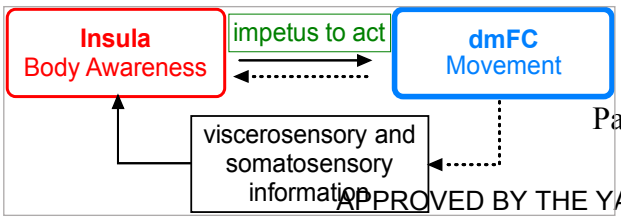

Fig.1. Insula-dmFC interaction model

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about the body (i.e., body awareness) is relayed to the dmFC and used to initiate new or to modify ongoing movements (Farrer and Frith, 2002; Paulus et al., 2009; Zapparoli et al., 2017). The insula then evaluates the outcome of the movement to reinforce adaptive movements in the future (Figure 1) (Brass and Haggard, 2010). During this iterative process an appropriate level of insula interaction with the dmFC is necessary to initiate and continue movement.
The insular cortex is one of the first cortical regions affected by the pathological process in PD suggesting an impairment in insula's role as a sensorimotor integrative hub in PD (Braak et al., 2006). Indeed, patients with PD have deficits in interoception (i.e., perception of the physiological milieu of the body) and kinesthesia (i.e., perception of limb and body motion) (Demirci et al., 1997; Ricciardi et al., 2016). Moreover, using resting-state fMRI, we demonstrated significantly reduced functional connectivity of the insula with the rest of the brain in patients with PD compared with controls (Tinaz et al., 2016a). This reduced functional connectivity also correlated with symptom severity and motor dysfunction.

1.2. Neurofeedback intervention has the potential to enhance the insula-dmFC functional connectivity strength, thus, improve sustained motor performance in patients with PD.

Neurofeedback enables subjects to obtain voluntary control over their brain activity through learning. With practice, subjects also learn to regulate the behavior that is associated with this brain activity. For instance, healthy subjects used mental strategies for emotion induction, which led to right insula activation, and learned to modulate this activity with neurofeedback (Caria et al., 2007). FMRI-based neurofeedback has been used successfully in symptom treatment of several neuropsychiatric disorders (e.g., anxiety, depression, addiction) (Hartwell et al., 2013; Scheinost et al., 2013; Young et al., 2014), but reports on its use in PD are scant. Two studies used fMRI-based neurofeedback in patients with PD and demonstrated significant increase in the SMA activity with neurofeedback Subramanian et al., 2011, 2016). This increase was accompanied by a clinically meaningful, but, compared with the control group, statistically insignificant improvement in motor function Subramanian et al., 2016). There is a knowledge gap regarding the mechanism of action, feasibility, and potential efficacy of neurofeedback in PD. We aim to fill this gap by employing a new technique that uses the functional connectivity strength between brain regions, as opposed to the activity in a single brain region, as neurofeedback (Megumi et al., 2015; Koush et al., 2017). In general, this technique is suitable for most neuropsychiatric conditions including PD because they are associated with dysfunction of neural circuits rather than of individual brain areas. It is particularly pertinent for our model that proposes that the insula and dmFC promote sustained intentional movement via their concerted effort. Therefore, we think that this new approach provides a neurobiologically more meaningful measure for use in neurofeedback.

1.3. Motor imagery is a suitable mental strategy for use in neurofeedback learning.

Motor imagery refers to the mental rehearsal of motor acts without overt body movement and recruits virtually the same brain regions that are involved in the actual planning and execution of motor tasks (Guillot et al., 2014). The duration of the imagined movements correlates with that of the real movements. Imagined and real movements also evoke similar autonomic responses. These similarities led to the notion of functional equivalence which likely explains the beneficial effect of motor imagery on motor performance in athletes (Guillot and Collet, 2008) and in rehabilitation of neurological disorders (e.g., stroke) (Di Rienzo et al., 2014). Surprisingly, motor imagery practice has been rarely employed in the motor rehabilitation of patients with PD, partly due to the discouraging viewpoint about its utility in PD (Dickstein and Tamir, 2010). However, one study demonstrated significant improvement in slowness during sequential movement tasks in patients with PD who received 12 weeks of motor imagery practice of everyday actions compared with the control group (Tamir et al., 2007). Neuroimaging studies in PD demonstrated reduced activation in the dmFC regions during motor

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imagery which was improved with dopaminergic treatment (Dickstein and Tamir, 2010). Patients with PD in the two fMRI-based neurofeedback studies discussed in the previous section also used motor imagery to increase the SMA activation and were tested when they were on dopaminergic medication (Subramanian et al., 2011, 2016). These findings suggest that patients with PD have the capacity to use motor imagery in neurofeedback learning. They can also benefit from its practice when the imagery tasks focus on activities of daily life to re-activate motor representations that are part of the patient's motor repertoire (Dickstein and Tamir, 2010).

The content of motor imagery also determines the brain activation patterns. Kinesthetic motor imagery (i.e., mental image of the sensation of movement) preferentially recruits the sensorimotor-related brain regions, whereas visual motor imagery (i.e., seeing the movement in mind's eye) preferentially recruits the visuospatial-related brain regions (Guillot et al., 2009; Guillot et al., 2014). Kinesthetic motor imagery has also been used successfully in healthy subjects during neurofeedback learning to enhance the activation in sensorimotor brain regions (Marchesotti et al., 2016). Kinesthetic motor imagery also fits our insula (sensation) - dmFC (movement) interaction model (Fig.1). We propose that patients with PD can use this strategy successfully to increase the functional connectivity strength between the insula and dmFC, which in turn will improve their kinesthetic awareness and motor performance.

In fact, in our pilot study, we demonstrated the feasibility of this strategy in eight subjects with PD. Using motor imagery during neurofeedback learning, these subjects were able to significantly increase the functional connectivity strength between the insula and dmFC after a total of 10-12 neurofeedback sessions.

4. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

2. Research Strategy

2.1. Overview:

This study is a Phase II randomized clinical trial. We plan on recruiting a total of 60 subjects with PD via the support group chapters of the local advocacy group Connecticut Advocates for Parkinson's and the Yale Movement Disorders Clinic. All subjects will undergo MRI safety and medical history screening. Eligible subjects will be randomized into two groups: PD-neurofeedback and PD-control. Subjects in both groups will complete four visits in about 4-5 weeks, but only the PD-neurofeedback group will receive fMRI-based neurofeedback training. All testing and scanning will take place at the Yale Magnetic Resonance Research Center (MRRC). The timeline of the experimental protocol is shown in Figure 2.

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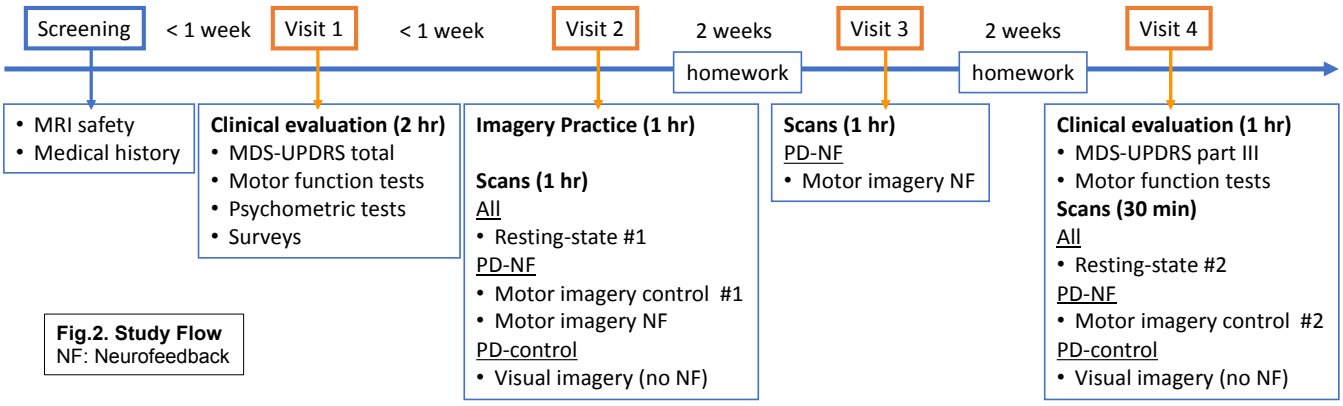

Fig.2. Study Flow
NF: Neurofeedback

2.2. Subjects:

Subjects who are interested in participating in the study will undergo medical history and MRI screening for eligibility in-person or via phone/email. The standard MRI Safety Questionnaire that was developed at the MRRC will be used. Subjects will also be asked detailed questions to determine whether they would be safely able and willing to comply with the requirement of holding the morning dose of their medication temporarily for research visits 1 and 4. Conditions that are related to being "off" medication by history such as excessive slowness and/or stiffness, freezing of gait, severe balance problems and/or falls, and severe anxiety will be deemed unsafe. Only subjects who would be safely able and willing to comply with this requirement will be enrolled.

2.3. MRI Scanning Parameters:

Subjects will always be scanned in the morning after they take the first dose of their dopaminergic medication. We will conduct the MRI experiments in a Siemens 3.0 Tesla human research magnet in the MRRC. A 32-channel head coil will be used to collect high-resolution anatomical and echo planar images for fMRI. First, T1-weighted MPRAGE anatomical images (voxel size: 1 x 1 x 1 mm) will be collected for an accurate localization of the fMRI data. T1-weighted FLASH axial images (voxel size: 0.9 x 0.9 x 4 mm, 36 slices, FoV: 224 mm, TR: 300 ms, TE: 2.47 ms, flip angle: 60°) will be collected as an intermediate scan to coregister MPRAGE and echo planar functional images for the neurofeedback sessions. Then, axial, T2-weighted, echo planar functional images will be collected (voxel size: 3.5 x 3.5 x 4 mm, 36 slices, FoV: 224 mm, TR: 2000 ms, TE: 25 ms, flip angle: 90°). The number of acquisitions will be 120 for the imagery sessions and 304 for the resting-state scans.

2.4. Research Visit 1:

2.4.1. Clinical Evaluation:

All subjects will be asked to temporarily hold the morning dose of their dopaminergic medication on Visit 1. Upon obtaining informed consent to participate in the study, Dr. Tinaz will perform an initial physical and neurological examination on all subjects. The diagnosis of idiopathic PD will be made according to the UK Brain Bank diagnostic criteria (Hughes et al., 1992). Cognitive and emotional problems may interfere with imagery performance. To rule out dementia and depression, the Montreal Cognitive Assessment test and Beck Depression Inventory-II will be administered, respectively (Nasreddine et al., 2005; Beck 1997). The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008) and Hoehn & Yahr staging (Hoehn and Yahr, 1998) are standardized clinical rating scales to determine disease severity and stage in PD. Part III of the MDS-UPDRS is the objective motor examination part that also includes Hoehn & Yahr staging. This part will be videotaped for all subjects. The videos will be viewed and exam features scored by another neurologist with movement disorders training (Dr. Patel) who is blind to subjects' group assignment. The standardized motor function tests (timed up and go, 10-m walking, 2-min endurance walking, five

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times sit-to-stand, turning in place 360 degrees, and Physical Performance Test) will be administered to measure movement speed and vigor. All of these are standardized tests and scales, and are commonly used in clinical practice to assess symptom severity in PD.

Immediately after this initial assessment, subjects will take their dopaminergic medication. Subsequently, subjects will be administered additional self-evaluation questionnaires. These include: Starkstein Apathy Scale (Starkstein et al., 1992), Spielberger State-Trait Anxiety Inventory (Spielberger et al., 1982), Parkinson disease Fatigue Scale (Brown et al., 2005), Parkinson disease quality of life scale (PDQ39) (Peto et al., 1995), Self-Assessment Parkinson's Disease Disability Scale (SPDDS) (Biemans, et al., 2001) and Multidimensional Assessment of Interoceptive Awareness (MAIA) questionnaire (Mehling et al, 2012). Motor imagery skills will be tested using the Movement Imagery Questionnaire-3 (MIQ-3) (Williams et al., 2012).

After visit 1, subjects will be randomized to PD-neurofeedback and PD-control groups (see 13. Statistical Considerations).

Note: Immediately after administering the BDI, Dr. Tinaz will calculate the subjects' BDI scores. The BDI cut-off score for moderate depression is 20-28. A BDI score of 20 will be the scoring threshold for counseling. Dr. Tinaz will counsel these subjects face-to-face in Visit 1 and encourage them to make an appointment with Yale Center for Anxiety and Mood Disorders or other counseling resources as appropriate. Assistance in making appointments will be provided if requested. Those requesting referrals outside the University will be given a list of referrals of therapists who specialize in mood disorders. Subjects will also be provided the contact information of the American Parkinson Disease Association Connecticut Chapter and Connecticut Advocates for Parkinson advocacy group. These organizations provide resources and support for the physical, emotional, and social wellbeing of individuals with Parkinson's disease. Dr. Tinaz will follow up with these subjects directly in the subsequent visits and provide further counseling, additional information, or referrals as requested.

Any subject who endorses a response of "I would like to kill myself" or "I would kill myself if I had the chance" to the BDI item 9 will be provided information about local suicide support and prevention services, suicide hotlines, and the National Suicide Prevention Lifeline. Should there be signs of imminent risk, the Yale New Haven Hospital (YNHH) Emergency Services will be called to transfer the subject to the YNHH Emergency Department for evaluation. The IRB will also be informed in cases where imminent risk of harm is discovered.

2.5. Research Visit 2:

Both groups will complete the self-evaluation questionnaires Perceived Stress Scale-Motor and Motor Function Survey.

2.5.1. Procedures for the PD-neurofeedback group:

There will be no interference with the medication schedule. Subjects will take their dopaminergic medications as scheduled.

2.5.1.1. Imagery Practice Session:

The aim of this session is to determine each subject's motor repertoire, identify their motor difficulties, and familiarize them with mindfulness body scan and motor imagery practices. Subjects will be informed about both practices and will be given time to ask questions. Subjects will be primed to experience body awareness by engaging in a mindfulness body scan practice during which they will listen to an audio recording guiding them to pay attention to sensations in different body parts. Subsequently, audio-recorded scripts with detailed descriptions of basic movements will be provided for each subject to practice. These scripts are based on the kinesthetic imagery component of the standard motor imagery questionnaires (Kinesthetic and Visual Imagery Questionnaire and Movement Imagery Questionnaire-3). Subjects will first perform the movements (e.g., raise your knee, lift up your arm, tap

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your foot, etc.), then imagine performing the movements while at the same time focusing on the sensations (e.g., proprioceptive, kinesthetic, interoceptive) evoked by the movements. Finally, subjects will practice guided kinesthetic motor imagery of whole body complex movements (e.g., walking, running, swimming, calisthenics) on their own. Subjects will be instructed to focus on the imagined bodily felt sense that the movements in these motor imagery tasks evoke.

2.5.1.2. Scanning:

2.5.1.2.1. Resting-State fMRI:

After the routine anatomical scan for localization (5 min), fMRI scans will be collected during resting-state for 10 min. Subjects will be instructed to keep their eyes closed and let their mind wander without focusing on a specific thought.

2.5.1.2.2. Neurofeedback-Guided Motor Imagery Scans:

Neurofeedback Paradigm:

Subjects will practice the kinesthetic motor imagery of complex movements as described in Section 2.5.1.1. in the scanner during neurofeedback learning.

A night sky picture on the screen will instruct subjects to engage in motor imagery for 40 s. This picture with subdued visual input was chosen to minimize interference during imagery. Subjects will be told not to change strategies within a block. The right insula-dorsomedial frontal cortex functional connectivity strength will be computed during the 40-s task block and presented to the subject in the form of a bar plot for 8 s at the end of the block to provide neurofeedback (blue bar: negative, red bar: positive neurofeedback) (Figure 3B). The magnitude of the bar will reflect the strength of the functional connectivity, and subjects will be instructed to increase this. There will be five motor imagery task blocks followed by feedback in each session. Each subject will complete a total of 6-7 sessions.

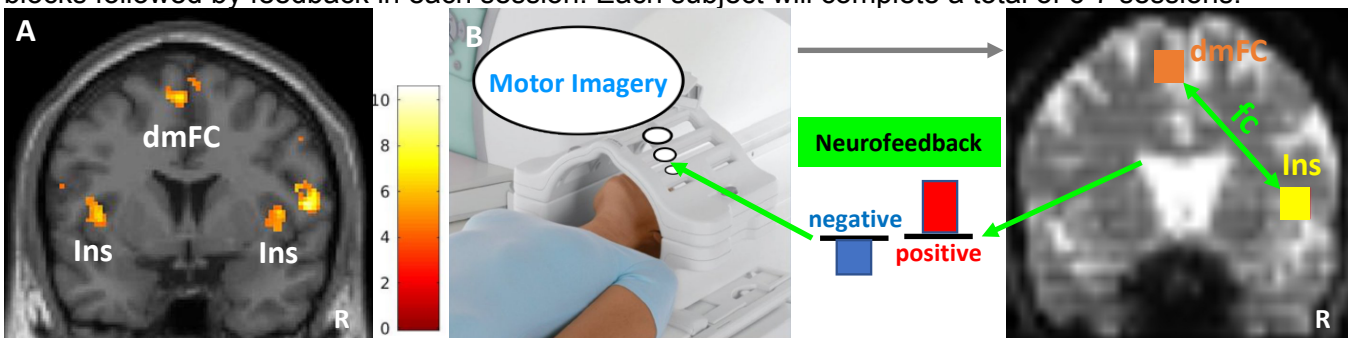

Fig.3. A. Group activations during the **heart-beat counting task** shown on a coronal slice. Color bar: t values ($p < 0.001$, uncorrected, cluster size: 10 voxels). dmFC: Dorsomedial frontal cortex, Ins: Insula, R: Right. **B**: dmFC and Ins masks are translated into each subject's functional space. Functional scans during motor imagery are collected and preprocessed in real-time. The signal time courses averaged across voxels within the masks are correlated with each other (fc: functional connectivity) and the z-transformed correlation values are plotted as bars to provide the neurofeedback.

Control scans:

The control scans without neurofeedback will be implemented in the same way as described in the neurofeedback paradigm, but a horizontal white line instead of a red or blue bar will be presented for 8 s after each task block. In other words, subjects will not be shown the right insula-dorsomedial frontal cortex functional connectivity strength as neurofeedback. Subjects will know that they will not receive neurofeedback on their performance during control scans. There will be two control scans. The first one will be collected in Visit 2 before the neurofeedback scans and the last one will be collected in Visit 4. The difference in performance between the first and last control scan will serve as a measure of learning.

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2.5.1.2.3. Real-time Functional Connectivity Analysis:

Previously, we used a silent heartbeat counting task during fMRI (Critchley et al., 2004) to functionally localize the insula and dmFC in a different group of subjects with mild PD (N = 10). Figure 3A shows the average group activations in the insula bilaterally (right>left) and dmFC. Our results are in line with previously reported activations in the insula and dmFC during the heartbeat counting task (Kurth et al., 2010; Simmons et al., 2013; Schulz 2016). We will create a cubic anatomical mask (6 x 6 x 6 mm) centered at the voxel with peak activity in the right insula (peak: x = 44, y = 4, z = 8) and dmFC (peak: x = -4, y = 2, z = 62). These anatomical masks will be created in the standard MNI brain space and then translated into each subject's functional space. Functional scans of each subject will be preprocessed and de-noised as described in Scheinost et al (2013b). The signal time course of the right insula and dmFC masks in a given subject will be computed as the average time course across all voxels within each of these masks. Finally, the time courses will be correlated and the r-values will be Fisher z-transformed. A Matlab program will plot the z-values as a bar and present them as neurofeedback (Figure 3B). The same procedures will be applied to the control scans with one exception: The z-values will be recorded, but not presented to the subjects as neurofeedback. Instead, subjects will see a horizontal white line.

2.5.2. Procedures for the PD-control group:

There will be no interference with the medication schedule. Subjects will take their dopaminergic medication as scheduled.

2.5.2.1. Imagery Practice Session:

To control for the imagery components in the PD-neurofeedback group, PD-control subjects will receive a visual imagery-guided relaxation training based on audio scripts. Guided visual imagery will include shapes, colors, spaces, but no motor imagery. Subjects will be informed about the practice and given time to ask questions. Subsequently, audio-recorded relaxation visual imagery scripts will be provided for each subject to practice.

2.5.2.2. Scanning:

2.5.2.2.1. Resting-state fMRI:

After the routine anatomical scan for localization (5 min), fMRI scans will be collected during resting-state for 10 min. Subjects will be instructed to keep their eyes closed and let their mind wander without focusing on a specific thought.

2.5.2.2.2. Visual Imagery Scans:

The same experimental paradigm will be followed as described in Section 2.5.1.2.2 for the control scans. Subjects will perform visual imagery in the scanner, but will not receive neurofeedback, instead, will be presented a horizontal white line. The right insula-dmFC functional connectivity will also be calculated in the same way as explained in Section 2.5.1.2.3 for the control scans.

2.5.3. Homework:

2.5.3.1. PD-neurofeedback group:

We will refine the scripts according to subjects' report on their most successful motor imagery strategies during neurofeedback runs in Visit 2, and ask them to practice these strategies at home for a total of 15 min every day (Tamir et al., 2007) between visits. Subjects will be provided a motor imagery diary and asked to keep a detailed log every day. We structured this diary based on the key elements of motor imagery practice including the duration, setting, content, and difficulty level of the

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motor imagery exercise, as well as the type and quality of body sensations evoked by imagined movements (Collins and Carson, 2017).

2.5.3.2. PD-control group:

Subjects will continue practicing visual imagery-guided relaxation exercises at home and also be asked to keep a detailed log every day about the duration, setting, content, difficulty level, and the associated body sensations of these imagery exercises.

All subjects will receive daily reminders via text messages or emails to ensure adherence to daily imagery exercises.

2.6. Research Visit 3

2.6.1. Procedures for the PD-neurofeedback group:

There will be no interference with the medication schedule. Subjects will take their dopaminergic medication as scheduled.

Subjects' diary entries and their overall experience with motor imagery will be reviewed and strategies for improvement and refinement will be discussed. Subsequently, subjects will complete 6-7 neurofeedback training runs as described in Visit 2. Subjects will again be instructed to continue practicing the successful motor imagery exercises at home as described in Visit 2.

2.6.2. Procedures for the PD-control group:

There will be no interference with the medication schedule. Subjects will take their dopaminergic medication as scheduled. Additional four surveys (Self-Efficacy, Self-regulation, Proactive Coping, Reflective Coping) and one cognitive rest battery specific for PD (SCOPA-COG) will be administered to match the study procedures (e.g., time spent with staff and engagement) between the PD-neurofeedback and PD-control groups. This additional material will be used as "filler" and will not interfere with any of the outcome measures or other study procedures.

Subjects' diary entries and their overall experience with visual imagery-guided relaxation will be reviewed and strategies for improvement and refinement will be discussed. Subjects will again be instructed to continue practicing the visual imagery exercises at home as described in Visit 2.

2.7. Research Visit 4:

All subjects will be asked to temporarily hold the morning dose of their dopaminergic medications.

2.7.1. Clinical Evaluation:

The MDS-UPDRS part III motor examination and the standardized motor function tests will be repeated for all subjects. The MDS-UPDRS part III will be videotaped and the videos will be scored by a neurologist with movement disorders training (Dr. Patel), who is blind to subjects' group assignment.

Immediately after this final assessment, subjects will take their dopaminergic medication.

2.7.2. Scanning:

The resting-state fMRI scan for 10 min will be repeated for all subjects. Subjects will be instructed to keep their eyes closed and let their mind wander without focusing on a specific thought.

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2.7.2.1. PD-neurofeedback group:

The control scan during which subjects perform motor imagery without neurofeedback will be repeated.

2.7.2.2. PD-control group:

The visual imagery scan, which is practically the same as the control scan, will be repeated.

2.8. Resting-State Imaging Data Analysis

2.8.1. Resting-State Data Preprocessing:

The Connectivity toolbox will be used for all resting-state data analysis steps (Whitfield-Gabrieli and Nieto-Castanon, 2012). Removal of the first four scans to reach magnetization steady state, motion correction, outlier detection, coregistration of functional scans with the anatomical scan, normalization to the standard MNI template, and smoothing with an 8-mm kernel to account for inter-individual anatomical variability will be performed. De-noising steps will include the elimination of signal originating from the white matter and cerebrospinal fluid, regression of motion artifacts and outliers from the time series, scrubbing, quadratic detrending, and bandpass-filtering ($0.008 < f < 0.1$ Hz) to capture the fluctuations of the blood oxygenation level-dependent signal that typically occur within this frequency range at rest.

2.8.2. Functional Connectivity Analysis:

For each subject, the resting-state signal time courses will be extracted from the voxels within the right insula and dmFC masks, averaged, and correlated with those extracted from the regions of the whole brain atlas in the Connectivity toolbox using Pearson correlation. The correlation values will be Fisher z-transformed for second-level statistical analysis. This analysis will yield a correlation map for the right insula and dmFC separately for each subject.

3. Research Strategy for the Exploratory Aims:

Subjects: We plan on recruiting 15 new subjects with PD. Subjects who are interested in participating in the study will undergo medical history and MRI screening for eligibility in-person or via phone/email. The standard MRI Safety Questionnaire that was developed at the MRRC will be used. All experimental procedures will be completed in one research visit. Subjects will continue to take their PD medications as scheduled throughout the research visit.

Clinical Evaluation: Dr. Tinaz will perform an initial physical and neurological examination on all subjects. The diagnosis of idiopathic PD will be made according to the UK Brain Bank diagnostic criteria (Hughes et al., 1992). The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008) and Hoehn & Yahr staging (Hoehn and Yahr, 1998) will be used to determine disease severity and stage of PD subjects. The Montreal Cognitive Assessment test will be administered to rule out dementia (Nasreddine et al., 2005). Self-evaluation questionnaires will be administered including: Beck Depression Inventory-II Beck 1997, Starkstein Apathy Scale (Starkstein et al., 1992), Spielberger State-Trait Anxiety Inventory (Spielberger et al., 1982), Parkinson disease Fatigue Scale (Brown et al., 2005), Parkinson disease quality of life scale (PDQ39) (Peto et al., 1995), and Self-Efficacy (Chen et al., 2011) and Self-Regulation (Schwarzer et al., 1999) scales. Imagery skills will be tested using the Questionnaire on Mental Imagery (Sheehan 1967).

Hybrid Mental Imagery Practice: Subjects will practice guided mental imagery of everyday task performance outside the scanner.

Video-Watching Practice: Subjects will watch sample video footage of everyday task performance outside the scanner for practice.

MRI Parameters: We will conduct the MRI experiments in a Siemens 3.0 Tesla human research

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magnet in the MRRC. A 32-channel head coil will be used to collect high-resolution anatomical and echo planar images for fMRI. First, T1-weighted MPRAGE anatomical images (voxel size: 1 x 1 x 1 mm) will be collected for an accurate localization of the fMRI data. Then, axial, T2-weighted, echo planar functional images will be collected (voxel size: 3.5 x 3.5 x 4 mm, 36 slices, FoV: 224 mm, TR: 2000 ms, TE: 25 ms, flip angle: 90°). The number of acquisitions will be 120 (4 min) for each mental imagery and video-watching session.

fMRI Tasks: Subjects will perform 4 scans of hybrid mental imagery and 4 scans of video-watching of everyday task performance (e.g., preparing a meal, grocery shopping). Each fMRI scan will last 4 min. After each scan subjects will answer basic questions about the imagery and video content by pressing buttons. The total scan time will not exceed 1 hour. There will be a short post-scan debriefing to assess memory of the imagery and video content.

fMRI Data Analysis: The Connectivity toolbox will be used (Whitfield-Gabrieli and Nieto-Castanon, 2012). Removal of the first four scans to reach magnetization steady state, motion correction, outlier detection, coregistration of functional scans with the anatomical scan, normalization to the standard MNI template, and smoothing with an 8-mm kernel to account for inter-individual anatomical variability will be performed. De-noising steps will include the elimination of signal originating from the white matter and cerebrospinal fluid, regression of motion artifacts and outliers from the time series, scrubbing, quadratic detrending, and highpass-filtering (0.008 Hz < f < Inf). For each subject, the signal time courses during imagery and video-watching tasks will be extracted from the regions of the whole brain atlas in the Connectivity toolbox using Pearson correlation. The correlation values will be Fisher z-transformed. This analysis will yield correlation maps for imagery and video-watching tasks for second-level statistical analysis.

5. Genetic Testing N/A ☒
   - **A.** Describe
     - i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
     - ii. the plan for the collection of material or the conditions under which material will be received *Write here*
     - iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
     - iv. the methods to uphold confidentiality *Write here*

   - B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
   - C. Is widespread sharing of materials planned? *Write here*
   - D. When and under what conditions will materials be stripped of all identifiers? *Write here*
   - E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
     - i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
   - F. Describe the provisions for protection of participant privacy *Write here*
   - G. Describe the methods for the security of storage and sharing of materials *Write here*

6. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

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There is no restriction for gender, race, or ethnicity. Fifty subjects with PD will be recruited for this study. The median age of onset of idiopathic PD is 62.4 years. In the US, the incidence of PD cases before age 40 is extremely low (Wirdefeldt et al., 2011). Therefore, individuals below the age of 40 will not be included. PD affects more males than females with a median 1.8:1 male:female ratio (Wirdefeldt et al., 2011). We will aim to reflect this ratio in subject selection. Local and non-local patients with PD are referred to our outpatient clinics. We will seek a racially and ethnically diverse enrollment. A cross-sectional epidemiological study based on Medicare records (Willis et al., 2010). 61 reported the following ratios for racial distribution of PD in the US: White:Black = 1.5 and White : Asian = 1.4. Hispanic was treated as a racial category and the White (non- Hispanic):Hispanic ratio was 1. The number of other racial categories was very small. The numbers in the planned enrollment table below were calculated based on these ratios.

Planned Enrollment

	Not Hispanic or Latino		Hispanic or Latino		Total
Racial Category	Female	Male	Female	Male	
Asian	4	8	0	0	12
Black or African American	7	11	0	0	18
White	7	13	4	6	30
Total	18	32	4	6	60

7. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children ☐ Healthy ☐Fetal material, placenta, or dead fetus
☐Non-English Speaking ☐ Prisoners ☐Economically disadvantaged persons
☐Decisionally Impaired ☐ Employees ☐Pregnant women and/or fetuses
☐Yale Students ☐ Females of childbearing potential

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

8. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?

Inclusion Criteria:

Subjects with a diagnosis of idiopathic PD defined according to the UK Brain Bank diagnostic criteria (Hughes et al., 1992) and on a stable dopaminergic medication regimen will be included.

Exclusion Criteria:

- Age < 40 years
- Non-English speaking
- Pregnancy
- Breastfeeding
- Excessive alcohol consumption (> 7 drinks per week for women, > 14 drinks per week for men) or substance use

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- History of a neurological disorder such as a brain tumor, stroke, central nervous system infection, multiple sclerosis, movement disorder (other than PD), or seizures
- History of schizophrenia, bipolar disorder, attention deficit disorder, or obsessive compulsive disorder
- History of head injury with loss of consciousness
- Metallic surgical implants or traumatically implanted metallic foreign bodies
- Inability to lie flat for about an hour
- Discomfort being in small, enclosed spaces
- Dementia (Montreal Cognitive Assessment score < 21)
- Hoehn & Yahr stage > 3 (i.e., able to stand and walk, but not fully independent)
- Focal neurological findings on exam that suggest cerebral pathology other than that associated with parkinsonism
- Motor symptoms that could potentially introduce too much motion artifact in the imaging data (e.g., MDS-UPDRS resting tremor score > 1 in limbs, head/chin tremor, or dyskinesia by history or exam).

9. How will **eligibility** be determined, and by whom? Write here

Eligibility will be determined based on age, MRI safety screening, and clinical criteria as listed in Inclusion/Exclusion Criteria. After subjects pass the MRI safety and medical history screening, Dr. Tinaz will determine eligibility.

10. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The proposed research plan involves a neurological examination, administration of questionnaires and paper-pencil tests, behavioral testing, and MRI. Subjects who are on dopaminergic medications (e.g., carbidopa/levodopa, dopamine receptor agonists) will be asked to hold the first morning dose of medications temporarily for research visits 1 and 4. Only patients who would be safely able and willing to comply with this requirement will be enrolled. Immediately upon completion of testing, subjects will resume their routine medication schedule. If at any point of testing the subjects experience discomfort as a result of being off their medication, the testing will be terminated and they will be given their medication. Subjects will always be scanned after they take their dopaminergic medications. The potential risks associated with individual study procedures are as follows:

<u>Clinical Evaluation:</u>

The clinical evaluation including neurological examination, questionnaires, and paper-pencil tests does not entail any medical risk. Subjects may choose to stop participating in the surveys/questionnaires at any time.

<u>MRI in 3 Tesla scanner</u>:

Subjects are at risk for injury from the scanner, if they have metal objects in their bodies (e.g., pacemakers, aneurysm clips, metallic prostheses, implanted delivery pumps, cochlear implants, shrapnel fragments). Welders and metalworkers are also at risk for injury because of possible presence of small metal fragments in the eye, of which they may be unaware. Individuals with fear of confined spaces (i.e., claustrophobia) may become anxious during MRI. The scanner makes a thumping noise created by the radiofrequency waves necessary for forming the images. The noise can be loud enough to damage hearing. Lying flat in the scanner for an hour might cause discomfort for some subjects. On rare occasions, some people might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly.

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11. Minimizing Risks: Describe the manner in which the above-mentioned risks will be minimized.

Informed consent:

Each subject will receive an oral and written explanation of the purposes, procedures, and risks of the study in language appropriate for the individual's level of understanding. The subjects will be given the opportunity to ask questions and discuss any concerns with the investigators. Subsequently, they will have to demonstrate understanding of the study procedures and what is expected of them. All members of the research team are trained to obtain informed consent. The signed consent form will be placed in the study record.

Subject Monitoring:

Subject's participation will be terminated under the following conditions: 1) Subject develops a serious medical condition. 2) Subject is not compliant with protocol evaluations. 3) Subject requests withdrawal from the study. During MRI, a member of the research team will always be present in the scanning room and monitor all subjects continuously. Scanning will be terminated immediately upon subject's request or if an adverse event occurs.

MRI-related risk management:

Subjects will be prescreened for MRI safety and excluded, if they are pregnant/ breastfeeding or claustrophobic, or have metal in their bodies. Subjects who report that they cannot tolerate lying flat on their back for an hour during scanning will be excluded.

All people involved with the study must remove all metal from their clothing and all metal objects from their pockets. They will also walk through a detector designed to detect metal objects before they enter the magnet room. No metal can be brought into the magnet room at any time. Also, once the subject is in the magnet, the door to the room will be closed so that no one from outside accidentally goes near the magnet. Subjects will be watched closely throughout the MR study.

Some subjects may feel uncomfortable or anxious. If this happens to, they may ask to stop the study at any time and we will take them out of the MR scanner. On rare occasions, some subjects might feel dizzy, get an upset stomach, have a metallic taste or feel tingling sensations or muscle twitches. These sensations usually go away quickly, but we will ask the subjects to tell the research staff if they have them.

Subjects will be fitted with ear plugs to protect their ears. Subjects will be provided a cushion underneath their knees for comfort and to release back strain from lying flat. The heart rate and breathing of the subjects will be monitored continuously during scanning. Subjects will be observed by the members of the research team at all times and be able to communicate with them throughout scanning via the intercom. Subjects will be removed from the scanner at their request, or in the event of an emergency or adverse reaction.

Safeguard for vulnerable populations:

Women of childbearing potential will not be included, if they are pregnant or breastfeeding. Women who are 50 years of age and older or who have absence of menses for two years will not receive pregnancy tests. All other women will receive urine pregnancy test.

Confidentiality:

Hard copies of all medical information collected from study participants will be kept in a locked filing cabinet. Unique identifiers will be used to label all data. Electronic files will be maintained on password-protected research computers. The imaging data will be stored on secure and HIPAA compliant servers in the MRRC. All team members will use password-protected research computers. Strict standards of confidentiality will be upheld at all times.

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12. Data and Safety Monitoring Plan: Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Minimal risk
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? *Write here*
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

    d. For multi-site studies for which the Yale PI serves as the lead investigator:
        i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? *Write here*
        ii. What provisions are in place for management of interim results? *Write here*
        iii. What will the multi-site process be for protocol modifications? *Write here*

13. Statistical Considerations: Describe the statistical analyses that support the study design.

Statistical Analyses:

Demographic and clinical data: Independent-sample t-tests will be performed to compare the baseline values between the PD-neurofeedback and PD-control groups ($p < 0.05$, two-tailed).

Aim 1: A 2x2 mixed ANOVA with an interaction term will be performed to assess group differences in right insula-dmFC functional connectivity (between-subject factor: group, within-subject factor: right insula-dmFC functional connectivity during the first and last control scan, interaction: group x insula-dmFC functional connectivity). Post-hoc tests will be Bonferroni-corrected, $p < 0.05$.

Aim 2: Within-group one-sample t-tests will be performed on the right insula and dmFC resting-state functional connectivity maps. A 2x2 mixed ANOVA with an interaction term will be performed to assess group differences in resting-state functional connectivity (between-subject factor: group, within-subject factor: resting-state functional connectivity pre- and post-intervention, interaction: group x resting-state functional connectivity). All group analyses will be corrected for multiple comparisons using the false discovery rate procedure ($p < 0.05$, two-tailed) (Genovese et al., 2002).

Aim 3: The scores (i.e., time required for completion) of the motor function tests will be z-transformed and summed to obtain a composite motor function score for each subject. A 2x2 mixed ANOVA will be performed to compare the differences in motor functioning between the groups pre- and post-training (between-subject factor: group, within-subject factors: MDS-UPDRS motor exam and composite motor function scores, interaction: group x motor assessment). Post-hoc tests will be Bonferroni-corrected, $p < 0.05$.

Exploratory Aims: A paired-sample t-test will be performed to assess the differences in the whole-brain functional connectivity associated with the imagery and video-watching tasks. The results will be corrected for multiple comparisons using the false discovery rate procedure ($p < 0.05$, two-tailed) (Genovese et al., 2002).

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Power analysis: The sample size calculation is based on the clinically important difference (CID) in the primary motor outcome measure. Approximately a 5-point decrease in the mean MDS-UPDRS motor exam score after an intervention has been defined as a moderate CID (Schrag et al., 2006; Shulman et al., 2010). In this study, we expect a moderate CID. We used the mean and standard deviation of the MDS-UPDRS motor exam scores (24 ± 9) of a large group of subjects with PD (N = 347) as the population mean and standard deviation (Shulman et al., 2010). Assuming $\alpha = 0.05$ and power = 0.80, 22 subjects are required for a moderate CID. Considering the possibility of a 35% drop-out rate between Visits 1 and 4, we will plan to recruit 30 subjects each for the PD-neurofeedback and PD-control group, total of 60 subjects. We will also perform an adaptive interim statistical analysis based on the primary motor outcome (Bauer and Kohne, 1994). If the p values fall between 0.023 (efficacy boundary) and 0.5 (futility boundary), then we will recalculate the sample size based on conditional power (e.g., 0.80). If the p value is < 0.023 (i.e., significant difference) or > 0.5 (i.e., no hope to find a significant difference), we will terminate the study.

Randomization: Group assignment of subjects will be determined by the end of Visit 1. We will use a covariate adaptive randomization method (Lin et al., 2015). Age and gender are important variables and need to be controlled during randomization. This method will take into account age and gender and sequentially assign each new subject accordingly. This approach will allow us to balance the two groups in terms of age and gender.

Potential problems: 1) Variability in neurofeedback learning will be expected. We aim to reduce variability by providing personalized and detailed motor imagery scripts and facilitate learning with homework. 2) In general, attrition rate can be an issue especially in control groups. Our active control design will help minimize this by controlling for subject engagement in tasks during visits and at home, and for time spent with research staff.

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SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

Write here

B. DRUGS/BIOLOGICS ☒N/A

B. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:
   a. Targeted for enrollment at Yale for this protocol: **70 subjects with PD**
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☐ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☒ Newspaper
☐ Departmental/Center newsletters	☒ Web-based clinical trial registries	☐ Clinicaltrails.gov
☒ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☐ Other:		

We will use the already approved language from the study flyer for the YCCI Recruitment database, Social Media, and Newspaper postings:

Mental Imagery Study in Parkinson's disease

If you are a Parkinson's disease patient who is 40+ years of age, fluent in English, able to pass an MRI metal screening, and are not claustrophobic, you may be eligible to participate in a free and confidential study that will help us understand how the brain changes and potential motor benefits associated with mental imagery training in Parkinson's disease. The study involves 4 visits that will include neurological assessment, paper-pencil tests, brief behavioral tasks, and MRI scans. Compensation up to $200 ($50 per visit).

To learn more or see if you are eligible to participate, email Sule Tinaz at sule.tinaz@yale.edu or call 203-785-2185.

* Requests for medical records should be made through JDAT as described at http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

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a. Describe how potential subjects will be identified.

Flyers will be handed out to potential subjects with PD in the Yale New Haven Hospital Movement Disorders Clinic. Study information will be posted on 1) internet/web postings/electronic newsletters of local PD support groups and organizations, 2) Web-based clinical trial registries (e.g., Research Match).

Text that will be used in study postings:

This study investigates the effects of mental imagery using functional magnetic resonance imaging (MRI). The aim of this study is to understand whether different types of mental imagery improve motor function and brain plasticity in individuals with Parkinson's disease.

MRI is a technique that uses magnetism and radio waves, not x-rays. We will use MRI to take pictures of your brain while you perform mental imagery tasks in the scanner.

We are inviting volunteers with Parkinson's disease who are above 40 years of age, fluent in English, able to pass an MRI metal screening, and not claustrophobic.

The study requires four visits to the Yale Magnetic Resonance Research Center in New Haven, CT.

You will have to participate in surveys, paper-pencil tests, neurological evaluations, and brain imaging sessions.

Volunteers will be compensated for participating.

We will also request from JDAT help with recruitment of patients with idiopathic Parkinson's disease aged 40 years and over who are followed in the Yale New Haven Hospital Movement Disorders clinics and who do not have an implanted deep brain stimulator or cardiac pacemaker.

1. For Sule Tinaz's (PI) own patients and patients of clinicians within the PIs Movement Disorders clinic who treat patients with diopathic Parkinson's disease:

   For this group, we will request from JDAT to do a search of patients from the clinic who meet the criteria for the study and who have NOT opted out of research. We will request from JDAT to provide us with a list of these patients. The PI will then contact these subjects by sending them a letter and the PI or study coordinator will follow-up with this group with a phone call if the PI/study coordinator does not hear from them within 10 days. A template letter has been attached to this submission.

2. We will also ask JDAT to build an EPIC query to identify all patients that meet study criteria. Patients who have an Epic MyChart account and meet basic inclusion /exclusion criteria will be notified of the study through a MyChart message. The notification will provide an overview of the study. Within MyChart, patients can indicate whether or not they are interested in the study. No patient data will be shared with a research coordinator unless requested by the patient. If a patient selects yes- they are interested in the study, the research coordinator will receive a message requesting that they contact the patient regarding the study. Research coordinators will then contact the patient for eligibility screening. If a patient selects "no," they are not interested in the study, they will not receive any additional messages about the study within Epic, and their information will not be shared with the research coordinator. A MyChart message template language has been attached to this submission.

b. Describe how potential subjects are contacted.

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Potential subjects will be contacted via email or phone.

c. Who is recruiting potential subjects?
Sule Tinaz and Jared Cherry will recruit potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?
☐Yes, all subjects
☒Yes, some of the subjects
☐No

If yes, describe the nature of this relationship.
Sule Tinaz might be the treating physician for some of the PD patients.

5. Request for waiver of HIPAA authorization: When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
Choose one:
☐ For entire study
☒ For recruitment/screening purposes only
☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:
ii. We are requesting a waiver of authorization for recruitment through JDAT and EPIC. Without the waiver, we would not know who to contact for recruitment

iii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: Potential subjects will be screened for eligibility over the phone or email. Only if they pass the screening phase, they will be enrolled in the study. It would be impracticable to obtain signed authorization from potential subjects during screening. However, potential subjects could always refuse to participate in screening and we would not contact them again.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

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6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Verbal consent will be obtained for MRI safety screening and medical history questionnaire over the phone. We are planning on using same day consent. Signed informed consent will be obtained at the beginning of the first research visit. A member of the research team authorized to obtain consent will give the subjects detailed information about the study and go over all aspects of the research. The purpose, research procedures, any risk that these procedures might entail, and any possible benefits will be discussed in detail. Subjects will be encouraged to ask questions and given enough time to discuss any aspect of the study with the research team. Once subjects understand the study, they will be asked if they wish to participate. If they do, they will be asked to sign the consent form.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

Capacity will be assessed directly in the course of attempting to obtain informed consent. When the member of the research team authorized to obtain consent has reviewed the study, he/she will ask the subject to explain the major elements of the study. Those elements are a) this is a research study (not routine treatment), b) participation is voluntary, c) study procedures, d) risks, e) benefits. Open-ended questions such as "Can you tell me the main things that you would do in this study? Can you tell me the main risks of the study?" will be used to assess understanding and appreciation of the facts. Subject will then be expected to make a rational choice: "Considering the risks and benefits we have discussed, would you like to take part in this study?" Based on the subject's responses the team member will make a final judgment about capacity for consent. If the subject has capacity and agrees to the study, they will sign the consent form.

When in doubt, the team member will consult the PI Sule Tinaz.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

Non-English speaking subjects will not be included.

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. *Please review the guidance and presentation on use of the short form available on the HRPP website.*

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

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9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☐Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☒ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☒

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☐ Requesting a waiver of consent:

☐ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☒
- Why would the research be impracticable to conduct without the waiver? We are requesting a waiver of consent for recruitment through JDAT and EPIC. Without the waiver, we would not know who to contact for recruitment
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? *Write here*

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? *Write here*

   HIPAA identifiers: Name, MRN, phone, email, address.

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Medical information: Handedness, alcohol/substance use, any history or current condition of a neurological or psychiatric disorder such as brain tumor, stroke, central nervous system infection, multiple sclerosis, movement disorder (other than PD), seizures, dementia, depression, bipolar disorder, schizophrenia, attention deficit disorder, obsessive compulsive disorder, history of head injury with loss of consciousness. The MRRC MRI Safety Questionnaire will be used for MRI screening. Videos of the MDS-UPDRS part III motor exam will be collected. The videos will include subjects' faces.

This protected health information about subjects may be used by or given to: Representatives from the Yale Human Research Protection Program, the Yale Human Investigation Committee who may inspect study records during internal auditing procedures. However, these individuals are required to keep all information confidential; those individuals at Yale who are responsible for the financial oversight of research including billings and payments; study coordinator and members of the research team; Data and Safety Monitoring Boards and others authorized to monitor the conduct of the study.

All health care providers subject to HIPAA are required to protect the privacy of subject information. The research staff at the Yale School of Medicine and Yale New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of subject information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose subject information in ways not mentioned in this protocol. However, to better protect subjects' health information, agreements are in place with these individuals that require that they keep subjects' health information confidential.

Subjects have the right to review and copy their health information in their medical record in accordance with institutional medical records policies.

2. How will the research data be collected, recorded and stored? *Write here*

Case report forms for each subject will be used to enter medical information, scores of paper-pencil tests, and behavioral data. All of this information will then be entered into an electronic database. Imaging data will be transferred securely to username- and password-protected workstations for analysis and stored on HIPAA-compliant secure servers in the MRRC. Videos of the MDS-UPDRS motor exam will be collected via encrypted mobile cameras. Videos will include subjects' faces, but will not be linked to the individual subjects in any other way and will not include any protected health information. Videos will not be used for any other purpose. Once the videos have been uploaded to the secure Yale Box electronic database, they will be removed from the mobile camera.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☒ Laptop Computer ☒Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
Clinical, behavioral, and MRI data will be recorded and stored electronically on password-protected computers and servers. Individual data files will not contain personally identifiable information and will be labeled using a coding system. The data labels will contain the subject code, date and time of recording, and mode and condition of recording. Only the PI, Sule Tinaz, will have access to the centrally and electronically stored and password-protected subject identification list to decode data files. The data will be collected specifically for this project.

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All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. *Write here*

   Upon completion of the study, study binders will be stored in a locked facility for the amount of time required by law. After this time, the study binders will be destroyed by shredding. The database that contains our case report form pages will stay on our computer until the study closes. The link to personal information will be kept until the end of the study, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

6. If appropriate, has a Certificate of Confidentiality been obtained? N/A

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

Subjects may experience a direct benefit from the mental imagery and neurofeedback training. Even if there is no direct benefit, the knowledge gained from this study may facilitate the design and implementation of a clinical trial, and lead to improvements in the diagnosis and treatment of PD in the future.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

   Subjects do not receive a specific, standard treatment in this study or forego any treatment in order to participate in this study. The alternative, therefore, is not to participate.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

Subjects will be compensated for their time and receive $50 for each completed session (maximum total of $200). The new compensation fee will apply only to new enrollments. The currently enrolled participants will not be affected. Payments will be made electronically through the YCCI Research Subject ePayment program via a prepaid Bank of America card. Subjects' name, address, and telephone number will be shared with Bank of America. On rare occasions, participants may need transportation to the study site and back. We will evaluate this need on a case-by-case basis and provide transportation (e.g., via taxi cab, Uber ride, etc.).

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

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Subjects will have to pay for their travel expenses including gas if they drive, or other transportation fees (e.g., bus, train, taxicab). Reimbursement for parking will be provided. Clinical evaluations will be provided at no cost to subjects.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

    a. Will medical treatment be available if research-related injury occurs? Yes.
    b. Where and from whom may treatment be obtained? Treatment may be provided by Yale New Haven Hospital or any health care provider chosen by the subjects.
    c. Are there any limits to the treatment being provided? All necessary treatment will be provided by the treating physician according to standard of care.
    d. Who will pay for this treatment? Yale School of Medicine and Yale New Haven Hospital do not provide funds for the treatment of research-related injury. Subjects or their insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.
    e. How will the medical treatment be accessed by subjects? If subjects are injured while on study, they will be advised to seek treatment and contact the study doctor Sule Tinaz as soon as they are able. The study doctor will provide assistance to the subjects in accessing medical treatment through referral, or the subjects may choose to access treatment on their own.

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IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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