Title: Neurobiological drivers of mobility resilience: the Dopaminergic System

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Neurobiological drivers of mobility resilience: the dopaminergic system

1. SPECIFIC AIM

Walking with age becomes both slower and less 'automated', requiring more attention and prefrontal resources[1,2]. As a result, older adults have a greater risk of adverse mobility outcomes and falls. Walking disturbances in the elderly have been linked to changes in both cerebral, in particular small vessel disease (cSVD), and peripheral systems[3]. There is an urgent need to identify factors that can help compensate for these harmful factors and reduce walking impairments, as there are currently no effective treatments available. Although effective mobility is the end result of the functional capacity of both central and peripheral systems, the brain's unique modulatory and adaptive capacity may provide clues for novel interventions. For example, we have recently discovered that ~20% of older adults maintain fast walking speed even in the presence of age-related cSVD and peripheral system impairments, thus appearing resilient to these harmful factors. Our work suggests that the nigrostriatal dopamine (DA) system may be a source of this resilience. As our recent findings suggest, DA neurotransmission positively predicts walking speed[4]; it also attenuates the negative effects of age-related cSVD and peripheral system impairments on walking speed. These findings are consistent with post-mortem evidence that a combination of loss of nigral DA neurons and cSVD best predict age-related walking impairment[5-7]. The nigrostriatal DA system plays a critical role in motor control; nigrostriatal DA neurotransmission regulates the automated execution of overlearned motor tasks via its connections with sensorimotor cortical and subcortical areas[8].

We hypothesize that higher nigrostriatal DA neurotransmission drives resilience to cSVD and peripheral system impairments, via higher connectivity of sensorimotor networks, thus increasing automaticity of walking and reducing prefrontal engagement while walking. Resilience due to the nigrostriatal DA system is a novel and highly promising area of inquiry. Unlike cSVD and brain structural impairments, DA neurotransmission is potentially modifiable, thereby offering novel approaches to treat non-resilient elderly in a targeted fashion. This translational pilot study will use a biomechanistic target engagement study mechanisms targeting dopamine using Carbidopa / Levodopa (C-L Dopa) administration in low DA non-resilient elderly to determine change in synaptic DA in relationship to brain imaging connectivity changes and quantitative motor tests.

Exploratory AIM: Does increased DA in non-resilient elderly with parkinsonian signs (incl. gait <1.0msec) improve walking in a mechanistic target engagement study?

Exploratory H1: One week of C-L Dopa treatment will improve walking by increasing DA in elderly with parkinsonian signs.

Exploratory Hy2: C-L Dopa treatment will have a mechanistic effect on functional and metabolic mobility networks in the brain in elderly with parkinsonian signs.

2. BACKGROUND

Rationale. This exploratory mechanistic target engagement study will assess the effect of brief DA supplementation on dopamine availability, nigro-striatal functional connectivity and mobility in a sample of older adults with parkinsonian signs.

The study will screen elderly people for the presence of slow walking (not explained by peripheral or musculoskeletal reasons) and/or other parkinsonian signs. Subjects will be contacted for participation in this study from an existing database in the lab. However, if enough subjects can't be recruited from this database then subjects will be recruited through external sources, such as a flyer posting, online registries, and the University of Michigan Movement Disorders Clinic and other physicians. These subjects will be screened using the telephone screening script, and after this screening they will be brought into the lab to screen for the presence of slow walking and/or other parkinsonian signs. If the clinical assessment does not show evidence for these parkinsonian signs then the person will be excluded from the C-L Dopa and imaging portions of the study (see study outline below).

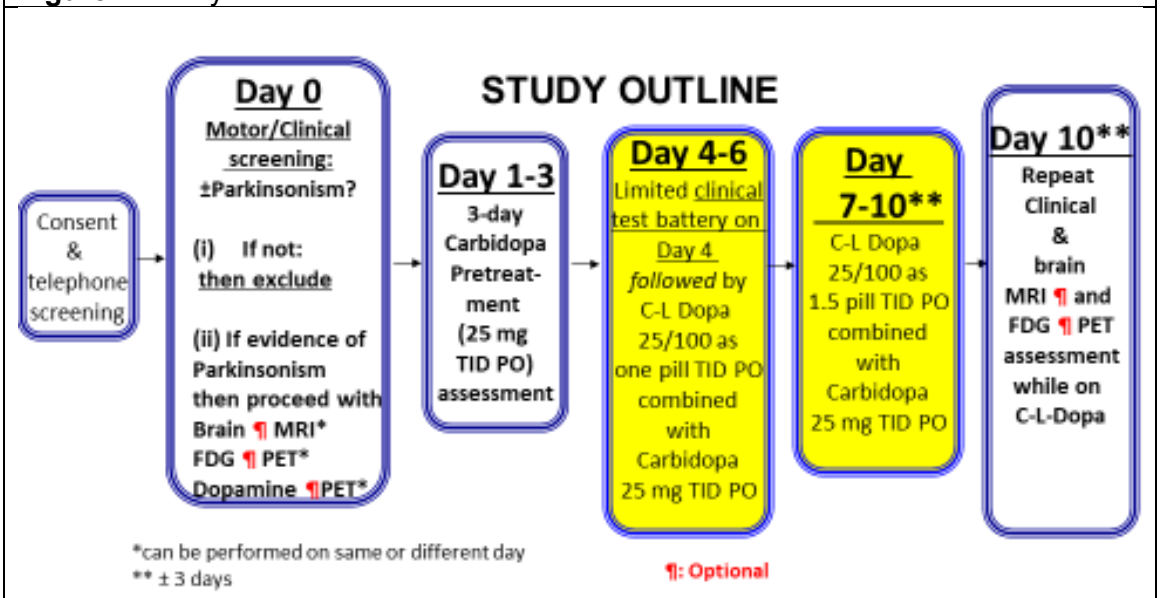
We will record eligibility, adherence, and tolerability to 1-week supplementation (3 days of carbidopa monotherapy and 7±3 days of C-L Dopa at one tablet PO TID for three days followed by an increase to 1.5 tablets PO TID the next day for the next 4 days (±3 days)), and the effects of C-L Dopa on mechanistic imaging measures of DA sensorimotor functional connectivity and on clinical mobility functions. This translational aim will provide preliminary information about the targeted modifiability of the DA system in non-resilient elderly with parkinsonian signs.

3. RESEARCH PLAN

General Overview:

Study design: Open-label study. An outline of the study is shown in Figure 1. After obtaining informed consent, subjects (max n=60) will undergo a screening exam to assess for parkinsonian signs, including slow walking speed. Elderly subjects without evidence of parkinsonian signs will be excluded from the C-L dopa and imaging portions of the study. Eligible subjects with evidence of parkinsonism (max n=20) will then complete a motor, including gait, cognitive test battery, [^{18}F]FDG PET scan (optional), and 3T brain MRI (optional) prior to starting the C-L Dopa treatment portion of the study (Refer to Table 1 and Table 3). Subjects will be pre-treated with carbidopa monotherapy 25 mg TID PO for 3 days. Prior to initiating C-L Dopa 25/100 one tablet PO TID for three days subjects will repeat a limited clinical test battery on day 4. Subjects will then increase to 1.5 tablets PO TID on day 7 (i.e., day 4 of C-L Dopa treatment) for the next 4 days (±3 days). Carbidopa monotherapy will be given to prevent possible side-effects of nausea and participants will stay on 25 mg carbidopa PO TID for the duration of the treatment period of the study. Participants are given the option to be clinically observed in the lab for their first dosage of C-L Dopa. This optional observation would be 60-120 min in length where the participant will take their first dose of C-L Dopa and be monitored by study personnel. After the week-long (±3 days) C-L Dopa 25/100 trial the complete test battery will be completed. An (optional) [^{11}C]PE2I dopamine PET scan will be performed for assessment of overall nigrostriatal degeneration. This target engagement study will allow for biomechanistic assessment of hypothesized changes in the DA sensorimotor network and will allow us to correlate the C-L Dopa mechanistic effects on DA sensorimotor connectivity changes before/after target engagement as assessed with multimodal graph analytical network methods using optional post-treatment [^{18}F]FDG and MRI of key relevant circuits related to DA. Dopamine PE2I PET scan will be used for post hoc covariate effects.

Figure 1. Study outline.



Subjects:
Eligibility: Non-resilient elderly non-PD subjects (F/M, age 60 yrs or older) with evidence of mild parkinsonian signs (MPS, slow gait (< 1m/s)). The UPDRS motor component (part III) will used to assess for evidence of parkinsonian signs, including bradykinesia, tremor, rigidity, and gait disturbances.

Inclusion:
1) Age 60 or older (M/F)
2) Evidence of mild parkinsonian signs (incl. MPS, slow gait (< 1m/s))

Exclusion:
1) Evidence of prior established diagnosis and/or treatment for PD[13].
2) Presence of clinically significant degenerative joint disease and/or neuropathy interfering with proper assessment of the motor UPDRS exam.
3) Presence of significant dementia.
4) History of stroke with residual clinical deficit interfering with walking.
5) For optional MR imaging only: Participants in whom magnetic resonance imaging (MRI) is contraindicated including, but not limited to, those with a pacemaker, presence of metallic fragments near the eyes or spinal cord, or cochlear implant.
6) For optional brain imaging only: Severe claustrophobia precluding neuroimaging procedures.
7) Participants that have been on monoamine oxidase inhibitors (MAOIs) within 2 weeks prior to starting study.
8) Inability to stand or walk without an assistive device
9) Hypersensitivity to the carbidopa, levodopa, and tablet components.
10) History of myocardial infarction (MI) with residual arterial, nodal or ventricular arrhythmia
11) History of peptic ulcer
12) Chronic wide angle glaucoma

13) Narrow angle glaucoma
14) Major psychotic disorder
15) Severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease
16) Subjects on dopamine D2 receptor antagonists, dopamine depleting agents, and metoclopramide.
18) Any other medical history determined by investigators to preclude safe participation.

Study Timeline:
The study will be performed over 2 years with anticipated net recruitment and completion of half of the subjects per year. A milestone of success will be recruitment of 5 subjects who have completed the CL Dopa treatment by the end of year 1. The last 2 months will be used for data analysis and report writing.

Dissemination plan:
Study findings will be published in peer-reviewed journals and presented at scientific meetings.

Design: Within-subject study design using after-before difference measures.

Sample size: This is an exploratory pilot study to generate sample size effects for future larger scale studies, with a net study completion goal of 20 treated subjects.

Impact: Data collected in the proposed study may help identify a novel therapeutic approach to gait slowing in non-resilient elderly with parkinsonian signs, which could have large public health ramifications given the prevalence and serious morbidity of non-specific parkinsonism in the elderly. This project also will elucidate the neurobiology of gait slowing at structural and functional levels of analysis, increasing our understanding of the interplay between these aging-associated processes and the brain network changes underlying late life mobility disorders. Exploring patient-level moderators of response to C-L Dopa may provide useful information to guide differential therapeutics and develop personalized medicine for non-resilient elderly.

Testing:

Table 1: Main components of the Test Battery, including detailed gait and balance assessments

Test	Primary outcome parameter	Admin. Time
Motor: MDS-UPDRS [2]	PIGD UPDRS sub-score	15 min
Gait: Timed walking tests (single & dual task gait). Optional: Electronic gait assessments using mats (Zeno Walkways, Protokinetics) and/or sensors (APDM) under single and dual test conditions and challenged gait.	Assessment of standard spatiotemporal gait parameters & variability measures	2 min
Dynamic balance: Mini-BESTest [3], with optional APDM sensors	Total Mini-BESTest score	15 min
Balance confidence/fear of falling: The Activities-specific Balance Confidence (ABC) scale [4]	Total ABC score	5 min
		Total: 35 min

Primary Outcome variables:

(a) Biomechanical gait and postural parameters
(b) Cognition
(c) Optional: Brain network connectivity analysis of DA networks using multi-modal MRI and metabolic connectivity based on FDG PET.

Study Treatment:

Carbidopa Monotherapy: Due to the small risk of nausea and vomiting from taking C-L Dopa, all subjects will be pretreated with carbidopa 25 mg orally (PO) three times a day (TID) monotherapy for 3 days prior to starting C-L Dopa.

C-L Dopa administration: A low dose (25/100 1 tablet orally (PO) three times a day (TID) of C-L Dopa immediate release will be used for the first three days of C-L Dopa treatment then if no side-effects will be increased on day 4 of the C-L Dopa treatment to 1.5 pills TID PO. All participants will continue to take carbidopa 25 mg TID PO for the whole duration of the treatment period.

Drug Supplies: Formulation, Preparation and Dispensing

Carbidopa Monotherapy:
Carbidopa will be prepared and dispensed by the Research Pharmacy at the University of Michigan.

C-L Dopa administration:
C-L Dopa will be prepared and dispensed by the Research Pharmacy at the University of Michigan.

Drug Storage and Drug Accountability

Carbidopa Monotherapy: Drug will be stored and accounted for at the Research Pharmacy at the University of Michigan per their established standing operating procedures.

C-L Dopa administration: Drug will be stored and accounted for at the Research Pharmacy at the University of Michigan per their established standing operating procedures.

Concomitant Medications

Use of both carbidopa monotherapy and C-L Dopa, has been contraindicated with concurrent use with nonselective monoamine oxidase inhibitors (MAOIs) or use within the last 14 days.

Other Considerations

High protein diets have the potential to impair C-L Dopa absorption as the levodopa ingredient competes with certain amino acids for transport across the gut wall or across the blood-brain barrier. For this reason, participants will be instructed to take the study drugs at least ½ hour before each meal (i.e., breakfast, lunch & supper). However, the pre-meal intake of these drugs can be combined with non-proteineous supplements, like fruit juices or fruits (banana, apple sauce, etc.).

Clinical Testing:
Clinical assessment (see also Table 3) includes a general demographic, medical and, neurological examination, the measurement of visual acuity, (optional) visual contrast sensitivity (Rabin test), (optional) color blindness (Munsell 15), orthostatic vital signs, weight and height in all subjects, general motor assessment, including the Movement Disorder Society revised UPDRS examination (13), modified Hoehn & Yahr (14) to provide assessment of general motor impairments of PD. Questionnaires to assess overall sedentarism and physical activity will be administered. Detailed cognitive testing will also be performed.

Clinical and functional assessment of motor features:
Several well-validated balance, gait, and fall-associated scales and tests will be used to further assess functional mobility in PD (see Table 3). In addition to these motor examinations we will also use questionnaires to assess for the presence of gait festination and freezing of gait [15-17]. In addition, finger tapping and Grooved Pegboard testing will be used to provide quantitative measures of upper limb bradykinesia and motor dexterity. Foot tapping will be used as a measure of lower limb bradykinesia. A specialized mobility and postural control test battery to capture gait and postural functions will also be performed. Some tasks may be performed while performing a secondary cognitive task (e.g. counting backwards by 3s).

Biological samples:
Saliva samples may be collected for analysis of dopamine and other related genotypes. Samples will be processed and analyzed at laboratories the Department of Human Genetics, or at other intra- or extramural institutions.

Neurocognitive and functional status assessments:
Table 2 provides an overview of the detailed neuropsychological examination. We will assess global cognitive changes over time based on the MMSE [18], MoCA [19], and a composite z-score encompassing the major cognitive domains from the test battery.

Table 2. Components of the neuropsychological test battery	
Overall mental status	Optional: Mini Mental State Exam [18] Montreal Cognitive Assessment Scale [19]
Attention	D-KEFS: Trail Making Test, Stroop Color Word Interference Test [20]
Learning & Memory	Optional: California Verbal Learning Test – II [21]
Executive/Working Memory	D-KEFS: Trail Making Test
Information processing speed	D-KEFS: Trail Making Test [20] Digit Symbol test, Optional: Reaction time Optional: Falling stick test

MR imaging (optional): MR imaging will be performed on a 3 Tesla Philips Achieva system (Philips) utilizing a 15-channel head coil and the 'ISOVOX' exam card protocol primarily designed to yield isotropic T_1 spoiled gradient (SPGR) spatial resolution. This protocol consists of a number of different sequences including a standard T_1-weighted series of a 3D inversion recovery-prepared turbo-field-echo will be performed in the sagittal plane with repetition time/echo time/inversion time = 9.8/4.6/1041 ms; turbo factor = 200; single average; field of view = 240 x 200 x 160 mm; acquired matrix = 240 x 200.

Slices (n = 160) will be reconstructed to 1mm isotropic resolution. This sequence maximizes contrast among grey matter, white matter and CSF and provides high resolution delineation of cortical and subcortical structures. Other standard sequences include FLAIR, DTI, resting state functional connectivity MRI, or other relevant series. The brain MRI scan can be performed on the same day as the clinical assessment or on a separate day prior to starting study drug treatment.

PET imaging (optional): All PET data will be acquired at the University of Michigan PET facility on a Siemens BioGraph TruePoint Model 1094 PET/CT scanner, which produces 109 slices, has an axial field-of-view of 22.0 cm with slice thickness of 2.027 mm, and intrinsic image resolution 4.2 mm full-width at half maximum (FWHM). Image reconstruction for both tracers will be done with fully 3D-iterative OSEM, using 4 iterations, 16 subsets, and post-reconstruction files of 3.0 mm FWHM, yielding images of ~5.0 FWHM. One low-dosage CT scan (130 kVp, 30 eff mAs, 6 x 3mm collimation, pitch =1, rotation time =0.6 second) of the head will be performed prior to each brain PET scan for attenuation correction purposes. “As low as reasonably achievable” (ALARA) techniques will be utilized to minimize subject radiation exposure.
Subjects will be studied supine, with eyes and ears unoccluded, resting quietly in a dimly lit room. [^{18}F]FDG and [^{11}C]PE2I PET ligands are non-approved radiopharmaceutical that will be used in accordance with Food and Drug Administration regulations (21 CFR 361.1). All tracers are prepared following standard synthesis routines at the University of Michigan PET Chemistry and Cyclotron facilities.

Daily life activity levels (optional): Overall activity levels during medication therapy will also be assessed. Subjects will be asked to wear an accelerometer based actigraphy device (Actigraph or ActivPAL) for the duration of the carbidopa monotherapy and carbidopa-levodopa mechanistic study.

Compliance Monitoring Phone Call: A compliance phone call will be performed by a research staff member during the 7±3 C-L Dopa medication stage.

Timeline: Refer to table 3 for timeline and test details. Day 0 may be completed over multiple visits. Once all tasks listed under Day 0 are completed Day 1 will start. Day 9(±3) tasks will be performed while participant is still taking C-L Dopa and may require multiple visits.

Table 3. Detailed components, test protocol, and timeline

	Pre-Rx (Day 0) Baseline	Day 1-3	Day 4	Day 4-6	Day 7-10(±3)	Day 10 (±3)
Informed Consent	✓					
Demographic Information	✓					
Inclusion/Exclusion Criteria	✓					
Clinical & Neurological Assessment	✓					✓
Optional: Saliva sample	✓					
MDS-UPDRS	✓		✓			✓

Mini-BESTest (optional: APDM Sensored)	✓		✓			✓
Regular timed walking single & dual-task Optional: Zeno Walkways Single, Dual, and challenged gait Task	✓		✓			✓
Optional: APDM Mobility assessments	✓		✓			✓
Optional: Oculovestibular	✓					✓
Pegboard	✓		✓			✓
Finger tapping	✓		✓			✓
Foot tapping	✓		✓			✓
Optional: Reaction Time Test/ Optional: React Stick Test	✓					✓
Optional: Four Square Step Test	✓					✓
Optional: Maximum Step Length Test	✓					✓
Activity questionnaire	✓					✓
Balance confidence/fear of falling: The Activities-specific Balance Confidence (ABC)	✓					✓
Optional: New-FOGQ	✓					✓
Optional: Short FES-I	✓					✓
Sensonics UPSIT	✓					optional: ✓
Optional: Eyetech OCAT	✓					✓
MoCA	✓		✓			✓
Optional: MMSE	✓					✓
DKEFS-STROOP	✓		✓			✓
DKEFS-TMT	✓		✓			✓
Optional: CVLT	✓					✓
Information processing	✓		✓			✓
General Feeling Questionnaire	✓					✓
Apathy Evaluation Scale	✓					✓
Geriatric depression scale	✓					✓
Spielberger anxiety scale	✓					✓
Optional: BPRS	✓					✓
Epworth Sleepiness Scale	✓					✓

Mayo Sleep Questionnaire (22)	✓					✓
FSS	✓					✓
Optional: Insomnia Questionnaire	✓					✓
Optional: Somnolence VAS	✓		✓			✓
Snellin Test	✓					✓
Optional: Rabin	✓					✓
Adverse event assessment	✓	✓	✓	✓	✓	✓
Optional MRI	✓					✓
Optional FDG PET	✓					✓
Optional PE2I PET (will occur only 1 time)	✓					✓
Optional DEXA	✓					
Optional 90-120 minute observation (post medication) after first intake				✓		
Carbidopa Monotherapy 25 mg TID PO		✓	✓	✓	✓	✓
C-L Dopa 25/100 1 tablet PO TID			✓	✓		
C-L Dopa 25/100 1.5 tablet PO TID					✓	✓
Compliance Monitoring Phone Call		✓			✓	
Optional: Actigraphy		✓	✓	✓	✓	✓

Analysis:
Statistical analysis: We anticipate that 90% of eligible subjects will complete the 1-week C-L Dopa supplementation; the effect of C-L Dopa administration on brain connectivity and mobility measures will be tested using a repeated measures design.

Comments: This exploratory open label pilot study will investigate the feasibility for future clinical trials of C-L Dopa therapy in non-resilient elderly with parkinsonian signs.

Data safety-monitoring plan: This study will adhere to a data safety-monitoring plan where the principal investigator will be responsible for regular (at least annual) monitoring of general progress of the study, such as subject recruitment, perform interim statistical analysis on the data (only when statistically feasible), review of outcome and adverse event data to determine whether there is any change to the anticipated benefit-to-risk ratio (which may require modification or termination of the study protocol), assessment of external scientific or medical developments that may have an impact on the safety of study participants or the ethics of the study. Dr. Vikas Kotagal, Assistant Professor of Neurology, will serve as an independent safety officer and will review twice yearly safety reports. The monitoring process will also include a review of study procedures aimed at the protection of the privacy of the research subjects and confidentiality of the research data. Adverse events will be reported to the IRB adverse events reporting guidelines. If the protocol needs to be modified or there is a change in the level of risk to subjects for this study, a

modification submission will be prepared for review by the IRB. All data collected on research subjects will be kept confidential as detailed above.

Risks (as described in informed consent form):
The known or expected risks will be defined as: Likely - occurring in more than 25% of people (more than 25 out of 100 persons); Common – occurring in 10% - 25% of people (in 10 to 25 out of 100 persons); Infrequent - occurring in 1 - 10% of people (1 to 10 out of 100 people); Rare - occurring in less than 1% of people (fewer than 1 out of 100 persons); or Very Rare - occurring in less than 0.1% of people (fewer than 1 in 1,000 persons).

The known or expected risks will be described in normal script.

The actions that the researchers take to minimize these risks will be described in italic script, as demonstrated in this paragraph.

General risks:
There is a very rare risk of breach of confidentiality, which may affect privacy, self-esteem, social standing, employability, and insurability.

Section 9.1 will provide more detailed information on how we protect your privacy. In general, study records will be kept in databases maintained by the investigators. These databases are kept separate from medical records, are protected by passwords, and only accessible to personnel involved in the study. If you withdraw from the study at any time, a record of the withdrawal and the reasons given for withdrawing may be kept as part of the study record.

There is a rare risk that you may experience some minor anxiety ('test anxiety'), become worried, or have an anxiety reaction in response to any of these tests and procedures. For example, you become worried about your health, or you may experience a sudden fear of the confined space while in the scanner.

Trained research staff will conduct all tests and procedures. The staff will be prepared to respond to your anxiety, concerns and behavioral changes, by temporarily suspending testing, breaking up testing sessions into several brief visits if needed, and/or answering your questions. During the MRI scans you will be able to talk to technologists throughout the scan and indicate right away if you wish to stop the study and leave the scanner. At the option of your personal physician, (s)he may prescribe sedation with lorazepam (Ativan) or diazepam (Valium) to be taken before the scan in accordance with the prescription directions.

None of the test results, including brain images, and procedures in this study will be reviewed or interpreted for making a medical diagnosis. Any result or abnormality that would be indicative of current or future disease will most likely not be discovered. However, if we do find a clinically relevant result or abnormality that deserves additional medical attention, we will communicate this to you and you will be urged to visit your primary health care provider. The research results of the brain images and genetic testing will NOT be communicated back to you.
You should consult your personal doctor if you have any health concerns

Clinical tests:
There is a very rare risk of physical fatigue during the clinical examination.

Trained research staff will conduct all the tests and administer all the questionnaires. The staff will be prepared to respond to your concerns by temporarily suspending testing and/or breaking up testing sessions into several brief visits if needed.

There is a common risk that you may have a dry mouth after providing the saliva sample.

You may drink some water after providing the sample.

Smell and vision tests:

There is a very rare risk of a mild allergic reaction to the scents of the smell identification test.

Testing will be discontinued if you experience an allergic reaction that prevents you from continuing the examination.

There is a very rare risk that you may experience some minor eye strain when doing the vision tests.

Rest breaks will be provided if needed. Any minor eye strain will disappear shortly after the test.

Motor testing:

Many of the tests are comparable to normal standing and walking conditions that you may experience in everyday-life. Nonetheless, there is an infrequent risk of falling or near-falling during these tests which may result in fall-related injuries.

Trained research staff will remain in close proximity to you at all times, and observe ('spot') you to prevent you from falling.

There is a very rare risk that the sensors to measure overall movement and balance may become detached and that you may trip. You may also trip on the pressure sensitive mat.

We will regularly check the sensors for appropriate attachment and you will be closely monitored.

Eye movements will be measured with video eye goggles (videonystagmography or VNG) while you are making small eye movements. There is rare risk that these protocols may cause some eye strain discomfort.

Rest breaks will be provided if needed. Any minor eye strain will disappear shortly after the test.

Neuropsychological and neurobehavioral tests:

There is an infrequent risk of boredom, frustration, and/or mental and physical fatigue during the neuropsychological and neurobehavioral testing.

Trained research staff will conduct all the tests and administer all the questionnaires. The staff will be prepared to respond to your concerns by temporarily suspending testing and/or breaking up testing sessions into several brief visits if needed.

MRI scan:

There is a minor risk of discomfort or anxiety from being in the confined space of the MRI scanner.

We will provide pads and blankets to make you as comfortable as possible. You will be able to talk to us throughout the study, and you will be able let us know right away if you want to stop the study and get out of the scanner.

The MRI scanner makes loud, vibrating noises.

You will wear foam earplugs to reduce the loud noises made by the scanner and prevent any hearing damage.

Some studies, like this one, have the potential to cause "peripheral nerve stimulation" (PNS). PNS is a light touching sensation on the skin surface, lasting only for a few seconds. It may cause mild discomfort, but is not harmful to you.

The MRI machine is operated within FDA guidelines so the potential for inducing PNS is low.

Sometimes, subjects report a temporary, slight dizziness, light-headedness or nausea during or immediately after the scanning session.

If you feel dizzy or light-headed, we will have you get up slowly from the scanner.

Because the strong electromagnetic fields can move metal objects and cause heating, there is a risk that loose objects (jewelry, keys) outside your body could be accelerated by the magnetic field and strike you, causing you injury. There is also a risk that the magnetic fields could disturb a metal fragment in your body, interfere with an implanted device, such as a pacemaker or neurostimulator, or cause metal (including foil-backed medication patches) on or in your body to heat up, causing you harm.

We keep the environment around the MRI scanner completely free of loose metal objects that could be moved by the magnetic field, and we will make sure that you have no metal on your body that could be affected by the MRI scanner. We will also ask you questions and have you complete an MRI screening form to make sure that you have no metal inside your body that would cause you harm during the MRI scan.

There is the potential that a magnetic resonance image may reveal an abnormality that is already in your body, such as a cyst or tumor. Many such abnormalities are not clinically significant, but you may need or want to investigate them further. Such a finding might require additional studies, and maybe even treatment, which would not be paid for by the investigators, the sponsor, or the University of Michigan.

PET scans:

There is an infrequent risk of bruising, bleeding, infection, or soreness associated with intravenous catheter placement, similar to the risks associated with routine blood testing. Also, you may feel dizzy or lightheaded or may rarely even faint when the tube is put in or taken out.

We will use highly trained personnel for placement and removal of the IV.

There is a very rare risk that you could experience an allergic reaction to the PET tracer. This could involve itching, skin rash or shortness of breath shortly after injection. However, because of the very small tracer amounts used in PET imaging, the risk is very rare.

A physician will be available and an emergency cart is located in the PET Facility for treatment of any adverse reactions that may occur.

During the course of this study, you may potentially be exposed to radiation from the DXA scan, the PET/CT transmission scans and the PET tracers [^{11}C]PE2I and [^{18}F]FDG.

The biological effect of radiation in humans is measured in terms of Sieverts (Sv) or mSv (1/1000 Sv), which is a unit of uniform whole body exposure. Exposure to a single PE2I PET-CT scan is 3.8 mSv (which is slightly above the annual level of natural background radiation of about 3 mSv). Exposure to a single FDG PET-CT scan is 3.7 mSv (which is also slightly above the level of annual natural background radiation).

The maximum amount of radiation you will be exposed to from this research project will be approximately 11.1 mSv for the FDG and PE2I scans combined. In the event

of a technical failure, one (1) of these scans may be repeated, which would expose you to a maximum exposure of 14.7 mSv. The effects on the body of this radiation exposure will be added to your overall lifetime radiation risk. The US Federal Government requires that the annual amount of radiation exposure of radiation workers does not exceed 50 mSv per year; the maximum radiation you will be exposed to with these two tracers is about 3/10th of this amount. Exposure to an (optional) DXA scan is less than 0.1% of annual background radiation exposure. Your lifetime radiation risk also includes any radiation you may have received in the past for diagnosis or treatment, and any such radiation you may be exposed to in the future. Please inform the investigators if you have had any major radiation exposure in the past, particularly in the past year, such as medical treatment with X-rays or radioactivity, or diagnostic X-rays, CT-scans or nuclear medicine scans. No PET scans will be performed on pregnant, nursing, or potentially pregnant women. A urine pregnancy test will be performed on all women of childbearing potential within 48 hours prior to the PET/DXA scanning session.

Genetic testing:

We will be testing for multiple genes that are related to clinical symptom presentation. There is a very rare risk that the genetic information we obtain from your samples could prove embarrassing to you, if somebody were able to link the genetic information with you.

We have a system of double-coding the genetic information, so that it is extremely unlikely that the genetic information would be connected with you. Most importantly, we will break the link between the genetic information and you once the study is completed, thus removing this risk entirely.

The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- *Health insurance companies and group health plans may not request your genetic information that we obtain from this research*
- *Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums*
- *Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment*
-

GINA does not apply to the following groups; however, these groups have policies in place that provide similar protections against discrimination:

- *Members of the US Military receiving care through Tricare*
- *Veterans receiving care through the Veteran's Administration (VA)*
- *The Indian Health Service*
- *Federal employees receiving care through the Federal Employees Health Benefits Plans*

Assessment of daily life activity:

There is a very rare risk of the movement monitor(s) (Actigraph or ActivPAL) detaching, which may result in a trip during the daily life monitoring of overall movement (actigraphy). It should be noted that the actigraphy only measures overall movement. Neither devices

record your geographical location or specific activities that you were performing, neither can this be derived at a later point from the data that is stored in the Actigraph or ActivPAL.

You will receive instruction for proper attachment of the Actigraph and/or ActivPAL system.

C-L Dopa-specific risks:

There is a common risk of nausea and an infrequent risk of vomiting.

Participants are given the option to come into the lab for their first dosage of C-L Dopa. This optional visit would be 60-120 min in length where the participant will take their first dose of 25/100 C-L Dopa and be monitored by study personnel. The peak dosage time for C-L Dopa is 60-90 min, so if a participant is going to experience nausea or vomiting it would be in the first 60-90 min after taking a dose.

The Carbidopa Monotherapy is done to reduce the chance of nausea and vomiting before starting C-L Dopa. All participants will receive three days of carbidopa monotherapy as a pre-treatment and will stay on this dose during the C-L Dopa treatment period.

Participants will be informed to take medication 30 minutes before a meal with a piece of fruit and with fruit juice to reduce chances of nausea and vomiting. Also, participants will be informed to not take medication with or after a protein filled meal, because this will increase the chance of nausea.

There is an infrequent risk of sleepiness.

Participants are given the option to come into the lab for their first dosage of C-L Dopa. This optional visit would be 60-120 min in length where the participant will take their first dose of 25/100 C-L Dopa and be monitored by study personnel.

You understand that you should not operate machinery or drive until these symptoms have disappeared.

There is an infrequent risk of orthostatic hypotension, insomnia, anxiety, confusion, abnormal dreams, hallucination, psychosis, diarrhea, and constipation.

Participants are given the option to come into the lab for their first dosage of C-L Dopa. This optional visit would be 60-120 min in length where the participant will take their first dose of 25/100 C-L Dopa and be monitored by study personnel.

If these symptoms are experienced at home, please contact study team immediately. Medication use may be suspended, and further action taken, including withdrawal from study.

There is a common risk of dizziness and headache. There is a rare risk of chest pain, dystonia, urinary frequency, ischemia, back pain, muscle cramps, and shoulder pain.

Participants are given the option to come into the lab for their first dosage of C-L Dopa. This optional visit would be 60-120 min in length where the participant will take their first dose of 25/100 C-L Dopa and be monitored by study personnel.

Please lay down until symptoms pass.

If these symptoms are experienced at home, please contact study team immediately. Medication use may be suspended, and further action taken, including withdrawal from study.

Given the very low dose of C-L Dopa we do not anticipate any significant withdrawal symptoms when stopping the medication as this is not observed at the 25/100 TID PO dose in clinical practice.

Subject compensation (as described in informed consent form):
You will receive $50 for each completed MRI scan. You will receive $50 for each completed FDG PET scan and PE2I PET scan. Payment for completion of the detailed clinical baseline test day will be $100 and $100 for follow-up. You will also receive $50 for completing the limited clinical test day and medication phase of the study. Compensation for your time and effort after full study completion may total a maximum of $500.

Overnight accommodations may be provided depending on personal circumstances or if you live far away. We will discuss with you the need for these accommodations as the research appointment(s) are being arranged. If eligible, overnight lodging can be arranged through the UMHS Patient and Visitor Accommodations Program either by a study team member or by you. However, you may decide to make alternative arrangements. In that case, please discuss with the study team first if you are eligible for reimbursement prior to making any reservations. We can only reimburse for expenses that have been approved in advance by the study team. You will need to provide receipts to the study team before expenses can be reimbursed. We will reimburse to a maximum of $300 for lodging and meals. You will receive a voucher for valet parking at the University Hospital. Parking at Domino's Farms is free.

Overnight accommodations may be provided depending on personal circumstances or if you live far away. We will discuss with you the need for these accommodations as the research appointment(s) are being arranged. If eligible, overnight lodging can be arranged through the UMHS Patient and Visitor Accommodations Program either by a study team member or by you. However, you may decide to make alternative arrangements. In that case, please discuss with the study team first if you are eligible for reimbursement prior to making any reservations. We can only reimburse for expenses that have been approved in advance by the study team. You will need to provide receipts to the study team before expenses can be reimbursed. We will reimburse to a maximum of $300 for lodging and meals. You will receive a voucher for valet parking at the University Hospital. Parking at Domino's Farms is free.

You will be paid after your last study visit or, in case you decide to withdraw from the study, you will be paid for the parts that you have completed. You will be paid by check, which will be sent to your home address. Alternatively, you may request a payment coupon for cash payment at the University Hospital. We do not keep cash for immediate payment.

If you receive payment of $600 or more for taking part in this study, the University of Michigan accounting department will collect your name, address, social security number, payment amount, and related information. For tax reporting purposes this information must be sent to the Internal Revenue Service (IRS).

Remote consent and remote assessments:

Data may be collected remotely (using Zoom for Health at U of M) or telephone call if feasible for assessment. Remote electronic consent may be obtained using SignNow, this is being done to reduce physical interactions between subjects and study staff.

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