CLINICAL STUDY PROTOCOL
Observational Study of Individual or Group Template

Effects of Cognitive Training on Everyday Cognitive and Brain Function in Parkinson's Disease

Protocol Number

Protocol Version
09/13/2023 Version #8

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Synopsis

Purpose

Parkinson's disease (PD) affects over six million individuals globally. With increasing life expectancy, this number is estimated to double by 2040. PD patients experience cognitive problems, especially executive dysfunction, even in the early stages of the disease affecting their everyday functioning. Currently, pharmacological treatment provides, at most, modest benefit for symptoms of PD-dementia and there is no effective treatment for milder cognitive problems.

Cognitive training programs in PD have gained popularity with varying degrees of success for the cognitive domain that is treated. However, the benefits have not been generalizable, and more importantly, not transferred to real-life tasks. Therefore, there is an urgent unmet need to develop effective treatment strategies to help PD patients independently manage the cognitive demands of everyday life.

Our previous work using guided motor and visual imagery training showed improved motor performance and increased functional connectivity in specific brain networks in PD patients. Grounded in this previous work, we now propose a phase 1 randomized clinical trial to determine the effectiveness of a 6-week mental imagery training program in improving cognitive functions during everyday tasks and to investigate the brain mechanisms of this training using functional magnetic resonance imaging (fMRI) and functional connectivity analyses in PD patients.

Our mental imagery training differs from existing cognitive training programs in important ways: It will 1) focus on cognitive functional improvement in relevant real-world tasks, 2) foster the development of personalized and practical skills that can be applied flexibly to real-life situations, and 3) measure whether the training effects are transferred to other standard tests of executive function.

PD patients (N=120) with mild-to-moderate disease, who do not have mild cognitive impairment according to the Movement Disorders Society Level II criteria will be randomly assigned in parallel to either the experimental (mental imagery, PD-MI) or control (psychoeducation, PD-Con) group. The PD-MI group will practice mental imagery of everyday tasks in a supervised manner and via homework, whereas the PD-Con group will receive psychoeducation on cognitive functioning and brain health in PD.

The primary cognitive target engagement outcome will be the self-reported improvement on cognitive functioning during tasks of daily life. The primary neurobiological target engagement outcome will be the task-specific changes in coordinated brain network interactions during naturalistic fMRI tasks that will mimic real-world demands. We will also examine whether the putative post-training changes in cognitive function and functional connectivity will be sustained over a 12-week period. Moreover, we will explore whether the functional connectivity changes will predict the cognitive outcomes at the 6- and 12-week timepoints. We will use mixed ANOVA tests to assess the short- and longer-term changes in outcomes before and after training.

Findings will provide critical early data for longer-term efficacy trials. If successful, mental imagery can be developed into a personalized neurocognitive rehabilitation program in PD.

Primary Objective

The primary objective of this study is to determine whether mental imagery training for 6 weeks will improve everyday cognitive functions and brain functional connectivity during naturalistic fMRI tasks in people with PD.

Secondary Objective

The secondary objective of this study is to determine whether the cognitive and imaging effects of mental imagery training will be sustained after a 12-week period in people with PD.

Study Design

We will conduct a phase 1 clinical trial with two groups of PD patients randomly assigned in parallel. The experimental group (PD-MI) will receive mental imagery training and the control group (PD-Con) will receive psychoeducation on cognition and brain health. The mental imagery training will be delivered one-on-one and via audio-recorded scripts. Psychoeducation will be delivered in pre-recorded lecture format. Other research procedures will include neurological exams, standardized cognitive tests, surveys, and MRI scans. The immediate and sustained training effects on cognitive function and brain functional connectivity will be tested at 6- and 12-weeks, respectively.

Study Date Range and Duration

The expected length of the study is 6 years.

Number of Study Sites

The Yale School of Medicine campus will be the only study site. Research procedures will take place at two sites: The Yale Magnetic Resonance Research Center (MRRC) and the Yale Center for Clinical Investigation (YCCI) Church Street Research Unit.

Primary Outcome Variables

1) **Quality of life in Neurological Disorders (Neuro-QoL) Scores**

Timeframe: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The Neuro-QoL is a set of self-report measures that assesses the health-related quality of life of adults and children with neurological disorders. Neuro-QoL instruments were developed through a collaborative, multisite NINDS-sponsored research initiative to construct psychometrically-sound and clinically-relevant health-related quality of life measurement tools for individuals with neurological conditions including PD. The Neuro- QoL instruments enable within-disease as well as cross-disease comparisons and are intended for use in both neurology clinical trials and clinical practice. We will use the Neuro-Qol version 2 Cognitive Function item bank to assess post-training self-reported changes in cognitive functions.

Change in the Neuro-Qol version 2 Cognitive Function scores from T0 to T1 and across T2 will be the primary cognitive outcomes of this study. Significant increase in the Cognitive Function scores at T1 will be considered significant improvement in self-reported cognitive function in everyday life. Significant increase in these scores across T2 will be considered sustained improvement in self-reported cognitive function in everyday life.

2) **Questionnaire on Mental Imagery (QMI) Vividness of Imagery Scale scores**

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The QMI is a measure of vividness of an individual's multisensory and motor imagery on a scale of 1 to 7 (1: perfectly vivid image, 7: no image present at all).

Change in the QMI scores from T0 to T1 and across T2 will serve as the manipulation check for the mental imagery intervention. Significant increase in these scores at T1 will be considered improved imagery vividness. Significant increase in these scores across T2

will be considered sustained improvement in imagery vividness.

3) **Task-specific whole-brain pairwise functional connectivity**

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will calculate the whole-brain pairwise functional connectivity during mental imagery and video-watching of naturalistic goal-directed tasks in the MRI scanner for each subject.

Change in task-specific pairwise functional connectivity from T0 to T1 and across T2 will be the primary imaging outcomes of the study. Significantly increased task-specific pairwise functional connectivity in major networks (e.g., default mode network during mental imagery and frontoparietal executive network during video-watching) at T1 will be considered improved task-specific functional reorganization of these networks. Significantly increased task-specific pairwise functional connectivity in major networks across T2 will be considered sustained improvement in task-specific functional reorganization of these networks.

Secondary and Exploratory Outcome Variables

1) **Composite executive function test scores (Secondary)**

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will calculate the composite z-scores of the executive function test scores (i.e., Stroop, F-A-S letter fluency, and Trail Making A-B tests) for all subjects.

Change in composite executive function test scores from T0 to T1 and across T2 will be the secondary cognitive outcomes of the study. Significant increase in these scores at T1 will be considered improved executive function. Significant increase in these scores across T2 will be considered sustained improvement in executive function.

2) **Local and global functional connectivity-based graph measures (Secondary)**

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will calculate the local (i.e., clustering coefficient) and global (i.e., betweenness centrality) network graph measures during mental imagery and video-watching tasks in the MRI scanner. These measures will provide information about the context-dependent changes in the functional organization of the brain networks.

Change in graph measures from T0 to T1 and change in graph measures across T2 will be secondary imaging outcomes the study. Significantly increased task-specific clustering coefficient in major networks (e.g., default mode network during mental imagery and frontoparietal executive network during video-watching) and significantly increased context-dependent betweenness centrality between major network nodes (e.g., stronger between the default mode and frontoparietal networks during mental imagery) at T1 will be considered improved task-specific functional differentiation of these networks. Significant increases in the same graph measures across T2 will be considered sustained improvement in task-specific functional differentiation of these networks.

3) Modified Six-Elements Test scores (Exploratory)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The Modified Six-Elements Test is a measure of goal-directed planning and execution.

Change in these test scores from T0 to T1 and across T2 will be the secondary cognitive outcomes of the study. Significant increase in these scores at T1 will be considered improved performance in goal-directed planning and execution. Significant increase in these scores across T2 will be considered sustained improvement of performance in goal-directed planning and execution.

4) Global cognition scores (Exploratory)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The Repeated Battery for the Assessment of Neuropsychological Status (RBANS) is a commonly used battery with alternate versions allowing repeated testing of the cognitive domains of attention, verbal and visual memory, language, and visuospatial functioning.

Change in total RBANS scores from T0 to T1 and across T2 will be the exploratory cognitive outcomes of the study. Significant increase in these scores at T1 will be considered improved global cognition. Significant increase in these scores across T2 will be considered sustained improvement of global cognition.

5) Post-training brain-cognition relationship (Exploratory)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will examine whether the post-training changes in whole-brain pairwise functional connectivity and graph measures will predict the post-training differences in the cognitive function in each group at T1 and T2.

Study Population

The study population will be people with PD defined according to the Movement Disorders Society (MDS) diagnostic criteria with mild-to-moderate PD, who do not have mild cognitive impairment, aged 40 and above, and are physically independent. Idiopathic PD is an adult-onset neurological disorder. In the United States, the incidence of idiopathic PD cases before the age of 40 is extremely low. Therefore, individuals with PD who are 40 years and older will be included and there will be no upper age limit for participation in the study.

There is no restriction for gender, race, or ethnicity. The approximate male-to-female ratio in PD is 1.5 to 1. This ratio will be reflected in the enrollment. We will seek a racially and ethnically diverse enrollment.

Subjects will be recruited through:

1. The Yale Movement Disorders outpatient clinics
2. The outpatient clinics in the new Yale PD Comprehensive Care Center

3. The local PD support groups and nonprofit organizations (e.g., American PD Association Connecticut Chapter, Beat PD Today exercise program) that provide educational and wellness programs for the greater PD community in Connecticut
4. Neurology practices in Connecticut who care for patients with PD.
5. JDAT recruitment services (EPIC/MyChart Alerts & mailing)
6. Departmental/Center newsletters
7. The YCCI recruitment database
8. Recruitment letters

Number of Participants
There will be 120 subjects.

Study Schedule
Verbal consent will be obtained for the initial screening visit over the phone or via email. Electronically signed informed consent will be obtained at the beginning of the Zoom video screening visit.
Time estimate for initial screening: 1 hour

There will be a total of 4 in-person visits:

Visit 1: Baseline Clinical Evaluation. Subjects will undergo detailed clinical evaluations to determine disease severity and level of cognitive functioning**.**
Time Estimate: 3 hours

Visit 2: Baseline Neuroimaging Experiments. Subjects will rate their mental imagery skills at baseline and perform fMRI tasks in the scanner. Subjects will also receive instructions on their respective training and homework assignments.
Time Estimate: 2 hours

Training: Subjects will receive their respective training 3 times per week for 4 weeks. On non-training days during the 4-week period and in the subsequent 2-week block, subjects will complete homework.

Visit 3: 6-Week Post-Intervention Assessments. All subjects will return for repeat cognitive evaluations as in Visit 1, and mental imagery vividness rating and fMRI scans as in Visit 2.
Time Estimate: 3 hours

Visit 4: 12-Week Post-Completion Assessments. All subjects will return for repeat cognitive evaluations and fMRI tasks. The same procedures as described in Visit 3 will be followed.
Time Estimate: 3 hours

Protocol Revision History

Version Date	Summary of Substantial Changes
August 26, 2022	Version #2 • More information has been provided about the neuropsychological tests (Modified Six Elements, RBANS, Stroop, F-A-S, Trails A/B, and Wechsler Adult Reading). • Consent process in the initial screening visit has been clarified. • More details about the recruitment process have been provided. • Reporting of AEs has been changed to 5 days. • Partial HIPAA waiver for screening purposes has been requested. • Total payment has been reduced from $700 to $650 by eliminating payment for the initial screening visit.
November 15th, 2022	Version #3 • The Epworth Sleepiness Scale, Beck Depression Inventory II, and Spielberger Trait Anxiety surveys have each been replaced with equivalents that are available in public domain without licensing restrictions: Scales for Outcomes in Parkinson's Disease – Sleep (SCOPA-Sleep), Geriatric Depression Scale (GDS long form), and the Parkinson Anxiety Scale (PAS). • Executive dysfunction is common in people with Parkinson's disease. Executive domain scores of up to 2 standard deviations below the normative data according to the MDS Level II criteria will be allowed to enroll people with PD with mild executive dysfunction in order to improve the generalizability of the study • For the sake of efficiency, MRI safety and medical history screening will take place during the initial phone call. If a subject fails the MRI safety screening or meets any of the exclusion criteria for medical history, they will not be enrolled. Subjects who are still eligible will be scheduled for a follow-up video-screening via the Zoom videoconferencing platform. • Paper study consent forms have been replaced by the use of REDCap to obtain electronic study consent. • REDCap will be used instead of Qualtrics for the administration of online surveys and completion of online training and homework. • A REDCap study database will replace the use of Eliapps for data storage. • The research team will record Zoom videoconference meetings to facilitate data collection of mental imagery content. Once data transcription is complete, the videos will be deleted. • The pre-recorded Powerpoint lectures assigned to the psychoeducational group now contain three multiple choice questions to assess comprehension of the content.
January 25th, 2023	Version #4 • The protocol has been updated to reflect the use of recruitment services offered by JDAT (EPIC/MyChart Alerts & mailing services),

	Departmental/Center newsletters, the YCCI recruitment database, and recruitment letters.
June 15th, 2023	Version #6 • 6.13 Funding Source on page 50 has been updated: The study will be funded through Dr. Tinaz's NINDS 1R01NS129540-01A1 grant.
August 9th, 2023	Version #7 • 6.13 Funding Source on page 50 has been updated: The study will be funded through Dr. Tinaz's NINDS 1R56NS129540-01A1 grant
September 13th, 2023	Version #8 • We have changed the eligibility cut-off on cognitive tests. To improve the generalizability of the study and include people with cognitive deficits in domains other than the executive domain, we will allow test scores of up to 2 standard deviations below the normative data in all cognitive domains in line with the MDS Level II criteria (see section 4.3.2 on page 29).

Statement of Compliance

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to the Common Rule at 45CFR46 (human subjects) and other applicable government regulations and Institutional research policies and procedures.

Abbreviations

Abbreviation	Explanation
EliApps	Google Workplace for Education
EPI	Echo Planar Imaging
FDR Correction	False Discovery Rate Correction
fMRI	Functional Magnetic Resonance Imaging
FoV	Field of View
gPPI	Generalized Psychophysiological Interaction
MCI	Mild Cognitive Impairment
MDS	Movement Disorder Society
MDS-UPDRS	MDS Unified Parkinson's Disease Rating Scale
MoCA	Montreal Cognitive Assessment
MPRAGE	Magnetization-prepared rapid gradient-echo
MRRC	The Yale Magnetic Resonance Research Center
Neuro-QoL	Quality of Life in Neurological Disorders
PD	Parkinson's Disease
PD-Con Group	Parkinson's Disease Active Control Group (Receiving psychoeducation)
PD-MI Group	Parkinson's Disease Mental Imagery Group (Experimental Group)
QMI	Questionnaire on Mental Imagery
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SPSS	Statistical Package for Social Sciences
YCCI	Yale Center for Clinical Investigation

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Glossary of Terms

Glossary	Explanation

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Table of Contents

1 Background/Literature Review

1.1 Background

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.[1] Cognitive deficits are common in PD and associated with poor outcomes, reduced quality of life, and significant caregiver burden.[2] PD patients frequently present with executive dysfunction causing problems in everyday life. Currently, there are no therapies to prevent cognitive decline in PD. Pharmacological treatment provides, at most, modest symptomatic benefit in PD dementia.[3] Cognitive training programs in PD have gained popularity with varying degrees of success for the cognitive domain that is treated. However, the benefits have not been generalizable, and more importantly, not transferred to real-life tasks.[2] Therefore, developing effective treatment strategies to help PD patients independently manage the cognitive demands of everyday life is critically important. Indeed, the PD community identified maintaining cognitive function as one of its major unmet needs.[2]

The proposed training protocol intends to meet this need and is inspired by our previous work using kinesthetic motor imagery training to improve kinesthetic awareness and motor function in PD patients.[4] Here, we will use mental imagery to train subjects with PD to simulate the planning and implementation process of goal-directed tasks in everyday life. This training is expected to improve the cognitive functioning in everyday life and functional connectivity of brain networks that support these cognitive functions in people with PD.

Executive dysfunction in PD

Executive functions are central, supramodal cognitive processes that control goal-directed behaviors comprised of multiple steps including goal formulation, self-initiation, plan execution, and processing of the outcome.[5] These control processes also call on working memory as well as internal and external attentional resources.[6,7] Even in the early stages of the disease, PD patients frequently present with executive dysfunction. Executive dysfunction may also be observed in people who are at risk of developing PD and cause problems in instrumental activities of daily living.[8] Specifically, PD patients have deficits in internal control of attention, set shifting, planning, inhibition, conflict resolution, dual task performance, and decision making.[9] Apathy and depression are also associated with executive dysfunction in PD.[9]

Knowledge gap: Executive dysfunction in PD has been established using standard cognitive tests, but the functional deficits in everyday life associated with executive dysfunction have not been investigated systematically. We aim to fill this gap by assessing executive dysfunction and post-training changes thereof in PD patients in daily life.

Neural substrates of cognitive/executive dysfunction in PD

Altered resting-state functional connectivity within and between the cognitive networks including the default mode, frontoparietal, dorsal attention, and salience networks plays a role in cognitive impairment in PD.[10] Reduced functional connectivity within the default mode network in PD patients with impaired cognition compared with those with normal cognition and healthy controls has been demonstrated.[11-16] Weakening of the natural anti-correlation between the default mode and task positive networks[11,17] and between the default mode and salience networks[18] has also been reported in PD patients with impaired cognition. Reduced functional connectivity between[11,19] and within the dorsal attention[11,20,21] and frontoparietal executive control networks,[16] and reduced degree in the salience network[18] have been reported in PD patients with cognitive impairment. Moreover, functional connectivity profiles mainly of the frontal nodes distinguished PD patients with cognitive impairment from those with normal cognition.[22] PD patients also exhibit different functional connectivity patterns depending on the type of their cognitive deficit. Dysexecutive deficits have been found to correlate with reduced functional connectivity in the sensorimotor network, and posterior

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cortical deficits (visuospatial skills, memory) to correlate with reduced functional connectivity in the frontoparietal executive network and increased functional connectivity in the temporal network.[15] Reduced cerebellar functional connectivity with occipital and frontal regions has also been demonstrated in PD patients with impaired cognition.[23]

Executive functions are supported by the frontostriatal circuits and particularly vulnerable in PD.[24-27] Functional MRI studies of executive dysfunction in PD have demonstrated abnormal activation in these circuits and aberrant activations in other brain regions depending on the medication status and task features.[28] For example, hypodopaminergic state is usually associated with reduced activation in the prefrontal cortex and dorsal striatum during planning and working memory tasks in PD.[27,29] Increased or decreased activation in the prefrontal cortex also depends on the basal ganglia involvement during the task.[30] Aberrant and compensatory frontostriatal hyperactivation has also been observed and is usually associated with worse and preserved executive performance, respectively.[31,32]

Knowledge gap: The neural substrates of executive functions in PD during tasks mimicking real-world situations have not been investigated. We will examine the baseline and post-training interactions within and between the brain networks supporting goal-directed behavior in PD patients using naturalistic fMRI tasks.[33,34]

Cognitive training in PD

Cognitive training programs have gained popularity with varying degrees of success for the cognitive domain that is treated, but usually without generalizable real-life benefits.[2] Most studies to date used structured paper-pencil tests,[35] games,[36] computerized tasks,[37] or strategy training[38] to target multiple cognitive domains for training in nondemented PD patients. Training periods, anywhere between 4-12 weeks, were usually administered in small groups at least once a week with some components administered in individual sessions, and usually combined with unsupervised practice (e.g., homework). In a meta-analysis of randomized clinical trials, cognitive training in nondemented PD patients was found to show a small but significant effect.[39] Larger effect sizes were noted on processing speed,[35] working memory,[36] and executive functions,[38] whereas effects on quality of life and instrumental activities of daily living were not significant.[38] Most studies focused on the rehabilitation of frontal executive dysfunction in PD and the effects were heterogeneous mainly due to the variability of cognitive profiles of subjects, small sample sizes, and lack of control groups in some studies.[40] A multi-pronged program in PD patients with mild cognitive impairment (MCI) demonstrated that the combination of cognitive, psychomotor, and real-world transfer training was superior to any of these components alone in promoting a more active life style and more confidence in activities of daily living. Importantly, cognitive training was found to be arduous at times and psychomotor training was preferred by the participants.[41] Only a few neuroimaging studies investigated the brain changes in PD as a result of cognitive training. After three months of cognitive training,[35] increased task-based activation within and increased resting-state functional connectivity between the temporal and prefrontal cortex were demonstrated in the PD training group compared with the PD control group.[42] After an 18-month follow-up period, the same PD group was found to retain the cognitive improvements and functional brain changes.[43]

Cognitive training is a promising non-pharmacological approach and the Institute of Medicine has established criteria for cognitive training programs.[44] The criteria include transfer to other laboratory tasks that measure the same cognitive construct as the training task, transfer of training to relevant real-world tasks, use of an active control group, determining the duration of post-training skill retention, and replicability across studies.

Knowledge gap: Currently, the cognitive training programs in PD do not fulfill all of the Institute of Medicine criteria.[2] Specific to the PD population, it has also been recommended to include subjects with homogeneous cognitive profiles, target executive/attention dysfunction, include supervised training, use a personalized approach, and include measures of (instrumental) activities of daily living.[40] Our proposed mental imagery training program

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provides a personalized approach targeting executive functioning in PD patients with the aim of improving everyday functioning in the setting of a randomized clinical trial. Moreover, our study will shed light on the brain mechanisms of training effects using fMRI. This is an early-phase study, the training effects will be tested immediately and again at 12 weeks.

1.2 Prior Experience

Neurofeedback-guided kinesthetic motor imagery in PD

In a randomized clinical trial, we tested whether neurofeedback-guided kinesthetic motor imagery of complex movements and activities can improve motor performance and functional brain plasticity in PD patients with normal global cognition.[4] The neurofeedback signal was based on the right insula-dorsomedial frontal cortex functional connectivity strength given the role of these structures in motivating intentional action.[45] In the scanner, the experimental PD group was instructed to increase this neurofeedback signal using motor imagery, whereas the control PD group performed visual imagery of objects and scenes without neurofeedback. Both groups also practiced their respective imagery tasks daily for 4 weeks.

Post-training, we did not find a significant increase in the neurofeedback signal in the motor imagery compared with the visual imagery group partially due to large between-subject variability. However, both groups showed significant improvement in their kinesthetic and visual motor imagery skills as well as in their performance of timed motor tasks. Notably, the motor improvement correlated with the increase in neurofeedback signal only in the motor imagery group. Moreover, both groups showed specific training effects in whole-brain functional connectivity with distinct neural circuits supporting kinesthetic motor imagery (insula and premotor cortex) and visual imagery (nodes in the ventral and dorsal visual streams) (Figure 1).[4]

These results provide a manipulation check and validate that the training targeted the expected brain networks, and are also in line with previous reports of differential activation patterns during kinesthetic motor[46,47] and visual imagery.[48] Importantly, the results demonstrate that PD patients are capable of mental imagery, can improve their imagery skills with practice, and the practice effects can be captured in the functional reorganization of specific brain circuits subserving the corresponding imagery modes

Self-regulation and self-efficacy in PD

We also investigated the behavioral and neural corelates of self-regulation and self-efficacy skills in community dwelling PD patients. Self-regulation and self-efficacy are metacognitive skills that enable people to mobilize the motivation and cognitive resources to exert control over events [49] and to guide their goal-directed activities over time and across changing circumstances.[50] These skills correlated negatively with apathy scores and global disease severity in our PD cohort. Moreover, a resting-state functional connectivity analysis including the main nodes of the major networks (i.e., default mode, dorsal attention, salience, sensorimotor, visual, language, and cerebellar) revealed that stronger functional connectivity between the salience network nodes including the dorsal anterior cingulate cortex and anterior insula correlated positively with self-regulation and self-efficacy scores. The self-regulation scores also showed a significant negative correlation with the functional connectivity between the dorsal anterior cingulate cortex and left lateral parietal cortex, which is a major node of the default mode network (Figure. 2).[51] These results suggest that attentional self-regulation and self-efficacy require a salience-detection mechanism in order to switch efficiently from a self-referential to a goal-oriented mental state. This mechanism seems to be subserved by the coupling among the nodes of the salience network and decoupling of the salience from the default mode network.

Figure 1

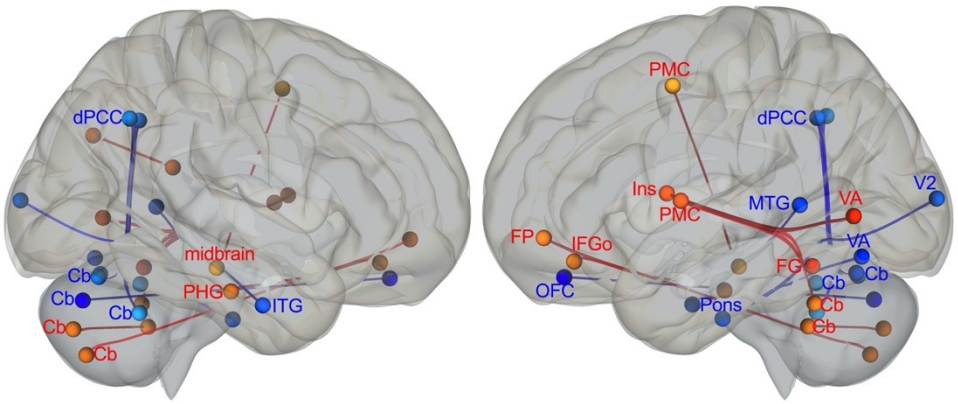

Fig. 1. **Whole-brain imagery task-based functional connectivity changes post-training**. **Red**: Stronger functional connectivity between nodes in the motor imagery group > visual imagery group. **Blue**: Stronger functional connectivity between nodes in the visual imagery group > motor imagery group. Cb: Cerebellum, dPCC: Dorsal posterior cingulate cortex, FG: Fusiform gyrus, FP: Frontal pole, IFGo: Inferior frontal gyrus, orbital part; Ins: Insula, ITG: Inferior temporal gyrus, MTG: Middle temporal gyrus, OFC: Orbitofrontal cortex, PHG: Parahippocampal gyrus, PMC: Premotor cortex, V2: Secondary visual cortex, VA: Visual association cortex (FDR-corrected $p < 0.05$, two-tailed). Nodes are based on the Shen Atlas.[52] Nodes and connections are displayed on the MNI brain template in the CONN Toolbox.[53]

Figure 2

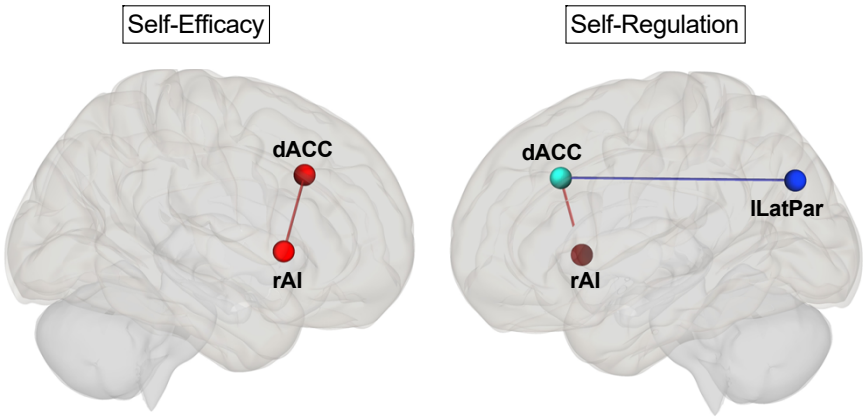

Fig. 2. **The pairwise functional connections that show significant correlations with self-efficacy and self-regulation scores** (FDR-corrected, $p < 0.05$). The nodes and connections are displayed on the MNI brain template in the CONN Toolbox.[53] dACC: Dorsal anterior cingulate cortex, rAI: Right anterior insula, lLatPar: Left lateral parietal. Red: Positive correlation. Blue: Negative correlation.

2 Rationale/Significance

2.1 Rationale and Study Significance

Mental imagery as a cognitive-behavioral intervention

Mental Imagery refers to the mental re-creation of perceptual experience across sensory modalities, of past or future events and scenarios, and of motor acts with the potential to

prepare the individual for action.[54,55] Mental imagery has been used extensively as a performance-enhancing strategy in sports and skilled performance,[56-58] as a mnemonic strategy,[59-61] and in cognitive behavioral therapy for regulation of anxiety and depression symptoms.[62,63]

It is important to note that mental imagery is not about passively viewing mental pictures, but rather about actively and intentionally constructing a mental picture and subjectively experiencing it.[64] The experiential and emotional aspects of mental imagery especially from a first-person perspective make imagery an efficient tool in therapy.[65] Similarly, the embodied and experiential aspects of mental imagery have been found to improve self-efficacy (e.g., to overcome fear of falling in older adults) [66], increase motivation, and promote engagement in planned activities and healthy behaviors such as exercise.[67-69]

Mental imagery also plays a fundamental role in episodic future thinking,[70] which refers to the ability to imagine the future and critically depends on episodic memory and frontal-executive systems.[71] Episodic future thinking serves decision making, emotion regulation, intention formation, and planning.[71] Nondemented PD patients were found to produce fewer spontaneous thoughts[72] and fewer episodic details[73] than controls when asked to imagine future events. The poorest performers in future thinking also had significant executive dysfunction.[73] This suggests that future thinking taxes the executive resources in PD by requiring active monitoring and combining of various sub-tasks. Episodic specificity induction that trains people to produce specific episodic details (e.g., people, places, time, objects, actions) has been shown to boost the episodic details in remembered past and imagined future events in young and older healthy people.[71]

Relevance of mental imagery for cognitive improvement in the PD population

Our mental imagery training will target cognitive/executive functioning in the service of goal-directed tasks in everyday life of PD patients. Subjects will learn to mentally simulate the planning and implementation steps of these tasks. The training will emphasize the experiential vividness and episodic richness of the imagined situations, enable the subjects to mentally and affectively prepare for the planned actions, and learn to self-regulate attention and executive resources as their plans unfold in real life. The training will be personalized, and once acquired as a skill, can be used flexibly in all real-life situations.

The study will also provide mechanistic insights into the neural correlates of cognitive functional difficulties of PD patients using naturalistic fMRI tasks. These correlates and the dynamic, context-dependent interactions among them will be the neurobiological targets of the mental imagery intervention. Moreover, we will examine whether the potential benefits of mental imagery training are sustained in the short term.

Our study has the potential to benefit people with PD directly. Cognitive problems create a significant burden on the individuals with PD, caregivers, and public health. Novel treatments are critically needed to alleviate the cognitive problems affecting everyday functioning of PD patients. If successful, mental imagery training can be incorporated into cognitive neurorehabilitation programs for patients with PD.

2.2 Purpose of Study/Potential Impact

The study aims to investigate the potential role of mental imagery training as a noninvasive and nonpharmacological intervention to improve 1) goal-directed cognitive functioning during tasks of daily living and 2) functional connectivity of cognitive brain networks in PD patients.

The study has the potential for high-impact findings and direct clinical significance for patients with PD:

1) The mental imagery training will be personalized, so that PD patients can continue to use the skills and strategies they have acquired during training and apply them flexibly and autonomously to real-life situations. If successful, mental imagery training could

also be incorporated into cognitive rehabilitation programs for PD.

2) The study will also provide mechanistic insights into the neural correlates of cognitive function of PD patients using naturalistic fMRI tasks mimicking real-world demands.

Research on the brain pathophysiology in PD, as a basis for novel treatment options, as well as investigation of the therapeutic potential of noninvasive and nonpharmacological interventions, such as mental imagery training, has the potential for improvement of the quality of life in a considerable proportion of the general older population.

Innovations in our study can be summarized as:

Innovations in experimental medicine approach

Our proposal builds on the basic tenets of the experimental medicine approach as laid out in the National Institutes of Health (NIH) Science of Behavior Change Program report.[74]

- This study will, for the first time, use mental imagery as an intervention targeting executive functioning to improve performance in goal-directed tasks in everyday life (putative cognitive target engagement).
- The proposed cognitive training program is unique in that it is directly linked to the naturalistic tasks of everyday living and promotes an implicit strategy (i.e., mental imagery) that can be personalized and flexibly applied to real-life situations.
- Real-world behavior is complex and multidimensional. Naturalistic fMRI paradigms representing real-world demands lend stronger ecological validity to human neuroimaging experiments.[33,34] This study will, for the first time, examine the specific interactions within and between core brain networks supporting goal-directed cognitive functioning in PD using mental imagery and video-watching of naturalistic tasks of daily life. We will determine the changes in the coordinated network interactions as a result of training and how they relate to the cognitive changes (putative neurobiological target engagement).
- Knowledge gained from our empirically-grounded and mechanism-based approach will help us refine the mental imagery intervention and predict treatment response in PD.

Innovations in clinical applications

- The proposed training has direct therapeutic implications, and if successful, can be developed into a personalized neurocognitive rehabilitation program in PD.
- The program could also be customized to meet the needs of PD patients with MCI.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

The proposed research plan involves screening for clinical history, MRI safety, and global cognitive impairment; online surveys; neurological and movement examination, cognitive evaluation, performance-based tests, training via videoconferencing, pre-recorded psychoeducation lectures, and daily homework (listening to imagery audio files and filling out online surveys for the experimental group and taking brief online quizzes for the control group); and MRI scans. The potential risks associated with individual study procedures are as follows:

Immediate risks

Medication status

Subjects who are on medications for PD (e.g., carbidopa/levodopa, dopamine receptor agonists) will always be tested and scanned early in the day while they are on their regular medication regimen. This will minimize the risk of occurrence of symptoms related to being off medication such as excessive slowness or stiffness, freezing of gait, balance problems or falls, and severe anxiety.

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Videoconferences for screening and training

The online Zoom platform will be used for videoconferences. There is no medical risk associated with videoconferences. There is a potential confidentiality risk (e.g., hacking of the conferences or user cameras).

Online surveys and homework

Online surveys and quizzes created on the Yale REDCap online database and survey platform will be emailed to subjects individually. Subjects will also submit their homework via REDCap. There is no medical risk associated with the online surveys and homework. No personally identifiable information will be collected, therefore, the surveys and homework do not pose a confidentiality risk.

Clinical, cognitive, and behavioral evaluation

The clinical evaluation including neurological and movement examination, paper-pencil tests for cognitive evaluation, and performance-based tests do not entail any medical risk. All of these evaluations will be performed in controlled laboratory settings. No personally identifiable information will be collected during these evaluations.

MRI in 3 Tesla scanner

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. 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. Subjects might experience discomfort from lying flat on their back during scanning.

Long-range risks

We do not foresee any long-range risks associated with this study.

Risk Minimization

Informed consent and assent

Verbal consent will be obtained for the screening visit over the phone or via email. Electronically signed informed consent will be obtained at the beginning of the video screening 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 in language appropriate for the individual's level of understanding. Subjects will be encouraged to ask questions and given enough time to discuss any aspect of the study with the research team. Subsequently, they will have to demonstrate understanding of the study procedures and what is expected of them. Once subjects understand the study, they will be asked if they wish to participate. If they do, they will be asked to electronically sign the consent form.

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, they 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.

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. Subjects may choose to stop participating in the clinical, cognitive, behavioral, and MRI evaluations at any time. During the experiments, the principal investigator or other members of the research team will be present at all times and monitor the subjects for adverse events. Subjects will maintain their regular medication regimen throughout the experiments. MRI scanning will be terminated immediately upon subject’s request or if an adverse event occurs.

MRI-related risk management

Magnetic resonance (MR) is a technique that uses magnetism and radio waves, not x-rays, to take pictures and measure chemicals of different parts of the body. The United States Food and Drug Administration (FDA) has set guidelines for magnet strength and exposure to radio waves, and we carefully observe those guidelines. Subjects will be watched closely throughout the MR study. Some people may feel uncomfortable or anxious. If this happens, they may ask to stop the study at any time and we will take them out of the MR scanner. 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 but subjects will be instructed to tell the research staff if they have them. There are some risks with an MR study for certain people. If subjects have a pacemaker or some metal objects inside their body, they may not be in this study because the strong magnets in the MR scanner might harm them.

Another risk is the possibility of metal objects being pulled into the magnet and hitting them. To lower this risk, all people involved with the study must remove all metal from their clothing and all metal objects from their pockets. We also ask all people involved with the study to walk through a detector designed to detect metal objects. 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 asked to read and answer very carefully the questions on the MR Safety Questionnaire related to their personal safety. They will be asked to tell us any information they think might be important. Subjects will be informed that this MR study is for research purposes only and is not in any way a complete health care imaging examination. The scans performed in this study are not designed to find abnormalities. Subjects will also be informed that the principal investigator, the lab, the MR technologist, and the Magnetic Resonance Research Center are not qualified to interpret the MR scans and are not responsible for providing a health care evaluation of the images. If a worrisome finding is seen on the subject’s scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact the subject, inform them of the finding, and recommend that they seek medical advice as a precautionary measure. Subjects will be informed that the investigators, the consulting physician, the Magnetic Resonance Research Center, and Yale University are not responsible for any examination or treatment that they receive based on these findings. The images collected in this study are not a health care MR exam and for that reason, they will not be routinely made available for health care purposes.

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 within two weeks before the scheduled MRI session.

Confidentiality

The data will be collected specifically for this project.

Hard copies of HIPAA identifiers, consent forms, clinical screening information, and MRI screening form will be kept in a locked filing cabinet.

The data 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 principal investigator, Dr. Tinaz, will have access to the centrally and electronically stored and password-protected subject identification list to decode data files.

Case report forms for each subject will be used to enter clinical evaluation results, and scores of paper-pencil tests, online surveys, and performance-based tests. All of this information will then be entered into a password-protected electronic database, which will be stored in a group-owned (Tinaz Lab) shared space on a Yale REDCap database. This is a secure web application for building and managing online surveys and databases. It is specifically geared to support online or offline data capture for research studies and operations. Case report forms, individual data files, and the electronic database 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 principal investigator, Dr. 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.

The username- and password-protected Yale REDCap platform will be used for the online surveys. Subjects will be emailed the survey links individually. Each survey will be linked to a record ID labelled according to the subject's unique study code.

Imaging data will be transferred securely to workstations for analysis and stored on HIPAA-compliant secure central storage servers ("Storage@Yale") provided by the Yale IT Department for a monthly fee. All team members will use encrypted research computers.

As a covered entity, Yale School of Medicine provides HIPAA Zoom accounts. The HIPAA-compliant and password-protected Zoom conferences will be conducted using an encrypted computer connected to the Yale secure network. The HIPAA Zoom has different features than the regular Zoom: 1) The ability to export, copy/paste or save chats is disabled. 2) Screen capturing and sending images are also disabled. 3) All messages are encrypted. 4) Cloud recording is disabled. Recordings are saved locally. To ensure security, each time a different invitation link with a unique meeting ID and password will be emailed to the subjects individually. As soon as the subject joins, the meeting will be locked to prevent others from joining. Meetings will be recorded by the research team to facilitate the collection of mental imagery content. Once the data has been transcribed, the videos will be deleted. Subjects will be permitted to record the meetings as well. Zoom software will be updated regularly to ensure that new security features are incorporated.

Due to the Covid-19 pandemic, the Yale Human Research Protection Program prepared an online Remote Research Visit Source Document for remote research visits conducted using Zoom or telephone in accordance with the ICH Good Clinical Practice standards of ALCOA-C [Attributable, Legible, Contemporaneous, Original, Accurate and Complete]. The document includes detailed information that needs to be entered (protocol number, PI, subject code, visit type/number/date, name of staff conducting the remote visit, documentation of the consent process, type of protocol assessment (e.g., demographics, medical history, questionnaires, etc.), details of intervention, and side effects). After each telephone encounter and Zoom visit this online document will be filled out and maintained with subjects' research records.

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 electronic database that contains the information in case report forms will stay on the password-protected research 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.

The principal investigator, research staff, and representatives from the Yale Human Research Protection Program and Yale Human Investigation Committee (for auditing purposes) will have access to the protected health information.

Safeguard procedure in the case of adverse events

Human subjects research will be conducted according to Yale University IRB guidelines for human subject protection in the setting of the Yale School of Medicine campus including the Yale MRRC and Yale Center for Clinical Investigation outpatient facilities, where – in addition to the medically credentialed principal investigator, Dr. Tinaz– physicians, nurses and code teams are on call to assist in any kind of unforeseen medical emergency.

Adverse events will be reported in accordance with federal and Yale University IRB rules. For each adverse event, the principal investigator, Dr. Tinaz, will record the onset, end, intensity, required treatment, outcome, seriousness, and action taken. Serious or unexpected adverse events will be reported immediately to the Yale University IRB, and in writing within 5 days if life-threatening, and within 15 days otherwise. Expected or non-serious adverse events will be reported at the time of continuing review.

Risk-benefit assessment

This study poses not more than minimal risk and has the potential for high-impact findings and direct clinical significance for patients with PD. Therefore, we think that the risk-benefit ratio for this study is reasonable given the potential benefits.

2.3.2 Potential Benefits

Immediate potential benefits

Subjects with PD in the experimental group will most likely experience a direct benefit from the mental imagery intervention in terms of improvement in cognitive functioning in everyday life. Similarly, subjects with PD in the active control group will most likely experience a direct benefit from psychoeducation in terms of gathering information about cognitive problems experienced in PD and management and coping strategies.

Long-Range Potential benefits

The knowledge gained from this study will facilitate the design and implementation of a phase 2 clinical trial. Ultimately, it is highly likely that mental imagery training will be incorporated into cognitive rehabilitation programs and will lead to improvements in the treatment of cognitive problems of individuals with PD.

3 Study Purpose and Objectives

3.1 Hypotheses

We hypothesize that our 6-week mental imagery training protocol will improve goal-directed cognitive functioning in everyday life of PD patients. Furthermore, we predict the effects of mental imagery will increase task-specific whole-brain functional connectivity and improved differentiation of core brain networks. We hypothesize that the training effects on A)

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goal-directed cognitive functioning and B) functional network re-organization will be sustained over the course of 12 weeks post-intervention in the PD-MI group, but not in the PD-Con group.

Lastly, we hypothesize that the putative task-specific within- and between-network functional connectivity changes in the PD-MI group at the 6- and 12- week timepoints will predict the corresponding self-reported, performance-based, and executive function test outcomes.

3.2 Primary Objective

The primary objective of this study is to determine whether mental imagery training will improve goal-directed cognitive functioning in everyday life and brain functional connectivity in patients with PD.

3.3 Secondary Objective

The secondary objective is to determine whether the behavioral and imaging effects (as outlined in the primary objective) of mental imagery training are sustained after a 12-week period in patients with PD. A final exploratory objective is to determine if there is a potential brain-cognition link to predict the corresponding cognitive functional outcomes.

4 Study Design

4.1.1 General Design Description

We will conduct a phase 1 clinical trial with two groups randomly assigned in parallel. The experimental group (PD-MI) will receive mental imagery training and the control group (PD-Con) will receive psychoeducation (see Figure 3).

Within two weeks of obtaining consent and completing initial phone and online video-screening, subjects will complete online surveys and arrive for an in-person visit to complete the screening process including the comprehensive evaluation of baseline cognitive functioning, performance-based tests, and neurological exam. At the end of this visit, eligible subjects will be randomized to two groups, PD-MI and PD-Con.

Within two weeks of Visit 1, subjects will return for Visit 2 to assess baseline imagery skills and perform fMRI tasks in the scanner. Subjects in the PD-MI group will be interviewed in Visit 2 to gather information about their daily activities and goals for imagery script development.

Following Visit 2, subjects will start their respective trainings for 6 weeks. The one-on-one training sessions will be delivered via videoconferencing.

We will guide the subjects in the PD-MI group using personalized scripts during one-on-one mental imagery training 3 times a week for the first 4 weeks. We will also record the mental imagery scripts (each 5-10 min) for self-practice on none-training days in the first 4 weeks and for daily homework in the subsequent 2-week block. After each daily practice in the 2-week block, subjects will be asked to submit a detailed mental imagery diary via the Yale REDCap online survey platform. Subjects will also be called once a week in the 2-week block for check-in.

The control group (PD-Con) will receive psychoeducation 3 times a week for 4 weeks regarding cognitive functioning and brain health in PD. Subjects will receive private video links with pre-recorded PowerPoint lectures covering topics such as basic brain anatomy, neuroplasticity, attention-executive function, memory, speech-communication, hallucinations and delusions, sleep, diet, physical activity, mood disorders, stress, and social bonds. On no-lecture days and in the subsequent 2-week block, subjects will receive online quizzes covering the lecture topics to be completed via Yale REDCap online survey platform. Subjects will also be called once a week in the 2-week block for check-in.

Upon completion of the 6-week training, all subjects will return for Visit 3 which will entail repeat cognitive evaluations and performance-based tests as in Visit 1, and mental imagery vividness rating and fMRI scans as in Visit 2. After Visit 3, subjects in the PD-MI group will be

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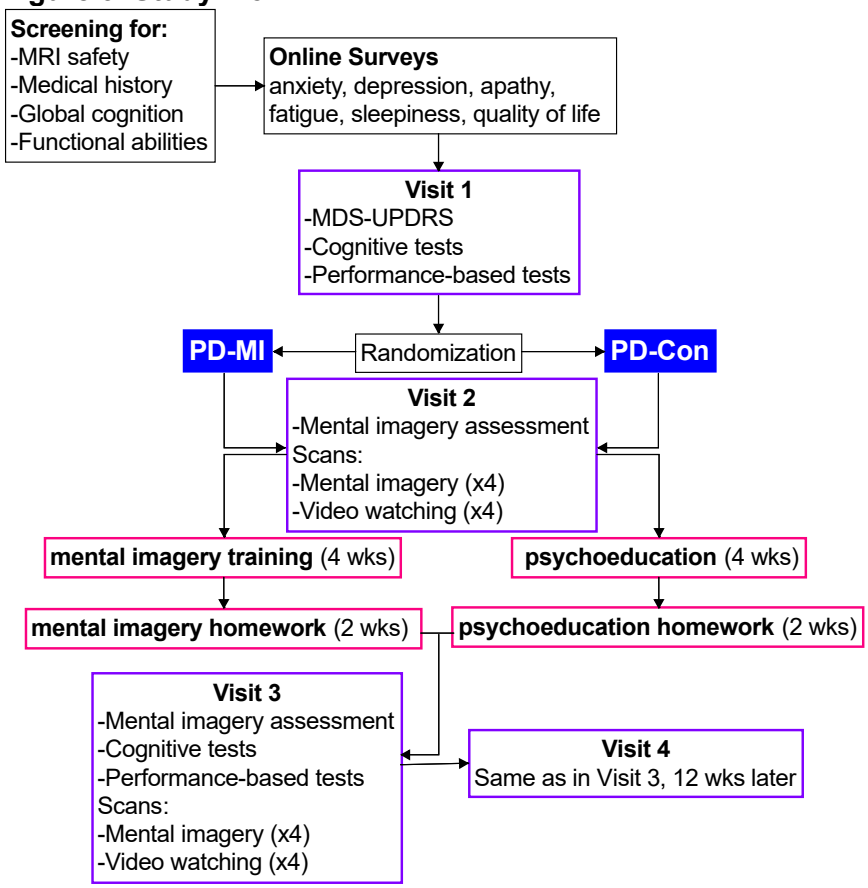
encouraged to incorporate goal-directed mental imagery into their daily life and those in the PD-Con group will be encouraged to retain the psychoeducation material they learnt.

Twelve weeks after Visit 3, all subjects will return for Visit 4 which will be the final visit and entail repeat evaluations of all cognitive and performance-based tasks and the fMRI tasks. The same procedures as described in Visit 3 will be followed.

Figure 3. Study Flow



4.1.2 Study Date Range and Duration

The expected length of the study is 6 years. See Table 1 below for the study timeline.

Table 1. Study Timeline

Year 1	Data collection and analysis for primary objectives. Start data analysis for secondary objectives.
Year 2	Data collection and analysis for primary and secondary objectives.
Year 3	Wrap up data analysis of primary objectives. Start writing manuscripts.
Year 4	Complete data collection. Wrap up data analysis for secondary objectives. Continue writing manuscripts.
Years 5-6	Complete all statistical analyses. Present and publish findings. Propose mental imagery training manual. Refine the study procedures and start implementing the phase 2 trial.

4.1.3 Number of Study Sites

The Yale School of Medicine campus will be the only study site. Research procedures will take place at two sites: The Yale Magnetic Resonance Research Center (MRRC) and the Yale Center for Clinical Investigation (YCCI) Church Street Research Unit. The YCCI Research

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Unit will be used as a backup for some of the longer clinical and psychometric evaluations (e.g., Visit 1).

4.2 Outcome Variables

4.2.1 Primary Outcome Variables

1) Quality of life in Neurological Disorders (Neuro-QoL) Scores

Timeframe: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The Neuro-QoL is a set of self-report measures that assesses the health-related quality of life of adults and children with neurological disorders. Neuro-QoL instruments were developed through a collaborative, multisite NINDS-sponsored research initiative to construct psychometrically-sound and clinically-relevant health-related quality of life measurement tools for individuals with neurological conditions including PD. The Neuro- QoL instruments enable within-disease as well as cross-disease comparisons and are intended for use in both neurology clinical trials and clinical practice. We will use the Neuro-Qol version 2 Cognitive Function item bank to assess post-training self-reported changes in cognitive functions.

Change in the Neuro-Qol version 2 Cognitive Function scores from T0 to T1 and across T2 will be the primary cognitive outcomes of this study. Significant increase in the Cognitive Function scores at T1 will be considered significant improvement in self-reported cognitive function in everyday life. Significant increase in these scores across T2 will be considered sustained improvement in self-reported cognitive function in everyday life.

2) Questionnaire on Mental Imagery (QMI) Vividness of Imagery Scale scores

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The QMI is a measure of vividness of an individual's multisensory and motor imagery on a scale of 1 to 7 (1: perfectly vivid image, 7: no image present at all).

Change in the QMI scores from T0 to T1 and across T2 will serve as the manipulation check for the mental imagery intervention. Significant increase in these scores at T1 will be considered improved imagery vividness. Significant increase in these scores across T2 will be considered sustained improvement in imagery vividness.

3) Task-specific whole-brain pairwise functional connectivity

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will calculate the whole-brain pairwise functional connectivity during mental imagery and video-watching of naturalistic goal-directed tasks in the MRI scanner for each subject.

Change in task-specific pairwise functional connectivity from T0 to T1 and across T2 will be the primary imaging outcomes of the study. Significantly increased task-specific pairwise functional connectivity in major networks (e.g., default mode network during mental imagery and frontoparietal executive network during video-watching) at T1 will be considered improved task-specific functional reorganization of these networks. Significantly increased task-specific pairwise functional connectivity in major networks across T2 will be considered sustained

improvement in task-specific functional reorganization of these networks.

4.2.2 Secondary and Exploratory Outcome Variables

1) Composite executive function test scores (Secondary)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will calculate the composite z-scores of the executive function test scores (i.e., Stroop, F-A-S letter fluency, and Trail Making A-B tests) for all subjects.

Change in composite executive function test scores from T0 to T1 and across T2 will be the secondary cognitive outcomes of the study. Significant increase in these scores at T1 will be considered improved executive function. Significant increase in these scores across T2 will be considered sustained improvement in executive function.

2) Local and global functional connectivity-based graph measures (Secondary)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will calculate the local (i.e., clustering coefficient) and global (i.e., betweenness centrality) network graph measures during mental imagery and video-watching tasks in the MRI scanner. These measures will provide information about the context-dependent changes in the functional organization of the brain networks.

Change in graph measures from T0 to T1 and change in graph measures across T2 will be secondary imaging outcomes the study. Significantly increased task-specific clustering coefficient in major networks (e.g., default mode network during mental imagery and frontoparietal executive network during video-watching) and significantly increased context-dependent betweenness centrality between major network nodes (e.g., stronger between the default mode and frontoparietal networks during mental imagery) at T1 will be considered improved task-specific functional differentiation of these networks. Significant increases in the same graph measures across T2 will be considered sustained improvement in task-specific functional differentiation of these networks.

3) Modified Six-Elements Test scores (Exploratory)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The Modified Six-Elements Test is a measure of goal-directed planning and execution.

Change in these test scores from T0 to T1 and across T2 will be the secondary cognitive outcomes of the study. Significant increase in these scores at T1 will be considered improved performance in goal-directed planning and execution. Significant increase in these scores across T2 will be considered sustained improvement of performance in goal-directed planning and execution.

4) Global cognition scores (Exploratory)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: The Repeated Battery for the Assessment of Neuropsychological Status (RBANS) is a commonly used battery with alternate versions allowing repeated testing of the cognitive domains of attention, verbal and visual memory, language, and visuospatial functioning.

Change in total RBANS scores from T0 to T1 and across T2 will be the exploratory cognitive outcomes of the study. Significant increase in these scores at T1 will be considered improved global cognition. Significant increase in these scores across T2 will be considered sustained improvement of global cognition.

5) Post-training brain-cognition relationship (Exploratory)

Time frame: This measure will be collected at baseline (T0), immediately after 6 weeks of intervention (T1), and 12 weeks thereafter (T2) from all subjects.

Rationale: We will examine whether the post-training changes in whole-brain pairwise functional connectivity and graph measures will predict the post-training differences in the cognitive function in each group at T1 and T2.

4.3 Study Population

The study population will be subjects with PD defined according to the Movement Disorders Society (MDS) diagnostic criteria with mild-to-moderate PD[75], who do not have mild cognitive impairment[76], aged 40 and above, and are physically independent.

Idiopathic PD is an adult-onset neurological disorder. In the United States, the incidence of idiopathic PD cases before the age of 40 is extremely low.[77] Therefore, individuals with PD who are 40 years and older will be included, and there will be no upper age limit for participation in the study.

There is no restriction for gender, race, or ethnicity. Parkinson's disease affects more males than females with most studies reporting a male-to-female ratio ranging from 1.3 to 2.[78] We will aim to reflect a male-to-female ratio of 1.5 in subject selection.

There is no restriction in participation regarding race or ethnicity. We will seek a racially and ethnically diverse enrollment. According to the United States Census Bureau, the 2020 census demographic data in Connecticut showed the following distribution:[79] White only 66.4%, Black only 10.8%, Asian only 4.8%, Hispanic or Latino 17.3%. The percentage of other racial categories was very small. The numbers in the planned enrollment table were calculated based on these ratios.

Subjects will be recruited through:

1. The Yale Movement Disorders outpatient clinics
2. The outpatient clinics in the new Yale PD Comprehensive Care Center
3. The local PD support groups and nonprofit organizations (e.g., American PD Association Connecticut Chapter, Beat PD Today exercise program) that provide educational and wellness programs for the greater PD community in Connecticut
4. Neurology practices in Connecticut who care for patients with PD.
5. JDAT recruitment services (EPIC/MyChart alerts & mailing)
6. Department/Center newsletters
7. The YCCI recruitment database
8. Recruitment letters

Table 2. Planned Enrollment

	Not Hispanic or Latino		Hispanic or Latino		Total
	F	M	F	M	
American Indian/Alaska Native	0	0	0	0	0
Asian	2	3	0	0	5
Native Hawaiian or other Pacific Islander	0	0	0	0	0

Black or African American	5	8	1	1	15
White	32	47	9	12	100
More than one race	0	0	0	0	0

4.3.1 Number of Participants

We will enroll 120 individuals. Eligible subjects will be randomly assigned to either the PD-MI (N=60) or PD-Con (N=60) group.

4.3.2 Eligibility Criteria/Vulnerable Populations

In order to be eligible for inclusion in the study, an individual must meet all of the following criteria:

- Subjects with a diagnosis of idiopathic PD defined according to the International Parkinson and Movement Disorder Society (MDS) Clinical Diagnostic Criteria for PD[75]
- Age ≥ 40 years
- Expected to be on a stable dopaminergic medication regimen throughout the study period

Any individual who meets any of the following criteria will be excluded from participation in this study:

- Age < 40 years
- Non-English speaking
- Pregnancy
- Breastfeeding
- Excessive alcohol consumption (> 7 drinks per week for women, > 14 drinks per week for men) or illicit substance use
- 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 longer than a few minutes
- Metallic surgical implants or traumatically implanted metallic foreign bodies
- Inability to lie flat for about an hour in the MRI scanner
- Discomfort being in small, enclosed spaces
- Dementia at screening (Video-Montreal Cognitive Assessment score < 21/30[80-82]
- Cognitive problems in activities of daily living suggestive of more than mild cognitive impairment (PD Cognitive Functional Rating Scale > 4[83])
- Mild cognitive impairment according to the MDS Level II comprehensive assessment criteria (> 2 SD below the norm in two tests in a single cognitive domain or in one test in two separate cognitive domains). Note: The cutoff of 2 SD below the norm will apply to all domains including attention, verbal and visual memory, language, visuospatial skills, and executive functions.[76]
- Hoehn & Yahr stage > 3 (i.e., able to stand and walk, but not fully independent[84])
- 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-Unified PD Rating Scale resting tremor score > 2 in limbs, head/chin tremor, or more than mild dyskinesia by history or exam[85])
- Failure to adhere to training and homework requirements (i.e., less than 75% adherence to one-on-one sessions and less than 50% homework completion rate)

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- Failure to adhere to protocol

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 in two weeks before the scheduled MRI session.

5 Study Methods/Procedures

5.1 Study Procedures

All study procedures will be performed for research purposes.

Recruitment:

We will recruit individuals with PD directly through the Yale Movement Disorders outpatient clinics. The outpatient clinics in the new Yale PD Comprehensive Care Center will also be a source of recruitment. PD patients will be informed about the study during their visit at the clinics and provided with the study material. Interested patients will be contacted directly by the study team for initial screening.

We will also attend meetings at the local PD support groups and nonprofit organizations (e.g., American PD Association Connecticut Chapter, Beat PD Today exercise program) that provide educational and wellness programs for the greater PD community in Connecticut to present the proposed study to potential subjects.

Recruitment flyers will also be mailed to the providers at the neurology practices in Connecticut who care for patients with PD. Letters including study flyers will also be mailed to interested candidates.

In addition, the recruitment services at the YCCI will be used. Specifically, we will be utilizing the YCCI recruitment database. YCCI has an ever growing “Help us Discover” database of more than 14,000 individuals who have expressed interest in clinical research at Yale. Emails are sent periodically to the group to maintain engagement and research interest. Researchers and study teams have found the communications have increased interest and clinical trial recruitment after each YCCI email campaign.

We will also make use of the recruitment services offered by JDAT (EPIC/MyChart alerts & mailing) and Department/Center newsletters.

Consent

Verbal consent will be obtained for the screening visit over the phone or via email. Electronically signed informed consent will be obtained at the beginning of the video screening 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 in language appropriate for the individual’s level of understanding. Subjects will be encouraged to ask questions and given enough time to discuss any aspect of the study with the research team. Subsequently, they will have to demonstrate understanding of the study procedures and what is expected of them. Once subjects understand the study, they will be asked if they wish to participate. If they do, they will be asked to electronically sign the consent form.

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, they 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

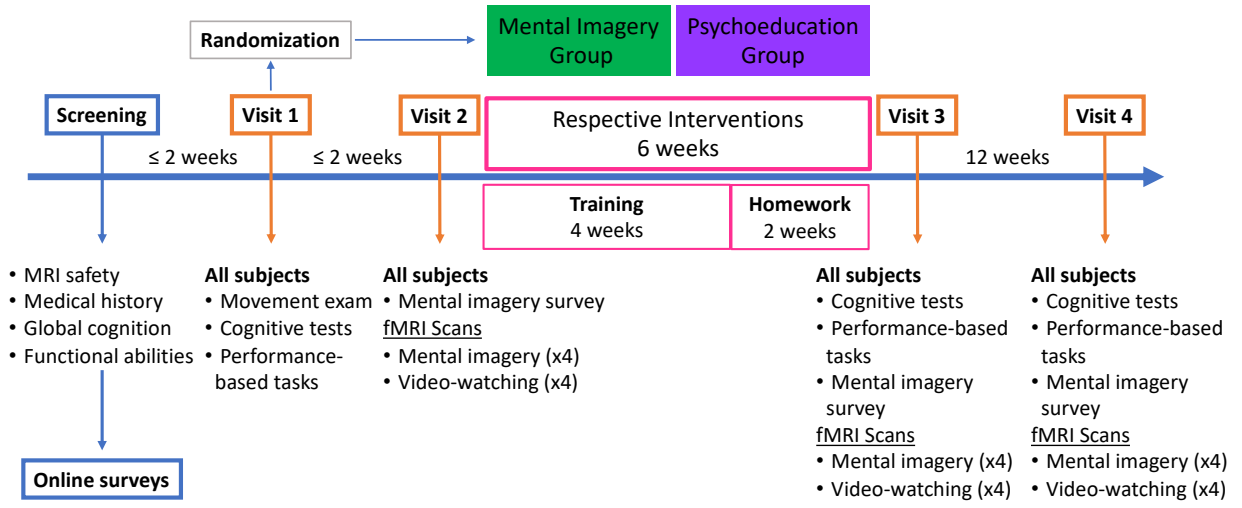
used to assess understanding and appreciation of the facts. Subject will then be expected to make a rational choice: "Considering the risks and benefits we have discussed, would you like to take part in this study?" Based on the subject's responses the team member will make a final judgment about capacity for consent. If the subject has capacity and agrees to the study, they will sign the consent form

Study Schedule

See also Figure 4 for study schedule and timeline.

Initial Screening: After obtaining verbal consent, subjects will complete an initial phone call screening for MRI safety and medical history. If the subject fails the MRI safety screening or meets any of the exclusion criteria for medical history, they will be excluded from the study. Subjects who are still eligible will be scheduled for a follow-up video-screening via the Zoom videoconferencing platform. Consent process will take place at the beginning of this visit. Subjects will electronically sign the consent form via REDCap. The screening will be for demographic data, global cognition, and functional abilities. We will administer the MoCA to assess global cognition.[80] We will use the PD Cognitive Functional Rating Scale for daily functional abilities.[83] If a subject scores below the eligibility criteria of our screening, they will be excluded from the study and their data will not be used.

Figure 4. Study Timeline.



Online Surveys: To evaluate the contribution of nonmotor factors to cognitive functioning, the Geriatric Depression Scale,[86] Parkinson Anxiety Scale,[87] Starkstein Apathy scale,[88] PD Quality of Life Questionnaire-39,[89] Parkinson Fatigue Scale,[90] and Scales for Outcomes in Parkinson's Disease – Sleep[91] via the Yale REDCap online survey platform to those who pass the initial screening.

Visit 1: *Baseline movement and cognitive evaluations to determine eligibility and baseline performance-based tasks:* Visit 1 will be scheduled within two weeks after initial screening to complete the screening process. We will determine the disease severity with the MDS-Unified PD Rating Scale (MDS-UPDRS)[85] that also includes the Hoehn & Yahr staging.[83] We will administer the Wechsler Test of Adult Reading[92] to determine premorbid IQ, and perform a comprehensive cognitive evaluation to rule out MCI according to the MDS Level II criteria[76] using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[93] and additional tests to assess frontal-executive functioning including the Stroop Test,[94] letter fluency (F-A-S),[95] and Trail Making Test parts A and B.[96] The tests will be scored immediately

to determine eligibility. Eligible subjects will be randomized to two groups: PD-MI and PD-Con. Brief description of the tests:
Weschler Test of Adult Reading: Is an assessment of intelligence that has participants pronounce 50 irregularly spelt words. The test typically takes 5-10 minutes to complete.
RBANS: Assesses 5 domains of cognition, 1) immediate memory, 2) Visuospatial/ Constructional, 3) Language, 4) Attention, 5) Delayed Memory. Completion time is roughly 30 minutes.
Stroop test: Is a measure of attention that has the participant read through a list of words or naming colors as quickly as possible within 45 seconds.
F-A-S verbal fluency test: Measures verbal fluency by having the participant verbally produce as many words as possible that begin with the letters F, A, and S, within a one-minute timespan.
Trail Making Tests A & B: Consist of 25 circles spread over a sheet of paper, the subject is tasked with connecting each circle by following a specific pattern in a 5-minute timespan.

For all eligible subjects*:* We will administer the Neuro-QoL version 2 Cognitive Function survey to eligible subjects to assess self-reported cognitive functioning in everyday life.[97] We will administer the Modified Six-Elements Test.[98] The test consists of three tasks (simple arithmetic, written picture naming, dictation) each of which has two subtasks. The subject is required to attempt at least part of each of the six subtasks within 10 min, but without switching directly between subtasks within the same task category. The tests assess the ability to create and maintain goals and intentions, formulate a plan, organize behavior over time, and execute the plan at appropriate times.[99]

For eligible subjects in the PD-MI group: We will perform a structured cognitive interview to determine the subject's cognitive difficulties during everyday tasks. Information gathered from this interview will help with personalized mental imagery guidance.

Visit 2: *Baseline neuroimaging experiments**:*** Visit 2 will be scheduled within two weeks following Visit 1. All subjects will complete the Questionnaire upon Mental Imagery (QMI) Vividness of Imagery Scale[100] for evaluation of baseline imagery skills. All subjects will then perform fMRI tasks in the scanner. The mental imagery tasks will always be performed before the video-watching tasks to avoid possible carryover effects from the videos.

Mental imagery tasks: All subjects will receive instructions on how to perform mental imagery of goal-oriented daily tasks and practice guided imagery first outside the scanner. Subjects will then perform mental imagery of four different goal-oriented tasks in the scanner. We will keep the goals constant across subjects, but will not prescribe the specific steps or events. After each imagery run in the scanner, subjects will give an account of their imagery content which will be recorded.

Video-watching tasks: All subjects will also watch videos of four different everyday tasks (e.g., grocery shopping, preparing a meal) in the scanner. After each video-watching run in the scanner, subjects will answer questions about the content of the videos.

Scanning procedures: We will conduct the MRI experiments in a Siemens Prisma 3.0 Tesla human research magnet with a 64-channel head coil in the MRRC. First, T1-weighted high-resolution 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°). There will be four mental imagery and four video-watching runs each lasting 4 min 18 s. During the mental imagery tasks, subjects will keep their eyes closed at all times and receive auditory instructions. During the video-watching runs, subjects will keep their eyes open and receive visual instructions.

Training period

Mental Imagery Training: Subjects in the PD-MI group will receive personalized training during one-on-one sessions 3 times a week for the first 4 weeks. Training will be offered via Zoom. Subjects will be guided to mentally simulate the planning and implementation of everyday tasks (e.g., going grocery shopping). The training sessions will last about 15-20 min. We will also record the mental imagery scripts for self-practice on no-training days in the first 4 weeks and for daily homework practice in the subsequent 2-week block. After practice, subjects will be asked to submit a detailed daily mental imagery diary via the Yale REDCap online survey platform. We will structure this diary based on the key elements of mental imagery including the setting of the activity, components of the activity, contextual cues, episodic details, emotional experiences, and vividness and difficulty level of the mental imagery exercise. Subjects will also be called once a week in the last 2 weeks for check-in.

Psychoeducation: Subjects in the PD-Con group will receive psychoeducation 3 times a week for 4 weeks regarding cognitive functioning and brain health in PD. Subjects will receive private video links with pre-recorded PowerPoint lectures covering topics such as basic brain anatomy, neuroplasticity, attention-executive function, memory, speech-communication, hallucinations and delusions, sleep, diet, physical activity, mood disorders, stress, and social bonds. The lectures will last about 15-20 min and will be accompanied by three multiple-choice questions to be completed via REDCap online survey platform to assess content comprehension. On no-lecture days in the first 4 weeks and in the subsequent 2-week block, subjects will receive quizzes covering the lecture topics to be completed via REDCap online survey platform. Subjects will also be called once a week in the last 2 weeks for check-in.

Visit 3: *Short-term outcome visit*. Upon completion of the 6-week training, all subjects will return for repeat 1) mental imagery assessment using the QMI, 2) cognitive evaluation using a different form of the RBANS and the frontal-executive tests, 3) Neuro-QoL survey, 4) Modified Six-Element Test, and 5) fMRI scans while performing mental imagery and video-watching of the same goal-directed daily tasks as in Visit 2. We will use modified versions of the videos to minimize learning effects. After Visit 3, subjects in the PD-MI group will be encouraged to incorporate goal-directed mental imagery into their daily life. Subjects in the PD-Con group will be encouraged to retain the psychoeducational information.

Visit 4: *Long-term outcome visit.* This will be the final visit. Twelve weeks after Visit 3, all subjects will return for repeat cognitive and imaging evaluations. The same procedures as described in Visit 3 will be followed.

5.1.1 Data Collection

The data will be collected specifically for this project. The information obtained in this study will be recorded in such a manner that the identity of the human subjects cannot be ascertained directly. The data 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 principal investigator, Sule Tinaz, will have access to the centrally and electronically stored and password-protected subject identification list to decode data files. All other study investigators will have access to the de-identified data. All study investigators will use encrypted research computers.

Data Recording

Case report forms for each subject will be used to enter clinical evaluation results, and scores of paper-pencil tests, surveys, and performance-based tests. All of this information will

then be entered into a password-protected electronic database, which will be stored in a group-owned (Tinaz Lab) shared space on a Yale REDCap database. This is a is a secure web application for building and managing online surveys and databases. It is specifically geared to support online or offline data capture for research studies and operations.

Imaging data obtained at the MRRC will be transferred securely to workstations for analysis and stored on HIPAA-compliant secure central storage servers ("Storage@Yale") provided by the Yale IT Department for a monthly fee. All team members will use encrypted research computers.

Sources of Data

Initial Screening: Data will be collected at meetings with the subjects via phone call and Zoom video platform.

- Demographic data (age, sex, ethnicity, level of education, etc.)
- MRRC MRI safety questionnaire
- Medical history questionnaire
- MoCA test for global cognition
- PD Cognitive Functional Rating Scale for daily functional abilities

Online Surveys: These surveys will be administered via the Yale REDCap online survey platform to those who pass the initial screening. The selected surveys aim to evaluate the contribution of nonmotor factors (e.g., mood disorders, fatigue) to cognitive functioning. The survey data will be exported from REDCap.

- Geriatric Depression Scale
- Parkinson Anxiety Scale
- Starkstein Apathy scale
- PD Quality of Life Questionnaire-39
- Parkinson Fatigue Scale
- Scales for Outcomes in Parkinson's Disease – Sleep

Online Homework and Quizzes: These will administered via the Yale REDCap online survey platform. Responses will be exported from REDCap.

- Quizzes on the psychoeducation material for the PD-Con group
- Surveys on the content of mental imagery homework for the PD-MI group

Clinical and Cognitive Evaluations:

- MDS-UPDRS and Hoehn & Yahr to assess disease severity (Visit 1)
- Wechsler Test of Adult Reading to determine premorbid IQ (Visit 1)
- RBANS test and executive function tests (Stroop, letter fluency (F-A-S), and Trail Making Test parts A and B) for a comprehensive cognitive evaluation (Visits 1, 3, and 4)
- Neuro-QoL survey (primary cognitive outcome) to assess the impact of cognitive functioning on activities of daily living (Visits 1, 3, and 4)
- Structured cognitive interview for the PD-MI group to determine subjects' cognitive difficulties during everyday tasks (Visit 1)
- QMI Vividness of Imagery Scale will serve as a manipulation check for the mental imagery intervention (Visits 2, 3, and 4)

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- Modified Six-Elements Test as a performance-based measure of goal-directed planning and execution (Visits 1, 3, and 4)

Case report forms for each subject will be used to enter clinical evaluation results, and scores of paper-pencil tests, online surveys, and performance-based tests. All of this information will then be entered into a password-protected electronic database, which will be stored in a group-owned (Tinaz Lab) shared space on a Yale REDCap database.

Imaging Data:

Functional MRI data during mental imagery and video-watching tasks will be collected in a 3 Tesla human magnet at the MRRC (Visits 2, 3, and 4). The fMRI data will be used for functional connectivity analyses to evaluate the changes in whole-brain functional connectivity (primary imaging outcome) and other network measures as a result of the mental imagery intervention.

Imaging data will be transferred securely to workstations for analysis and stored on HIPAA-compliant secure central storage servers ("Storage@Yale") provided by the Yale IT Department for a monthly fee.

5.1.2 Adverse Events Definition and Reporting

An Adverse Event will be defined as any untoward or unfavorable occurrence in a human research subject (physical or psychological harm) temporally associated with the individual's participation in the research (whether or not considered related to participation in the research).

Attribution of Adverse Events:

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by the principal investigator, Dr. Tinaz, according to the following categories:
Definite: Adverse event is clearly related to investigational procedures
Probable: Adverse event is likely related to investigational procedures
Possible: Adverse event may be related to investigational procedures
Unlikely: Adverse event is likely not to be related to the investigational procedures
Unrelated: Adverse event is clearly not related to investigational procedures

Plan for Grading Adverse Events:

The severity of adverse events noted during the study will be graded as mild, moderate, or serious.

Plan for Determining Seriousness of Adverse Events

In addition to grading the adverse event, the principal investigator will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it results in any of the following outcomes:

1- Death
2-A life-threatening experience in-patient hospitalization or prolongation of existing hospitalization;
3-A persistent or significant disability or incapacity;
4-A congenital anomaly or birth defect; OR
5-Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An adverse event may be graded as severe but still not meet the criteria for a SAE. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. The principal investigator will consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

Reporting of Adverse Events

Adverse events will be reported in accordance with federal and Yale University IRB rules. For each adverse event, the principal investigator, Dr. Tinaz, will record the onset, end, intensity, required treatment, outcome, seriousness, and action taken. Serious or unexpected adverse events will be reported to the Yale University IRB, within 5 days. Expected or non-serious adverse events will be reported at the time of continuing review.

We will submit information summarizing the number and frequency of adverse events experienced by participants in each group, regardless of whether or not they were anticipated or unanticipated. We will also provide the time frame for adverse event data collection and specify whether the collection approach for adverse events was systematic or non-systematic.

5.2 Study Schedule

See also Figure 4 for study schedule.

Verbal consent will be obtained for the initial screening visit over the phone or via email when the potentially eligible subject is first contacted. Electronically signed informed consent will be obtained at the beginning of the initial Zoom video screening visit via REDCap.
Time estimate for initial screening: 1 hour

There will be a total of 4 in-person visits:

Visit 1: Baseline Clinical Evaluation. Subjects will undergo detailed clinical evaluations to determine disease severity and level of cognitive functioning**.**
Time Estimate: 3 hours

Visit 2: Baseline Neuroimaging Experiments. Subjects will rate their mental imagery vividness at baseline and perform fMRI tasks in the scanner. Subjects will also receive instructions on their respective training and homework assignments.
Time Estimate: 2 hours

Training: Subjects will receive their respective training 3 times per week for 4 weeks. On non-training days during the week and in the subsequent 2-week block, subjects will complete homework.
Visit 3: 6-Week Post-Intervention Assessments. All subjects will return for repeat cognitive evaluations as in Visit 1, and mental imagery vividness rating and fMRI scans as in Visit 2.
Time Estimate: 3 hours

Visit 4: 12-Week Post-Completion Assessments. All subjects will return for repeat cognitive evaluations and fMRI tasks. The same procedures as described in Visit 3 will be followed.
Time Estimate: 3 hours

5.3 Informed Consent

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participants and written documentation of informed consent will be required prior to starting intervention/administering study intervention. Consent form will be emailed to the

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research participant. The authorized study member will obtain consent electronically at the start of the initial screening visit via Zoom.

The written consent form is submitted with this protocol.

5.3.1 Screening

The research assistant, Jared Cherry, will screen subjects over the phone for MRI safety and medical history. Eligible subjects will then be scheduled for a Zoom online video platform call to electronically sign the consent form via REDCap and undergo video-screening for demographic data, global cognition, and functional abilities. The initial screening will last approximately 1 hour.

5.3.2 Recruitment, Enrollment and Retention

Recruitment

We will recruit individuals with PD directly through the Yale Movement Disorders outpatient clinics. The outpatient clinics in the new Yale PD Comprehensive Care Center will also be a source of recruitment. Potentially eligible PD patients will be informed about the study during their visit at the clinics and provided with the study flyer. Interested patients will be contacted directly by the study team for initial screening. More specifically, Dr. Tinaz and Dr. Vives-Rodriguez are both movement disorders neurologists who have a direct or indirect treatment relationship with PD patients in the Yale Movement Disorders Clinics. They (or the research assistant Jared Cherry) will inform the patients with whom they have a direct treatment relationship either during clinic visits or via phone. Dr. Tinaz and Dr. Vives-Rodriguez will review the EPIC clinic visit progress notes of PD patients with whom they are not in a direct treatment relationship to determine eligibility (based on DOB, sex, past medical history, and movement exam scores). They will then ask the treating movement disorders neurologists in their practice to inform these potentially eligible PD patients about the study and ask them for permission to release contact information.

We will also attend meetings at the local PD support groups and nonprofit organizations (e.g., American PD Association Connecticut Chapter, Beat PD Today exercise program) that provide educational and wellness programs for the greater PD community in Connecticut to present the proposed study to potential subjects.

Recruitment flyers (see attached) will also be mailed to the providers at the neurology practices in Connecticut who care for patients with PD. Letters including study flyers will also be mailed to interested candidates who have agreed to be contacted by the study investigators.

In addition, the recruitment services at the YCCI including the YCCI clinical trials website and the YCCI social media support will be used to advertise the study. The same language in the study flyer will be used for advertisements. We will also utilize the YCCI recruitment database. YCCI has an ever growing “Help us Discover” database of more than 14,000 individuals who have expressed interest in clinical research at Yale. Emails are sent periodically to the group to maintain engagement and research interest. Researchers and study teams have found the communications have increased interest and clinical trial recruitment after each YCCI email campaign.

Lastly, we will also make use of the recruitment services offered by JDAT (EPIC/MyChart alerts & mailing) and Department/Center newsletters.

Enrollment

See Table 2. Planned Enrollment and explanations in Section 4.3.

Retention

We will ensure that the logistics of the study is straightforward in order to maximize subject compliance and retention. The Yale MRRC and YCCI are located in the Yale School of Medicine campus in close proximity to each other. No other research sites will be involved. We will email subjects the video link of a virtual tour of the MRRC and YCCI outpatient facility, so that they can familiarize themselves with the research sites (lobby, waiting area, behavioral testing rooms, scanner rooms, etc.) prior to their visit. Subjects will also be provided written directions and maps to the research site. Parking is always available in two garages near both research sites. Subjects who do not feel comfortable driving and have nobody else to drive them will be offered transportation. Subjects will be compensated for their participation and for travel expenses (e.g., parking, cab ride).

The one-on-one mental imagery training for the experimental group and psychoeducation for the control group will be administered via the Zoom video platform and private video links, respectively, eliminating the burden of in-person visits on the subjects. The video visits will be scheduled at convenient times for the subjects. Several surveys will also be administered online via the Yale REDCap survey platform, which will provide the subjects with enough time and flexibility to fill them out. All subjects will also submit their homework via REDCap, which will allow us to monitor compliance in a timely fashion.

At the first screening visit, the study procedures, expectations, and the importance of their participation will be explained to subjects in detail and all questions will be answered. Plans to minimize risk and discomfort and to ensure safety and confidentiality will be discussed, and subjects will be encouraged to ask questions. At their first visit, subjects will receive a study folder containing brief descriptions of the study procedures, specific instructions for each research visit, calendar of research activities throughout the study period, and appointment cards. The subsequent visits will be scheduled considering the best availability of the subjects to avoid scheduling conflicts. Regular reminders for upcoming visits will be sent via email and/or phone. Subjects will be encouraged to contact the study team via email or phone anytime if they had questions, concerns, or requests.

In our previous imagery study, the dropout rate was approximately 15%. This included subjects who did not complete the study and those who were not compliant with homework requirements. The dropout rate was not significantly different between the experimental and control groups. All others (a total of 44) successfully completed four research visits spanning 6-8 weeks each of which lasting 2-3 hours. Subjects remained fully compliant and motivated throughout the study period. We expect a similar level of compliance and motivation, and not more than 15% dropout in the current study. We also considered specific factors regarding the control group in the current proposal that will help minimize the attrition rate. The control group will be actively engaged in psychoeducation tasks during video lectures and will complete homework (quizzes). Time spent with staff during research visits will also be matched between the experimental and control groups. We will explain to all subjects that their effort and compliance will play a major role in their success and potential benefit from the intervention. Therefore, we do not anticipate attrition problems related to subject motivation.

In our sample size calculations, we have accounted for a 15% dropout rate between visits. If we experience a higher rate, we will identify the challenges of study participation and determine new or additional ways to facilitate retention (e.g., adjust the start time of visits, offer meals during long visits).

In summary, we believe that the study design and logistics, as well as the resources for clinical research available at Yale will allow us to reach the recruitment and retention goals of the study within the proposed time frame.

5.3.3 Study Visits

Initial Phone Call Screening: 15 minutes

Obtain the following information and data:
- MRRC MRI safety questionnaire
- Medical history questionnaire

Screening via Zoom: 45 Minutes

Obtain the following information and data:
- Electronically signed informed consent
- Demographic data (age, sex, ethnicity, level of education, etc.)
- MoCA test
- PD Cognitive Functional Rating Scale

Online Surveys: self-paced, total of 30 min
- Geriatric Depression Scale
- Parkinson Anxiety Scale
- Starkstein Apathy scale
- PD Quality of Life Questionnaire-39
- Parkinson Fatigue Scale
- Scales for Outcomes in Parkinson's Disease – Sleep

There will be a total of 4 in-person visits:

Visit 1. Baseline Clinical Evaluation: 3 hours
Within two weeks after the initial screening visit.
Detailed clinical and cognitive evaluations including:
- MDS-UPDRS and Hoehn & Yahr
- Wechsler Test of Adult Reading
- RBANS test and executive function tests (Stroop, letter fluency (F-A-S), and Trail Making Test parts A and B)
- Neuro-QoL survey
- Structured cognitive interview for the PD-MI group
- Modified Six-Elements Test
- Structured cognitive interview for the experimental PD-MI group

Visit 2. Baseline Neuroimaging Experiments: 2 hours
Within two weeks after Visit 1.
- QMI Vividness of Imagery Scale
- Functional MRI scans during mental imagery tasks (x4) and video-watching tasks (x4)
- Instructions on respective training and homework assignments.

Training: Immediately after Visit 2. Mental imagery training and psychoeducation 3 times per week for 4 weeks. On non-training days during the week and in the subsequent 2-week block, subjects will complete homework.

Visit 3. 6-Week Post-Intervention Assessments: 3 hours. All subjects will return for repeat cognitive evaluations as in Visit 1, and mental imagery vividness rating and fMRI scans as in Visit 2.

Visit 4. 12-Week Post-Completion Assessments: 3 hours. All subjects will return for repeat cognitive evaluations and fMRI tasks. The same procedures as described in Visit 3 will be followed.

5.4 Statistical Method

5.4.1 Statistical Design

This is a phase 1 randomized clinical trial aiming to enroll 120 subjects with Parkinson's disease (PD) assigned in parallel to the experimental PD-MI (N=60) and active control PD-Con (N=60) groups. The units of observation are the subjects in these groups. Subjects will be enrolled continuously and randomized to two groups using the "minimization" method.[101] After truly randomly allocating the first 10 subjects, each subsequent subject will be allocated to either group considering the factors age, gender, and disease stage. This method will allow us to minimize the imbalance between the groups in terms of demographic and clinical characteristics while at the same time preserving the randomness of group allocation.

We will use independent-sample t-tests and nonparametric Mann-Whitney U tests to compare subjects characteristics between the PD-MI and PD-Con groups.

We will use mixed ANOVA tests with interaction terms to assess the short- and longer-term changes in cognitive and imaging outcomes before and after training.

Our overall statistical approach is designed to address the outcomes of four different aims:

AIM 1: To determine the effects of mental imagery training on goal-directed everyday cognitive functioning in PD

Primary outcome: Change in Neuro-QoL version 2 Cognitive Function scores.[97]

Manipulation check*:* Change in QMI Vividness of Imagery Scale scores.[100]

Neuro-QoL version 2 Cognitive Function scores (Visit 1) and QMI scores (Visit 2) obtained at baseline and immediately upon conclusion of the 6-week intervention (Visit 3) will be compared between the PD-MI and PD-Con groups using a 2x2 mixed ANOVA with an interaction term (dependent variables: test scores, between-subject factor: group, within-subject factor: time with two levels, i.e., baseline and post-training, interaction: group-by-time) ($p < 0.05$, two-tailed).

Secondary outcomes: Change in composite z-scores obtained from the executive function tests.

We will calculate a composite z-score from the executive function test scores (i.e., Stroop,[94] F-A-S letter fluency,[95,] and Trail Making A-B tests[96]) for all subjects.

Composite executive function test z-scores obtained at baseline (Visit 1) and immediately upon conclusion of the 6-week intervention (Visit 3) will be compared between the PD-MI and PD-Con groups using a 2x2 mixed ANOVA with an interaction term (dependent variables: test scores, between-subject factor: group, within-subject factor: time with two levels, i.e., baseline and post-training, interaction: group-by-time) ($p < 0.05$, two-tailed).

Exploratory outcomes: 1) Change in RBANS scores,[93] 2) and change in The Modified Six-Element Test scores.[98]

The RBANS and Modified Six-Element Test scores obtained at baseline (Visit 1) and immediately upon conclusion of the 6-week intervention (Visit 3) will be compared between the PD-MI and PD-Con groups using a 2x2 mixed ANOVA with an interaction term (dependent variables: test scores, between-subject factor: group, within-subject factor: time with two levels, i.e., baseline and post-training, interaction: group-by-time) ($p < 0.05$, two-tailed).

AIM 2: To determine the brain effects of mental imagery training in PD.

Primary outcome: Change in task-specific whole-brain pairwise functional connectivity.

We will generate group-level, task-specific, pairwise functional connectivity maps for the mental imagery and video-watching tasks using the CONN Toolbox.[53] These maps at baseline (Visit 2) and immediately upon conclusion of the 6-week intervention (Visit 3) will be compared between the PD-MI and PD-Con groups using a 2x2 mixed ANOVA with an interaction term (dependent variables: whole-brain pairwise functional connectivity maps, between-subject factor: group, within-subject factor: time with two levels, i.e., baseline and post-training,

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interaction: group-by-time). We will use the false discovery rate (FDR)-correction for multiple comparisons ($p < 0.05$, two-tailed).[102]

Secondary outcomes: Change in task-specific graph-based local and global network measures.

Based on the pairwise functional connectivity maps, we will compute the clustering coefficient and betweenness centrality representing local and global graph measures, respectively, using the CONN Toolbox.[53] These graph measures associated with the mental imagery and video-watching tasks performed at baseline (Visit 2) and immediately upon conclusion of the 6-week intervention (Visit 3) will be compared between the PD-MI and PD-Con groups using a 2x2 mixed ANOVA with an interaction term (dependent variables: graph measures, between-subject factor: group, within-subject factor: time with two levels, i.e., baseline and post-training, interaction: group-by-time). We will use the FDR-correction for multiple comparisons ($p < 0.05$, two-tailed).[102]

Behavioral scanning data: We will add up the number of key elements of the recorded mental imagery descriptions for each scan (e.g., entities, sensory descriptions, spatial/temporal references, thoughts, actions, emotions, task components) and average them across scans to obtain an average imagery content score per subject. We will also average the number of correct answers to content-related questions after video-watching scans to obtain an average accuracy score per subject. The average mental imagery content and video-watching accuracy scores performed at baseline (Visit 2) and immediately upon conclusion of the 6-week intervention (Visit 3) will be compared between the two groups using a 2x2 mixed ANOVA with an interaction term (dependent variables: average scores, between-subject factor: group, within-subject factor: time with two levels, i.e., baseline and post-training, interaction: group-by-time) ($p < 0.05$, two-tailed).

AIM 3: To determine whether the cognitive and brain effects of mental imagery training in PD are sustained

The primary, secondary and exploratory outcomes as outlined in Aims 1 and 2 will also apply to Aim 3. All cognitive and functional MRI tasks will be repeated 12 weeks after the completion of the training program (Visit 4). These results will then be compared with those obtained at baseline and 6-week post-intervention using a 3x2 mixed ANOVA with an interaction term (dependent variables: cognitive test scores and functional connectivity and graph measures, between-subject factor: group, within-subject factor: time with three levels, i.e., baseline, 6-weeks post-intervention, and 12-weeks post-completion, interaction: group-by-time) ($p < 0.05$, two-tailed). A significant interaction will be followed by post hoc simple effects tests to determine the level(s) of interaction.

AIM 4: To explore the brain-cognition link associated with mental imagery training in PD

Exploratory Aim: We will examine the post-training brain-cognition relationship at the 6-week and 12-week timepoints in each group. We will test whether the post-training changes in task-specific whole-brain pairwise functional connectivity and graph measurements will predict the post-training differences in the Neuro-QoL Cognitive Function and composite executive test scores in each group.

Exploratory outcomes: This brain-behavior relationship at 6 weeks will be the exploratory outcome of Aim 2 and that at 12 weeks will be the exploratory outcome of Aim 3.

5.4.2 Sample Size Considerations

We calculated the sample size based on the primary cognitive outcome, i.e., Neuro-QoL version 2 Cognitive Function scores. The Neuro-QoL Cognitive Function validation study with 120 PD patients who had mild disease (Hoehn & Yahr stage 2) showed mean ± SD = 50.46 ±

7.25.[97] A change of 2-6 T-scores have been considered a minimally important change in patient-reported outcome measures.[103]

We estimated the sample size based on the assumption that there will be an average of 4 T-score improvement after mental imagery training using the G*Power 3.1 software[104,105] The repeated-measures ANOVA between-subject factor model with two groups and two measurements, with an effect size of f=0.266 (corresponding to a moderate effect size d=0.53), alpha 0.05, and power 0.80 yielded a total sample size of 86 (43 in each group). With an estimated 15% drop out (86/0.85 ≈ 101) during the 6-week intervention period and another 15% drop out (101/0.85 ≈ 120) in the subsequent 12-week period, we plan to recruit 120 subjects in total.

In our previous work with PD patients using motor (N=22) and visual (N=22) imagery training, we showed robust task-specific pairwise functional connectivity changes post-training especially in the respective motor and visual networks.[4] Therefore, we think this sample size will also be adequate for the primary imaging outcome.

5.4.3 Planned Analyses

Analysis of executive function and performance-based tests

We will obtain a composite executive function score by averaging the z-transformed individual scores on the Stroop, letter fluency (F-A-S), and Trail Making A-B tests.[94-96] A total score will be calculated for the RBANS. We will calculate the Modified Six-Element Test score as the number of subtasks attempted minus the number of violations of the task switching rules.[98]

Analysis of behavioral data during scanning

We will adopt the qualitative analysis approach used in our previous study.[4] We will add up the number of key elements of the recorded mental imagery descriptions for each scan (e.g., entities, sensory descriptions, spatial/temporal references, thoughts, actions, emotions, task components) and average them across scans to obtain an average imagery content score per subject. We will also average the number of correct answers to content-related questions after video-watching scans to obtain an average accuracy score per subject. These scores will then be used in statistical analyses.

Preprocessing of fMRI data

We will use the CONN toolbox for all fMRI data analysis steps.[53] 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, linear detrending, and high-pass filtering (0.008 < f < Inf).

Pairwise functional connectivity analysis

To compare the task-specific whole-brain functional connectivity changes between the groups, we will perform pairwise functional connectivity analyses using the generalized psychophysiological interaction (gPPI) model. We will first convolve the 3-min task blocks in each mental imagery and video-watching run with the canonical hemodynamic response function. We will use the functionally defined cortical and subcortical nodes (N=268) of the whole-brain Shen atlas.[52] For each subject, we will extract the average blood oxygenation level-dependent signal time courses calculated via the gPPI model from these nodes and correlate them with each other using Pearson correlations. The r values will correspond to the functional connectivity strength between node pairs. We will Fisher z-transform the r values and obtain group-level functional connectivity maps for statistical analyses.

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Graph analysis

To compare the task-specific changes in local and global network properties between the groups, we will perform graph analyses on the pairwise functional connectivity data. Specifically, we will compute the 1) clustering coefficient, which shows the connectivity strength between neighboring nodes and is a measure of local network efficiency, and 2) betweenness centrality, which shows how well-connected a particular node is with all other nodes and is a measure of that node's potential as an integrative hub.[106] These graph measures will then be used in statistical analyses.

Sex as a biological variable

Sex differences in normal cognitive aging have been reported.[107] Reports on sex differences in PD-related cognitive decline have been variable. Sex differences in cognition in de novo PD patients have been found to be similar to those in normal aging.[108] On the other hand, male sex was found to be associated with PD-MCI,[109] and poorer performance in male vs female PD patients in executive functioning and processing speed have been demonstrated.[110] In our study, both groups will be sex-matched and we will use sex as a covariate in separate analytical models to examine the potential sex-related differences in training response.

5.4.4 Analysis of Subject Characteristics

We will perform independent-sample t-tests to compare the normally distributed continuous baseline data (e.g., MoCA, MDS-UPDRS) and nonparametric Mann-Whitney U tests to compare the discrete baseline data (e.g., symptom onset side, Hoehn & Yahr score) and non-normally distributed continuous data between the PD-MI and PD-Con groups ($p < 0.05$, two-tailed) using the statistical software package SPSS (IBM SPSS Statistics version 28). If the nonmotor survey data (e.g., mood, fatigue) differ significantly between the groups, we will use them as covariates in the mixed ANOVA tests explained above.

5.4.5 Interim Analysis

N/A

5.4.6 Handling of Missing Data

We assume that the missing data will be missing at random. If the proportion of missing data is not more than 5%, we will ignore the missing data and perform complete case analyses. Otherwise, we will use multiple imputation to replace the missing data at follow-up for the primary cognitive outcome. Regardless of the proportion of missing data, we will constrain the voxelwise imaging analyses to complete cases because to our knowledge, there is no validated method to correct for missing data in such analyses.

6 Trial Administration

6.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

Possible Deception

There is no possibility for deception.

Payment

Subjects will be compensated for their participation and for travel expenses (e.g., parking, cab ride). The in-person visits are lengthy and training sessions require daily time commitment. Therefore, we think it is important to reimburse subjects for their time.

Each in-person visit $100 (x4)
Each completed training week $50 (x4)
Total for parking $50

Discovery of Previous Unknown Conditions

If a worrisome finding is seen on the subjects imaging scan, a radiologist or another physician will be asked to review the relevant images. Based on his or her recommendation (if any), the principal investigator or consulting physician will contact the subject, inform the subject of the finding, and recommend that they seek medical advice as a precautionary measure.

Permanent Medical Records

No information will be added to the subject's permanent medical records.

Consent

Consent forms will be Yale IRB-approved and the participant will be asked to read and review the document. A member of the research team authorized to obtain consent will explain the research study to the participant and answer any questions that may arise. This conversation will take place in a private environment via Zoom.

Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates, or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records.

The purpose, research procedures, any risk that these procedures might entail, and any possible benefits will be discussed in detail in language appropriate for the individual's level of understanding. Subjects will be encouraged to ask questions and given enough time to discuss any aspect of the study with the research team. Subsequently, they will have to demonstrate understanding of the study procedures and what is expected of them. Once subjects understand the study, they will be asked if they wish to participate. If they do, they will be asked to electronically sign the consent form at the Zoom video-call screening visit.

Evaluation of Subject's Capacity to Provide Consent

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, they 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.

Subject Coercion

The voluntary nature of the study will be stressed and reiterated throughout conversations with potential participant during the consent process. It will be made clear that the individual's refusal to participate will in no way affect the care which they are entitled to.

Sensitive Data and Privacy

Hard copies of HIPAA identifiers, consent forms, clinical screening information, and MRI screening form will be kept in a locked filing cabinet.

Study data 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 principal investigator, Dr. Tinaz, will have access to the centrally and electronically stored and password-protected subject identification list to decode data files.

De-identified data will be stored on username- and password-protected servers provided by the Yale University and managed by the Yale IT Department.

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 electronic databases will stay on the password-protected research computers 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.

6.2 Institutional Review Board (IRB) Review

This will be a phase 1 randomized clinical trial.

Modifications and Updates

The protocol will be submitted to the IRB for review and approval. No research activity will commence until IRB approval received. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

A study closure report will be submitted to the IRB after all research activities have been completed.

Unanticipated Problems

Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, they will be reported in accordance with federal and Yale University IRB rules.

Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or UPIRSOs that may require a temporary or permanent interruption of study activities will be reported immediately, followed by a written report within 5 calendar days of Dr. Tinaz becoming aware of the event to the IRB and any appropriate funding and regulatory agencies (using the UPIRSO Reporting Form 710 FR 4). Serious or unexpected adverse events that are not life-threatening will also be reported immediately followed by a written report within 5 calendar days of Dr. Tinaz becoming aware of the event to the IRB and any appropriate funding and regulatory agencies. Expected or non-serious adverse events will be reported at the time of continuing review. For each adverse event, Dr. Tinaz will record the onset, end, intensity, required treatment, outcome, seriousness, and action taken.

Dr. Tinaz will apprise study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings.

6.3 Subject Confidentiality

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict

confidence. No information concerning the study or the data will be released to any unauthorized third party.

All research activities will be conducted in as private a setting as possible.

The representatives of the Yale IRB or regulatory agencies may inspect all documents and records required to be maintained by the investigator.

The study participant's contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the Yale IRB and Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored on username- and password-protected servers provided by the Yale University and managed by the Yale IT Department in Dr. Tinaz's lab. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in Dr. Tinaz's lab.

Access

Only the principal investigator, Dr. Tinaz, will have access to the centrally and electronically stored and password-protected subject identification list to decode data files. Principal investigator and research staff will have access to study data to perform statistical analyses and to monitor fidelity of the data.

Recorded Identifiers

The following information for research will be collected and recorded for each subject:

- HIPAA identifiers: Name, date of birth, sex, phone, email, postal address. Postal address will be used to mail the debit card in a nondescript envelope to subjects for study payments.
- Clinical screening information: Handedness; any history or current condition of alcohol/substance use, neurological or psychiatric disorders 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; and history of head injury with loss of consciousness.
- The Yale MRRC MRI Safety Questionnaire will be used for MRI screening.

Storage and Security

Risk for potential breach of confidentiality will be minimized by the use of non-identifying labeling and the secure storage of electronic and paper files. All team members will use encrypted research computers.

Hard copies of HIPAA identifiers, consent forms, clinical screening information, and MRI screening form will be kept in a locked filing cabinet in Dr. Tinaz's lab.

De-identified paper records will be kept in binders in Dr. Tinaz's lab.

Data on paper records will also be entered in electronic databases and stored on secure Yale servers (Yale REDCap).

Imaging data will be transferred securely to workstations for analysis and stored on HIPAA-compliant secure central storage servers ("Storage@Yale") provided by the Yale IT Department for a monthly fee.

6.4 Deviations/Unanticipated Problems

This study is considered to pose not more than minimal risk. There will not be a DSMB.

The principal investigator, Dr. Tinaz, will identify and report deviations within 5 working days of identification of the protocol deviation. All deviations will be addressed in study source documents and the Yale IRB per their policies.

The principal investigator will report unanticipated problems involving risks to participants or others including any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The principal investigator will report unanticipated problems (UPs) to the Yale IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported immediately, followed by a written report within 5 calendar days of Dr. Tinaz becoming aware of the event to the IRB.
- Any other UPs that are not life-threatening will also be reported immediately followed by a written report within 5 calendar days of Dr. Tinaz becoming aware of the event to the IRB in accordance with policy 710.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 5 business days of the IRB's receipt of the report of the problem from the investigator.

Inclusion or exclusion criteria may have to be modified or added safety monitoring practices may have to be put in place to mitigate risk newly identified by a UPIRSO. Newly identified risks will be outlined in the informed consent if changes do not completely address the problem. Past participants will also be informed of newly identified risks if applicable. If needed, trial enrollment will be suspended until safety measures and/or criteria modification can be implemented to address the risk.

IRB and all investigators will immediately be notified about risk newly identified by a UPIRSO. During the conduct of the study, there will be ongoing review and surveillance by the principal investigator, Dr. Tinaz, and other study investigators. Any protocol deviation and/or adverse event will be formally written up by and submitted to the IRB by Dr. Tinaz. Protocol deviations and actions to limit future deviations will be arbitrated by IRB with the help of study investigators. Written report of UPIRSO will include protocol title, number, PI name, and IRB project number. A detailed description of the event or outcome will be relayed as well as an explanation of the basis for determining that the event represents an UP. Finally, any changes to the protocol or addition of safety measures will be described to the IRB.

6.5 Data Quality Assurance

The trial will be registered in clinicaltrials.gov within one of week of the start of enrollment. Dr. Tinaz has built the infrastructure for this study in her lab and will further implement and maintain quality assurance and quality control system with written standard operating procedures to ensure that the trial is conducted and data are generated, recorded, and reported in compliance with the protocol, good clinical practice, and applicable regulatory requirements. Dr. Tinaz will review the data in the databases for evidence of data entry errors and omissions.

6.6 Study Records

The documents that will be considered study records are:

Recruitment

- Recruitment flyers

Health and Safety Records

- Demographic Data
- Clinical screening information
- The Yale MRRC MRI Safety Questionnaire

Clinical and Cognitive Evaluation Records

- Case reports forms
- MDS-UPDRS and Hoehn & Yahr
- MoCA test
- PD Cognitive Function Rating Scale
- Neuro-QoL
- QMI mental imagery vividness scale
- Modified Six-Elements
- Executive Function tests (i.e., Stroop, F-A-S letter fluency, and Trail Making A-B test)
- RBANS test
- Structured cognitive interview forms

Online Surveys

- Geriatric Depression Form
- Parkinson Anxiety Scale
- Starkstein Apathy scale
- PD Quality of Life Questionnaire-39
- Parkinson Fatigue Scale
- Scales for Outcomes in Parkinson’s Disease – Sleep

Online Homework

- Mental imagery practice logs
- Responses to psychoeducation quizzes

Imaging Data

- Structural and functional MRI Data

Other

- Consent form

6.7 Access to Source

Source data will be maintained per Medical Records policy in a password protected, secure, Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based electronic database with a built-in audit trail.

Only Institutional Review Board (IRB) approved research team members who have current HIPAA and Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) and human subjects protection training will be authorized to access records.

For detailed description of source documents, data recording, and data storage, please see section 5.1.1.

The data will be collected specifically for this project. The information obtained in this study will be recorded in such a manner that the identity of the human subjects cannot be ascertained directly. The data 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 principal investigator, Sule Tinaz, will have access to the centrally and electronically stored and password-protected subject identification list to decode data files. All other study investigators will have access to the de-identified data. All study investigators will use encrypted research computers.

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. Anonymous data will be made accessible to other researchers on free web-based platforms such as the Neuroimaging Data Repository of the Neuroimaging Tools & Resources Collaboratory (NITRC) (www.nitrc.org).

6.8 Data or Specimen Storage/Security

For detailed description of data recording and storage, please see section 5.1.1.

6.9 Retention of Records

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 electronic databases will stay on the password-protected research computers 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.

If permission is needed to move or destroy the records, Dr. Tinaz will need to be contacted.

6.10 Study Monitoring

This study presents minimal. There will be no DSMB. The study will be monitored by the internal team:

- Principal Investigator: Dr. Sule Tinaz
- Co-Investigators: Dr. Ana Vives-Rodriguez and Dr. Emily Sharp
- Research Assistant: Jared Cherry

We will hold biweekly team meetings to discuss research progress and address potential issues. Dr. Tinaz will be responsible for oversight of the study, immediate reporting of any protocol deviations, and the reporting of unanticipated problems or adverse events.

6.11 Study Modification

Any modifications to the study will be discussed with all investigators. Amendments will be submitted to the IRB to allow for any protocol modifications. No protocol modifications will take place until approval from the IRB is received.

6.12 Study Completion

We estimate it will take 6 years to complete the study. IRB will be notified through continuing reviews and finally with study closure documents.

6.13 Funding Source

The study will be funded through Dr. Tinaz's NINDS 1R56NS129540-01A1 grant.
Salary support for Dr. Tinaz for this study is provided by the NINDS 1R561NS129540-01A1 grant.

6.14 Conflict of Interest Policy

The research which will be done as part of this protocol is investigator initiated and free from influence from any pharmaceutical or private company. None of the investigators has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution). Any conflicts of interest which may arise as part of this research will be presented to Yale IRB and the conflict will be reviewed by the appropriate committee at Yale University.

6.15 Publication Plan

Abstracts will be submitted to the Movement Disorders Society, American Academy of Neurology, Organization Human Brain Mapping or other relevant subspecialty meetings as appropriate.

Manuscripts will be written and submitted to scientific journals at the intersection between neuroimaging and Parkinson's disease such as Movement Disorders and NeuroImage.

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List of Tables

1. Table 1. Study Timeline
2. Table 2. Planned Enrollment

List of Attachments

1. Case report form
2. Demographic and medical screening form
3. MRI Safety Questionnaire
4. Structured cognitive interview
5. Study Flyer
6. Scales for Outcomes in Parkinson's Disease – Sleep
7. Geriatric Depression Scale
8. Movement Disorder Society- Unified Parkinson's Disease Rating Scale (includes Hoehn and Yahr)
9. Montreal Cognitive Assessment
10. Neuro-Quality of Life Version 2- Cognitive Functions
11. Parkinson's Disease Fatigue Scale
12. Parkinson's Disease Cognitive Functional Rating Scale
13. Parkinson's Disease Questionnaire-39
14. Questionnaire Upon Mental Imagery Vividness of Imagery Scale
15. Parkinson Anxiety Scale
16. Starkstein Apathy Scale

Please note we are not attaching copyright protected testing material.

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