Protocol Title:

Effects of Exercise on Glymphatic Functioning and Neurobehavioral Correlates in Parkinson's Disease

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Effects of Exercise on Glymphatic Functioning and Neurobehavioral Correlates in Parkinson's Disease

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Effects of Exercise on Glymphatic Functioning and Neurobehavioral Correlates in Parkinson's Disease

Study Description: This study will assess patients with a clinical diagnosis of Parkinson's disease (PD) over prior and following participation in a 12-week community-based exercise program, assessing neuroimaging (beta-amyloid deposition, glymphatic flow), and clinical severity (motor, cognitive, sleep disturbance, mood).

Objectives:

Primary Objective:
Evaluate the glymphatic functioning and beta-amyloid burden response to 12 weeks of a community-based exercise course in PD patients.

Secondary Objectives:
Quantify the association between glymphatic functioning, beta-amyloid burden, and neurobehavioral dysfunction in PD.
Evaluate the degree to which neuroimaging-based response to exercise mediates clinical improvement in PD.

Tertiary Objectives:
Evaluate whether the association between glymphatic functioning, beta-amyloid burden, and neurobehavioral dysfunction in PD differs between cognitively healthy and cognitively impaired PD phenotypes.
Evaluate whether the neuroimaging and clinical response to exercise differs between cognitively healthy and cognitively impaired PD phenotypes.

Quaternary Objectives:
Develop a normative reference group for the Brief Estimate of Seconds Test (BEST) to facilitate PD score interpretation and establish how PD-related neurodegeneration affects time perception. In addition, determine how BEST scores correlate with disease severity, neuroanatomical ROIs, and neuropsychometric cognitive data collected in the previous objectives.

Endpoints:

Primary Endpoints:
Glymphatic flow (DTI-ALPS score)
PET/CT (cortical:cerebellar SUVr ratio)

Secondary Endpoints (also used for Tertiary Endpoints):
Unified Parkinson's Disease Rating Scale III (UPDRS-3)
Actigraphy
Mini-BEST-est
Freezing Gait Questionnaire
6-minute Walk Tesdt
Hopkins Verbal Learning Test-Revised (HVLT)
Trail Making Test – A & B (TMT)
Stroop Test (Stroop)

	Letter Fluency (FAS) Simon Task (Simon) PROMIS – Sleep Disturbance short forms (PROMIS-Sleep) Hospital Anxiety and Depression Scale (HADS) <u>Tertiary Endpoints:</u> Clinical Dementia Rating Scale (CDR) Brief Estimate of Seconds Test (BEST) <u>Quaternary Endpoints:</u> Brief Estimate of Seconds Test (BEST)
Study Population:	PD cohort: Patients with a clinical diagnosis of Parkinson's, as defined by neurologic examination, from ages 55-80, with and without mild cognitive impairment (MCI) Healthy cohort: healthy adults (ages 18-90) without neurological or psychiatric/developmental pathology.
Phase:	Observational
Description of Sites:	Vanderbilt University Medical Center
Description of Study Activities:	PD cohort: MRI Brain scan, PET/CT Brain scan, Neurological and Neuropsychological exams, continuous Actigraphy, 12-week community-based exercise program Healthy cohort: Neuropsychological exam
Study Duration:	PD cohort: 36 months Healthy cohort: 24 months
Participant Duration:	PD cohort: 3 months Healthy cohort: 1 day
Medical Monitor:	Katherine McDonell, MD, will act as the independent medical/research monitor overseeing this study. The research monitor may perform functions such as observing enrollment procedures for individuals, groups, or units; overseeing study interventions; overseeing data matching, data collection, and analysis. The research monitor shall have authority to stop a research protocol in progress, remove human subjects from the research protocol if necessary, and protect the safety of human subjects until the IRB assesses the monitor's report, and shall have the responsibility to promptly report their observations and findings to the IRB or other designated official and the HRPO.

1.2 SCHEMA: PD COHORT

Week 0, Day 0 Screening

- Obtain informed consent
- Obtain history, screen potential participants by inclusion and exclusion criteria

Week 1, Day 1-7 Baseline

- MRI brain scan
- PET brain scan
- Neurological & Neuropsychological exam

Week 2-13, Day 8-91 Interval

- Baseline PT assessment
- Twice-weekly participation in community-based exercise program
- Continuous actigraphy & Neurametrix
- Follow-up PT assessment

Week 14, Day 92-99 End of Study Assessments

- MRI brain scan
- PET brain scan
- Neurological exam, neuropsychological exam, document

Schedule of Activities (SoA) – Assessment Only

Procedures	Screening Day - 0	Baseline (VUMC) Day 1-7	Baseline (RSB; first day)	Interval / Exercise Day 8-91	Follow-up (RSB; last day)	Follow-up (VUMC) Day 92-99
Informed consent	x					
Demographics / Medical history / Exclusion & Inclusion	x					
Vital Signs/orthostatic blood pressure/ weight		x				
Blood sample		x				x
Neurologic exam		x				x
UPDRS-3	X (on-med)	X (off-med				x
Neuropsychological exam (all cognitive measures)		x				x
Questionnaires (sleep, mood)		x				x
Actigraphy		x----------x				
MRI Brain		x				x
PET/CT Brain		x				x
Physical status assessment (Mini-BESTest, Freezing Gait Questionaire, 6-minute Walk Test)			x		x	

VUMC = Vanderbilt University Medical Center site
RSB = Rock Steady Boxing site

The Healthy cohort will complete only a single visit, for 10 minutes, in which they will complete the informed consent and the BEST, as well as asked about demographics, medical history, and exclusion/inclusion criteria.

2 STUDY DESIGN

2.1 OVERALL DESIGN

For the PD cohort, participants will be recruited from Vanderbilt University Medical Center Neurology's Behavioral and Cognitive and Movement Disorder Clinics by Drs. Claassen and Considine. We will prospectively enroll participants with idiopathic Parkinson's disease (n=50; age range=55-80 years), equally distributed and matched for age and sex between groups with (n=25) and without (n=25) mild

cognitive impairment. These populations provide a cohort to evaluate the potential relationship between glymphatic flow and beta-amyloid burden, given the elevated risk of beta-amyloid accumulation associated with PD and MCI conditions. Patients will have medical and motor presentation indicated for the community-based exercise program. Those patients with clinically-defined MCI, will be without evidence of vascular cognitive impairment, primary mood disorder, or comorbid medical condition that could contribute to cognitive symptoms (e.g. pulmonary, hematologic, metabolic, or vitamin deficiency). Potential participants will undergo a neurological and neuropsychological examination (including cognitive exam and behavioral/symptom questionnaires) to characterize their medical and neurobehavioral status. They will then undergo baseline neuroimaging protocols, both MRI brain scan (DTI-ALPS) and PET/CT (C11PiB) brain scan. Actigraph will be attached to the patient to continuously monitor motor activity. A background monitor of typing cadence will be activated on their computer to monitor for changes in fine motor control. The cohort will complete the same clinical and neuroimaging assessments after they participate in a 12-week community-based exercise intervention. Specifics about assessments and the exercise program are as follows.

For the healthy cohort, participants will be recruited from the general population and a database of individuals who have elected to be contacted about future research or for this study through a contact form. They will be adults between the ages of 18 and 90 without neurological or psychiatric pathology (N = 75). Under the supervision of the clinical coordinator, the participants will be asked to complete the Brief Estimate of Seconds Task (BEST) in person or via Microsoft Teams. These data will aid in the creation of a normative reference group for the BEST, dependent on sex and age. Using data collected in both the PD and healthy cohorts, we will perform subsequent analyses to determine the relationship between PD BEST scores and clinical disease severity (UPDRS), neuroanatomical ROIs, and standard neuropsychometric cognitive measures. These findings will elucidate the origins and extent of time perception changes in PD

2.2 STUDY DESIGN SPECIFICS

Clinical Assessments

PD cohort

All potential participants will undergo neurological and neuropsychological examination to determine eligibility, categorize MCI status, and provide quantification of neurocognitive functioning and neuropsychiatric symptomatology.

Screening data (see inclusion/exclusion criteria) from eligible enrollees will be also used as part of clinical baseline assessment.

Neurological examination will include the Unified Parkinson's Disease Rating Scale III (UPDRS-III)[56] and the Clinical Dementia Rating (CDR)[57] scale. Vitals and a blood sample (10mL) will be collected as part of this examination. Medical history will include an inquiry as to whether the participant is actively dieting.

The neuropsychological examination protocol will consist of a memory measure (i.e., the Hopkins Verbal Learning Test – Revised [HVLT-R][58], consisting of Learning, Recall, and Recognition subcomponents), executive functioning measures (i.e., Trail Making Test – A & B[59], Verbal Fluency [FAS][60], Stroop[61]), and exploratory measures of cognitive-performance thought potentially sensitive to PD-related pathology (Brief Estimate of Seconds Test [BEST][62], Simon Task[63]). To evaluate sleep disturbance symptomatology,

PROMIS – Sleep Disturbance (SD) and Sleep-related Impairment (SRI) short forms will be administered[64]. To evaluate mood symptomatology, the Hospital Anxiety and Depression Scale (HADS)[65] will be administered.

Physical assessment is routinely completed at the first and last visit of the community-based exercise program, including rating/timing of ability to complete simple posture and gait tasks, as well as self-reported difficulty with gait initiation. UPDRS-III will also be administered at screening (on-drug), baseline assessment (off-drug), and follow-up assessment (off-drug) Additionally, between enrollment and competition, the patients will wear an actigraph to continuously measure motor activity.

Healthy cohort:
All participants will be administered the Brief Estimate of Seconds Test (BEST) in person or via Microsoft Teams.

Imaging

PD cohort
MRI. Participants will begin with MRI in the morning after their 16-hour dopaminergic washout the night/evening prior. Self-reported total sleep time the night prior will be recorded. They will be free to re-initiate therapy after MRI is complete. The following imaging and angiography sequences will be completed. We will apply our previously-reported 3T methods (16-channel neurovascular coil) with the below 50 min protocol:

- Anatomical imaging. T_1-weighted (MPRAGE; spatial resolution=1.0x1.0x1.0mm^3; 3D turbo-gradient-echo; TR/TE=8.2/3.7ms), and T_2-weighted (FLAIR; spatial resolution=0.9x1.1x3.0mm^3; turbo-inversion-recovery; TR/TI/TE=11000/2800/120ms) imaging, and intracranial (spatial resolution = 0.5x0.8x1.4mm^3; 3D gradient echo; TR/TE=23/3.5ms) and extracranial (spatial resolution=0.9x0.9x3.0mm^3; 2D gradient echo; TR/TE=18.6/3.2ms) time-of-flight (TOF) MR angiography (MRA).
- Microvascular hemodynamic compliance. A single-shot gradient echo echo-planar-imaging (EPI) scan (TE=30 ms), multiband-factor=3, isotropic spatial resolution=2 mm, SENSE-factor=2.5, and TR=1s will be acquired with whole-brain coverage. The scan will utilize a hypercapnic normoxic (5% CO_2 / 21% O_2 / 74% N_2) stimulus. The stimulus will be administered through a tight-fitting non-rebreathing oxygen facemask from compressed gas cylinders (flow rate=12 L/min) with the following paradigm: 180s normocapnic normoxia / 90s hypercapnia repeated once, followed by 180s normocapnic normoxia. Heart and respiration rate, $EtCO_2$, and FiO_2 will be recorded.
- CSF flow. 2D-Qflow measurements will be performed in the cerebral aqueduct (Fig. 7). V_{enc}=12 cm/s, spatial resolution = 0.5x0.5x4 mm^3, field-of-view = 200x200x4 mm^3, and 30 frames per heart cycle. Scan durations vary with heart rate, but are generally 2-4 min. Reproducibility has been determined by repeating the flow measurements in six subjects (Fig. 7). Background correction will be performed with a method previously developed for quantification of blood flow velocity in small perforating arteries[4].
- Lymphangiography for lymph vessel visualization. 3D turbo-spin-echo with variable refocusing angle sweep=40-110°, driven equilibrium module, dynamic DANTE flip angle sweep=0–8°, TE=600/TR=2500ms, slices=80, spatial resolution=1x1x1mm^3. We have shown that this method provides sensitivity to long T_2 slow flow species, such as lymph, and we have evaluated this method for sensitivity to lateralizing lymphedema and MLD therapy[26] (Figs. 3,4).

- Susceptibility weighted imaging (SWI) for identification of medullary veins. Whole-brain 3D turbo-gradient-echo (TR/TE_1/ΔTE=31/7.2/6.2 ms; flip angle=17°) with spatial resolution=0.6x0.6x2 mm^3 (slices=130) will be acquired with the same slice angulation as DTI.
- Diffusion tensor imaging (DTI) for perivascular flow determination. Whole-brain 2D spin echo EPI (TR/TE=10000/60 ms) in 32 directions (2 mm isotropic spatial resolution) using sequential acquisitions with b=0 s/mm^2, b=1000 s/mm^2, and b=2000 s/mm^2.
- Spin labeling for cervical LN perfusion. Spin labeling will be performed with an 11-ms hypersecant inversion (labeling) prepulse, followed by an inversion time range of 300 to 2400 ms in 300 ms increments, which will enable blood transit time and perfusion quantification. Other parameters: labeling=STAR; TE=11 ms; spatial resolution=2x2x2 mm3; averages=14.

PET/CT. A single administration of approximately one-time intravenous administration of 555 MBq (15 ± 1.5 mCi) C11PiB, then a 70-minute dynamic PET/CT acquisition (4 x 15, 8 x 30, 9 x 60, 2 x 180, 10 x 300 second frames frames) will be performed. Images will be reconstructed using an ordered subset Estimate algorithm (4 iterations, 16 subsets, with a post-reconstruction Gaussian filter of 5 mm), and corrected for scatter and attenuation. Images will be co-registered to the high spatial resolution T_1-weighted image as we have performed previously and a mean cortical:cerebellar SUVr will be calculated as the primary parameter of interest. For exploratory evaluation, we will also record SUVr in bi-temporal, bi-occipital, bi-frontal, and bi-parietal lobes.

Exercise

PD cohort

Patients will undergo an initial evaluation with Colleen Bridges, the Rock Steady Boxing instructor. Each class consists of 60 minutes of intense aerobic exercise. Of note, this class is specifically designed for patients with gait, balance, and motor symptoms common to Parkinson's disease. Individuals with symptoms that preclude safe participation are screened out as part of the program's routine initial evaluation. All components of the class are non-contact, and strictly aerobic in nature. They will receive 20 class credits (over two installments), as the program recommends attempting to attend roughly twice per week. As this is an observational study, participants will not be excluded based on their attendance, though this variable will be monitored to aid in analyses and interpretation. As noted above, a final physical evaluation will also be conducted on their last class.

Follow-up

PD cohort

Clinical and neuroimaging assessments will be conducted within 1 week of completion of the exercise program.

2.3 END OF STUDY DEFINITION

PD cohort

A participant is considered to have completed the study if he or she has completed both baseline and follow-up assessment phases of the study, as well as attended at least 1 of the community-based exercise classes.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

Healthy cohort
A participant is considered to have completed the study if they have completed the BEST.

3 STUDY DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

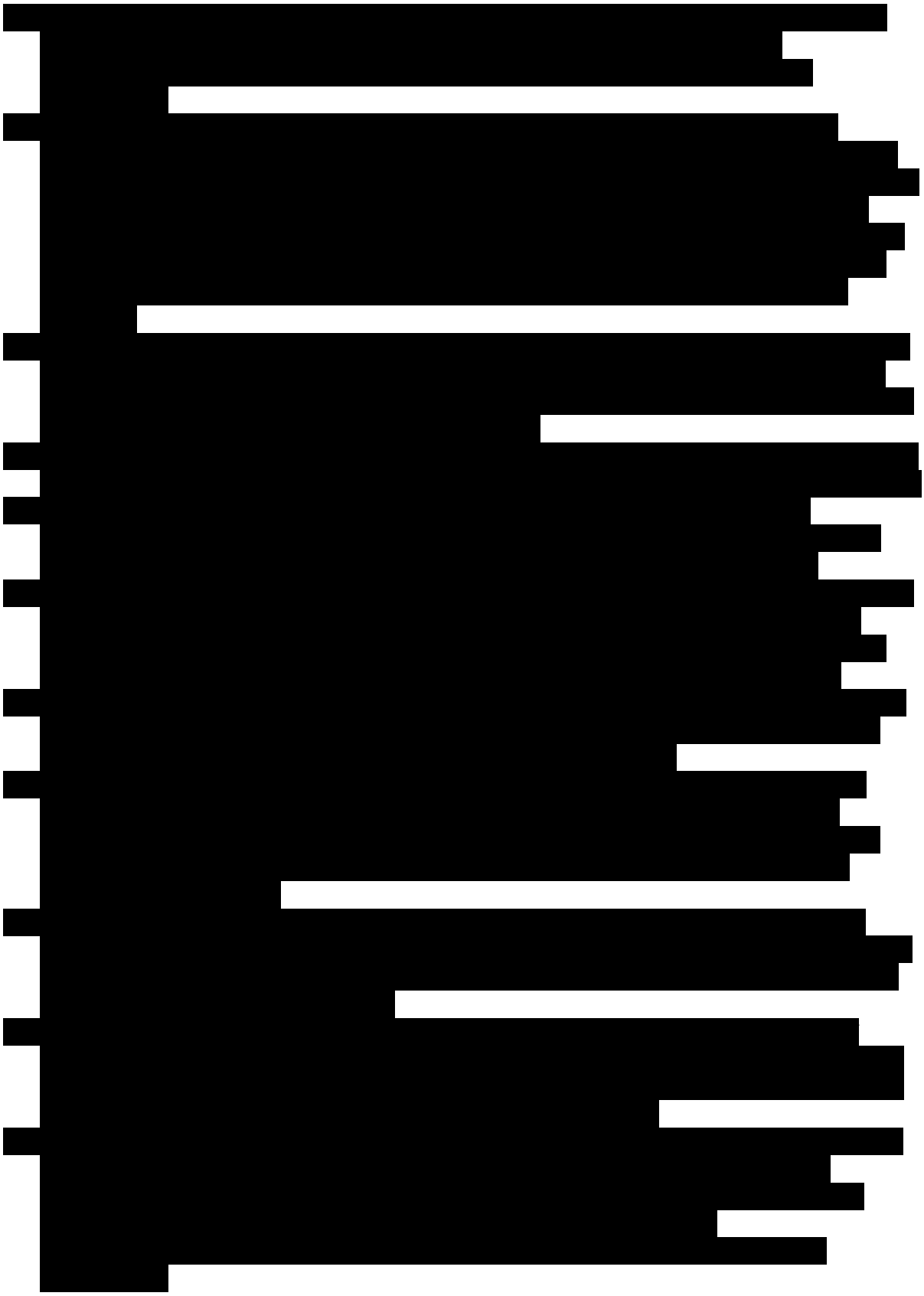
3.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

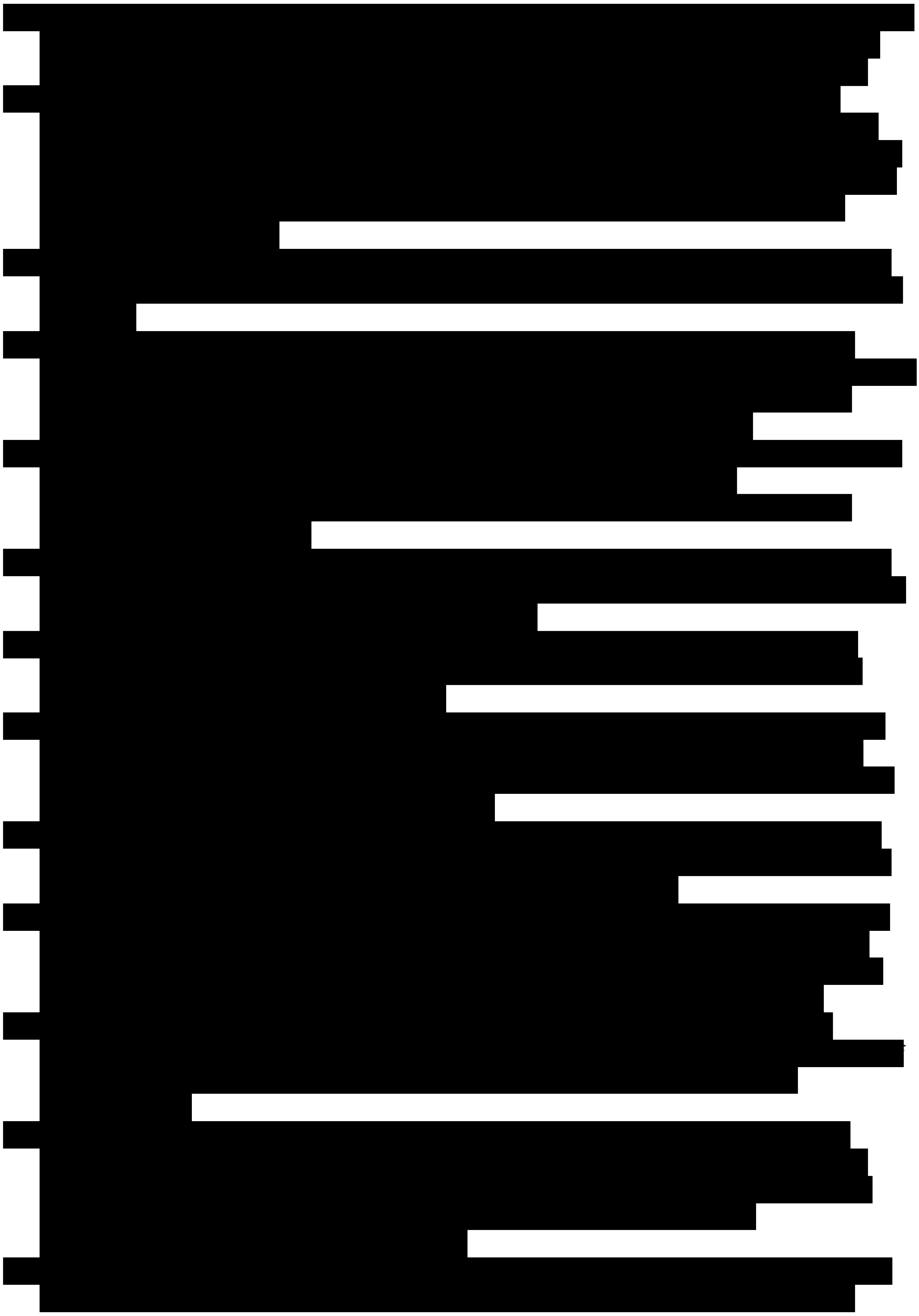
Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance or lost to follow-up
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to complete follow-up assessments.

The reason for participant discontinuation or withdrawal from the study will be recorded.

4 REFERENCES (TOTAL CITATIONS; NONRELEVANT BLACKED OUT)





56. Fahn, S., & Elton, R. L. (1987). UPDRS program members. Unified Parkinson's disease rating scale. *Recent Developments in Parkinson's Disease, 2*, 153-163.
57. Hughes, C. P., Berg, L., Danziger, W., Coben, L. A., & Martin, R. L. (1982). A new clinical scale for the staging of dementia. *The British Journal of Psychiatry, 140*(6), 566-572.
58. Shapiro AM, Benedict RH, Schretlen D, Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. Clin Neuropsychol. 1999;13(3):348-58. doi: 10.1076/clin.13.3.348.1749. PubMed PMID: 10726605.
59. Reitan RM. The relation of the trail making test to organic brain damage. J Consult Psychol. 1955;19(5):393-4. PubMed PMID: 13263471.
60. Tombaugh TN, Kozak J, Rees L. Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. Arch Clin Neuropsychol. 1999;14(2):167-77. PubMed PMID: 14590600.
61. Troyer AK, Leach L, Strauss E. Aging and response inhibition: Normative data for the Victoria Stroop Test. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2006;13(1):20-35. doi: 10.1080/138255890968187. PubMed PMID: 16766341.
62. Considine, C.M. & Abeare, C.A. (2015). Brief Estimate of Seconds Test (BEST). Unpublished instrument.
63. Simon, J. R. (1969). Reactions towards the source of stimulation. Journal of experimental psychology, 81, 174–176.
64. Yu, L., Buysse, D. J., Germain, A., Moul, D. E., Stover, A., Dodds, N. E., … Pilkonis, P. A. (2011). Development of short forms from the PROMIS sleep disturbance and Sleep-Related Impairment item banks. *Behavioral Sleep Medicine*, *10*(1), 6–24. https://doi.org/10.1080/15402002.2012.636266. PubMed PMID: 22250775
65. Zigmond, A. S., & Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica, 67*(6), 361-370.