UNIVERSITY OF MICHIGAN

CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title:

Neurobiological drivers of mobility resilience: the dopaminergic system

Company or agency sponsoring the study:

National Institutes of Health (NIH)

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):

Nicolaas Bohnen, MD, PhD, University of Michigan, Departments of Radiology and Neurology

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying the use of an FDA approved medication for Parkinson's disease called carbidopa-levodopa (C-L Dopa or Sinemet), but in this study, we will be using this medication in people who are not diagnosed with Parkinson's disease but have symptoms that can be seen with this disorder and thus is considered investigational. You will be screened for these symptoms. If these are not present you will not be eligible for the study and will be excluded. In this investigational study we will use this medication in a small number of people to learn about its effect on elderly subjects with slow walking. Your health-related information will be collected as well as subjects will receive medications, undergo extensive cognitive and motor testing, two optional magnetic resonance images (MRIs), two optional brain glucose FDG PET scans and one optional dopamine PE2I PET scan, wear an activity monitor for about a week, and optional saliva donation for genetic testing for this research study.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include new symptoms from use of the carbidopa-levodopa such as nausea. More detailed information will be provided later in this document.

This study may not offer any benefit to you now but may benefit others in the future by providing important new insights into better treatment options for slow gait in the elderly. This may ultimately result in development of pharmaceuticals for this treatment. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be 10-14 days. However, this is an estimate, and this may vary depending on how many visits are needed to complete testing.

You can decide not to be in this study. Alternatives to joining this study include not participating.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues below.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Symptoms that can occur in Parkinson's disease, like slow walking, are also common in elderly people. We have also shown that lower levels of dopamine are associated with slow walking. We propose to use an FDA-approved medication for Parkinson's disease called carbidopa-levodopa that will increase the brain dopamine level in order to determine if this may improve walking and balance problems. As a possible study option, we may also look at brain MRI and glucose PET scans to see if we see changes of improved connections within the motor control areas. We will perform detailed walking and other motor tests prior to and at the end of the medication treatment. A dopamine brain PET scan is also optional. We will also administer general clinical tests (blood pressure, pulse, vision) and cognitive (memory, attention) tests. We will also ask you to complete questionnaires about your health, sleep and how you feel.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

Elderly men and women who are 60 of age or older, can participate in this study. Participants should be willing and able to comply with study requirements. People who, in the opinion of the investigators, would be at increased risk or who are unable to perform or tolerate the research procedures will be excluded. People who have any contraindication for MRI imaging such as a pacemaker, metal fragment(s) in their body, or severe claustrophobia may not be eligible.

3.2 How many people are expected to take part in this study?

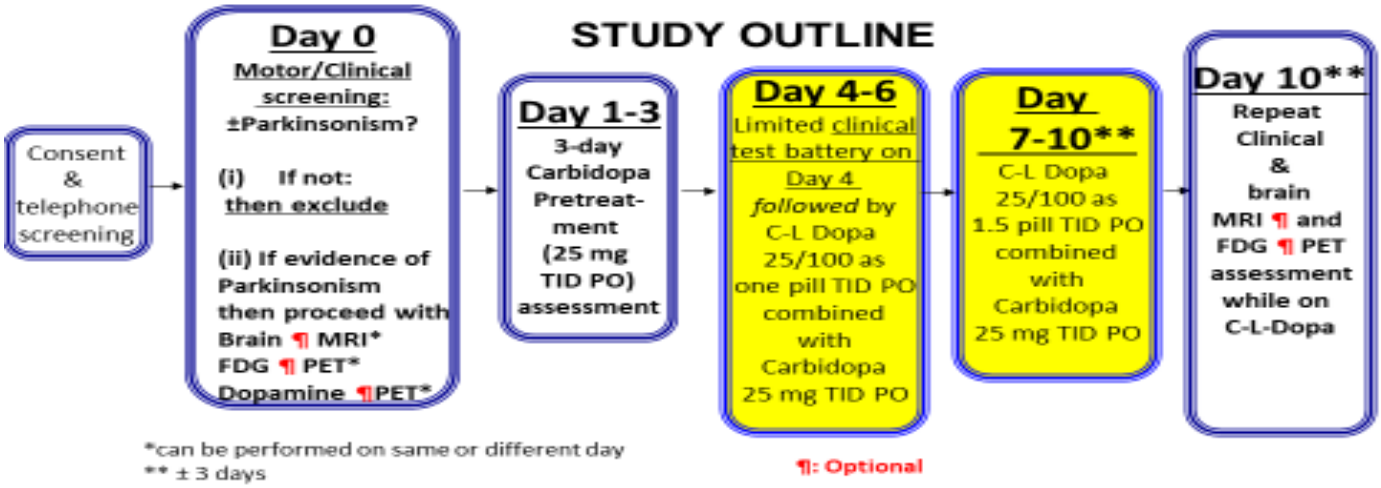
A total of 20 people are expected to participate in the treatment study but we expect to screen up to 60 people for the presence of slow walking or other Parkinson signs.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

After having passed the initial screening process, and if you agree to take part in this study, you will be asked to sign this informed consent form before testing will begin. During the screening process we will ask questions to determine if you are eligible to participate in this study.

An outline of the study is shown below:



Note: C-L Dopa = carbidopa-levodopa (Sinemet)

A summary of the minimum and optional tests are shown in the table below:

Study Events	
Visit 1 (Day 0)	• Informed Consent • General and clinical information • General medical and neurological exam • Visual assessments • Smell Assessments • Motor Assessments • Memory, reasoning and mental concentration assessments • Questionnaires • (Optional) Saliva Sample: (If there is no evidence of slow walking/Parkinson signs then you will stop with the study at this time. If there is evidence of slow walking/Parkinson signs, then you will continue with the imaging and treatment portions of the study.) • (Optional) MRI scan (can be performed on different day) • (Optional) FDG or optional PE2I dopamine brain PET scan (can be performed on different day) • (Optional) DXA scan
Day 1-3	• Three-day carbidopa pre-treatment 1 tablet three times a day • (Optional) Assessment of daily life activity
Visit 2 (Day 4) and Day4-6	• **Day 4** Repeat of limited clinical test battery from visit 1 prior to starting: • **Day 4** Optional in-lab observation to take first C-L Dopa dose • Carbidopa-Levodopa 1 tablet three times a day combined with carbidopa 1 tablet

	three times per day • (Optional) Assessment of daily life activity
Day 7-10 (±3)	• Carbidopa-Levodopa 1.5 tablets three times a day combined with carbidopa 1 tablet three times per day • (Optional) Assessment of daily life activity
Visit 3 (Day 10 (±3))	• General and clinical information • General medical and neurological exam • Visual assessments • Motor Assessments • Memory, reasoning and mental concentration assessments • Questionnaires • (Optional) Smell Assessments • (Optional) MRI scan • (Optional) FDG brain PET scan • You can stop the Sinemet medication after you have completed all testing and return the bottle to the study staff. • You can stop the Sinemet medication after you have completed all testing and return the bottle to the study staff.

Baseline clinical test day (Visit 1)

Clinical tests: You will receive a physical and neurological examination ("medical check-up") including the measurements of weight, height, pulse and blood pressure as well as an evaluation of your ability to move and walk. We will also ask you questions about your health and medications and screen your cognitive abilities and take a saliva sample. We will also ask questions to see if you're eligible to undergo (optional) MRI scans. In addition, we will ask you for some general demographic and clinical information.

Smell and vision tests: Your sense of smell will be tested by administering tests that will assess your sense of smell. We will also test your visual acuity and do tests to assess for color blindness and contrast sensitivity. As a possible option we may also test your eye movements where you will be wearing video goggles that measure your eye movements while following a dot. You will also have your eyes tracked while viewing numbers on a computer screen.

Motor tests: Walking and balance tests will be performed while you will be walking on an electronic mat. Small sensors will also be put on your body (pelvis, ankles). You will undergo several balance tests. Fine movements of the hands, fingers and feet will be examined by finger and foot tapping devices and a pegboard test device (a timed test where subjects put pegs in holes). As a possible option, we may place small sensors at your wrist, ankles, and around your chest and waist to measure your body movements while you perform different balance and gait tasks. Some of the walking will be tested while walking on an electronic gait mat.

Thinking and neurobehavioral tests: The cognitive (thinking) tests are designed to get an overall estimate of your memory, concentration, and ability to think. These functions will be measured with standard tests. We will also ask you questions about your mood. Other questions are about sleep and fatigue.

Assessment of daily life activity: As a possible option, you may be asked to wear an activity monitor during the medication administration to monitor your normal overall daily-life movement, so-called "actigraphy". This device is very similar to a pedometer that some people use to count the number of steps that they take every day. We will provide instructions on how to attach this device to your body and when to use it. This requires also keeping track in a logbook when you are wearing the device and document selected activities (for example when you took the device off to take a shower or when you were playing sports).

OPTIONAL Sub-study: Saliva sample/Genetic testing: A small saliva sample will be taken to look for genetic factors related to how your body handles dopamine. To this end, we are collecting a saliva sample to analyze a sample of your DNA. You may decline to provide a sample for genetic analysis. If you decline to participate in the genotyping study, you can still do the all the other parts of the study. Your sample will be given a special code, which we will keep separate from your name. In fact, it will only be linked to your name by a second code. The samples may be stored and analyzed in laboratories at the Department of Human genetics, University of Michigan, or at other locations. Research teams will analyze the genetic samples for variants in the DNA sequence. Once analysis is performed, we will break the links between the DNA and your name. There is a risk that someone could use information from the sample you submitted, via DNA, to identify you if it were matched with another DNA samples provided by you. However, any user of this sample must agree not to use it for that purpose, and the risk, while real, is small. You have the right to withdraw from this research project at any time. If possible, any samples you contributed will be discarded if you request this; however, because of the sample and data-marking, we may not always be able to identify which samples were donated by you. We will not be returning results to donors.

If the clinical assessment does not show evidence of slow walking and/or other Parkinsonian signs, then you will be excluded from the treatment and imaging parts of the study.

Baseline imaging day (Part of Visit 1)

OPTIONAL DXA scan: An optional brief (~ 10 minute) DXA (bone mineral density/fat soft tissue) scan can be performed during the clinical test battery of visit 1 while you are at the Functional Neuroimaging, Cognitive & Mobility Laboratory at Domino's farms.

_____(initials) I discussed participating in an optional DXA scan and I agree to participate.

_____(initials) I discussed participating in an optional DXA scan and I do not agree to participate.

OPTIONAL MRI scan(s): Optional MRI scans allow the investigators to visualize the brain in detail by using a large magnet. An MRI scan of the brain involves lying on a table, which slides into a scanner. You will be instructed to remove all jewelry and other metal-containing objects for the MRI scan. During the MRI scan loud noises may be heard. The MRI scan will be performed in FDA-approved MRI scanner at the Department of Radiology at the University of Michigan Hospital.

_____(initials) I discussed participating in an optional single brain MRI scan and I agree to participate.

_____(initials) I discussed participating in an optional single brain MRI scan and I do not agree to participate.

_____(initials) I discussed participating in an optional repeat brain MRI scan and I agree to participate.

_____(initials) I discussed participating in an optional repeat brain MRI scan and I do not agree to participate.

OPTIONAL PET scans: The optional PET scans will allow the investigators to "see" the specific marker of glucose (sugar) use in the brain (called FDG PET) and dopamine (a chemical messenger molecule in the brain). You may receive an FDG PET scan before and at the end of the C-L Dopa treatment. A single dopamine PE2I PET scan is also optional. To establish this, in separate sessions, a radiotracer will be injected into your vein through an i.v. (intravenous line or plastic "tube" inserted in an arm vein). A tracer refers to a small amount of a radioactive substance that does not alter body function, but that can be detected (imaged) in the PET scanner. The PET scanner looks like a hollow machine resembling an X-ray scanner (CT or CAT). Images of your brain will be obtained over a period of time. During the PET scans we also may take blood samples for further analysis of tracer

characteristics. Women of childbearing potential may be required to provide a urine sample for a urine pregnancy test within 48 hours prior to the PET scan. If one of these scans fails, they may be repeated.

_____(initials) I discussed participating in an optional single brain FDG PET scan and I agree to participate.

_____(initials) I discussed participating in an optional single brain FDG PET scan and I do not agree to participate.

_____(initials) I discussed participating in an optional repeat brain FDG PET scan and I agree to participate.

_____(initials) I discussed participating in an optional repeat brain FDG PET scan and I do not agree to participate.

_____(initials) I discussed participating in an optional brain dopamine PE2I PET scan and I agree to participate.

_____(initials) I discussed participating in an optional brain dopamine PE2I PET scan and I do not agree to participate.

Medication Involvement

You will be asked to participate in the following study with a medication that may affect your dopamine receptors. The FDA has approved both medications for use in Parkinson's disease; carbidopa monotherapy (Lodosyn) and Carbidopa/Levodopa (C-L Dopa or Sinemet) are approved to treat motor symptoms of Parkinsons Disease. Both medications will be given at the standard FDA-approved doses.

Carbidopa Monotherapy: You will be pre-treated with carbidopa, 25 mg (one tablet) three times a day, for 3 days prior to initiating carbidopa-levodopa (C-L Dopa or Sinemet) and will stay on this medication during the time that you will be treated with carbidopa-levodopa. Carbidopa is given to prevent or reduce possible side-effects of nausea, which may occur with carbidopa-levodopa. This carbidopa monotherapy may be started on the same day of visit 1 when you are completing of all baseline testing or a day following completion. You should take the carbidopa medication ½ hour before each meal three times per day. You can combine it with a fruit or fruit drink if preferred.

Carbidopa-levodopa (C-L Dopa or Sinemet): You will receive a medication called carbidopa-levodopa (C-L Dopa or Sinemet) for approximately 7(+/-3) days. After completing the 3-day pre-treatment with carbidopa you will take carbidopa-levodopa 25/100 as ONE pill three times per day for 3 days (study days 4-6) while continuing taking carbidopa 25 mg three times per day at the same time. If you have no side-effects, you will increase carbidopa-levodopa 25/100 to 1.5 pills three times per day (while continuing combining this with carbidopa 25 mg three times per day). You will stay on this dose for the remaining four treatment days of this study, which is study day 10 ($\pm$3 days). We will provide you with an information sheet with specific instructions on how many pills you should take and how many times per day. You are given the option to come into the lab for your first dosage of carbidopa/levodopa. This optional visit would be 60-120 min in length where you will take their first dose of 25/100 C-L Dopa and be monitored by study personnel. This visit is completely optional, if participants do not wish to come in to the lab to takes this first dose they can still participate in the study. You should take the carbidopa medication ½ hour before each meal three times per day. You can combine it with a fruit or fruit drink if preferred.

We will call you during the treatment period to see how you are doing and if you may have possible side-effects. You should also call us if you experience difficulties on the medications.

_____(initials) I discussed participating in the optional observation during visit 2 to take the first dose of carbidopa/levodopa and I agree to participate.

_____(initials) I discussed participating in the optional observation during visit 2 to take the first dose of carbidopa/levodopa and I do not want to participate.

It is important that if you are in this study that you call the study team at your earliest convenience if you experience any unexpected (mild or serious) side effects. If you experience any serious problems that may require immediate attention, please call 911 or go to a nearby emergency room.

Some assessments throughout this protocol may be performed remotely using Zoom for Health at U of M or over a telephone call.

Limited clinical test day prior to starting Sinemet (Visit 2)

A selected number of tests from Visit 1 screening day will be repeated on this clinical visit.

Follow-up clinical test day while taking Sinemet (Visit 3)

Most clinical test components from Visit 1 screening day will be repeated on this clinical visit.

OPTIONAL: Follow-up imaging day (Part of Visit 3)

The MRI and FDG PET scans will be repeated as part of the follow-up visit. The single dopamine PE2I PET scan may occur also at the end of the study (and treatment).

As a subject participating in this research study, you have certain responsibilities that may apply to this study, such as ensuring that you arrive at all of your scheduled appointments, take your study medication as directed, and report any adverse reactions you may have during the study.

4.2 How much of my time will be needed to take part in this study?

Most of the testing for this study takes place at the Functional Neuroimaging, Cognitive and Mobility Laboratory located at Domino's Farms, Suite B1000 and Suite B1200 in Ann Arbor. MR and PET imaging will take place at the University of Michigan Health System Hospital (University Hospital).

The baseline clinical testing day (Visit 1) will require 4-6 hours at the Functional Neuroimaging, Cognitive and Mobility Laboratory, as well as an (optional) MRI scan that will take approximately 75 minutes and an (optional) FDG PET scan that will take approximately 45 minutes at the University Hospital. An optional brain dopamine PE2I PET scan may also be performed. The MRI and/or PET scans may occur on the same day as the clinical testing but will more likely require a separate visit or visits. The baseline clinical visit day will take approximately 1-2 days.

Following this, subjects will be in the medication phase of the study and be taking carbidopa pre-treatment medication during days 1-3 prior to returning to the lab on day 4 for a repeat but limited clinical test battery. On day 4 subjects will start carbidopa-levodopa (Sinemet) to be taken three times per day while continuing carbidopa.

This study participation will require you to come back for a follow-up visit at day 10 (±3 days), which will contain most clinical testing (4-6 hours), an (optional) MRI (75 minutes), and an (optional) repeat FDG PET scan (45 min). This is Visit 3, and this visit will require 1-2 days.

4.3 When will my participation in the study be over?

Study participation will end after all testing has been completed.

4.4 What will happen with my information and/or biospecimens used in this study?

Your biospecimens and collected information may be shared with National Institute of Health (NIH).

With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

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(s):

There is a **likely** 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.

In **very rare** situations, 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 scan(s):

There is an **infrequent** risk of bruising, bleeding, infection, or soreness associated with intravenous and/or arterial catheter placement during the PET scan, 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 be exposed to radiation from the PET transmission scans, the Dopamine and FDG PET radiotracers.

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 dopamine PET 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 less than 3/10th of this amount.

Exposure to an (optional) DXA scan will be less than 0.1% of annual background radiation. 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

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 or DXA studies 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.

You are given the option to come into the lab for your first dosage of C-L Dopa. This optional visit would be 60-120 min in length where you will take your 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 you are 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. You will receive three days of carbidopa monotherapy.

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

There is an **infrequent** risk of sleepiness or nasal congestion after taking a C-L Dopa pill.

You are given the option to come into the lab for your first dosage of C-L Dopa. This optional visit would be 60-120 min in length where you will take your 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.

You 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 you will take your first dose of 25/100 C-L Dopa and be monitored by study personnel.

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

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

Please lay down until the symptoms pass.

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

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. However, others may benefit from the knowledge gained from this study. Participation in this study may provide important new insights into better treatment options for walking disturbances and balance problems affecting older adults. This may ultimately result in development of pharmaceuticals for these issues.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?

You do not have to participate in this study. You may drop out of the study at any time without penalty.

This study will involve investigational treatments for walking disturbances and balance problems affecting older adults. Please note that there may be other experimental treatments. Your doctor can tell you more about these other treatments, their risks and their possible benefits. You should have this discussion about the risks and benefits or other alternatives prior to making your decision about whether or not you wish to take part in this research study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 “Contact Information”.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

There is no harm in leaving the study before it is finished. However, if you decide to leave the study during some of the procedures, we may ask you to stay until it is deemed safe to leave. Please notify the study investigators immediately if you decide to leave the study so we can determine that is safe for you to stop taking the medication.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researcher’s telephone number listed in Section 10.1.

If you are injured or in the event of a medical emergency, dial 911 or visit your nearest Emergency Room. If you believe the study has made you sick or caused you injury, contact one of the people listed in section 10 of this document (Contact Information). If taking part in the study makes you sick or causes you injury, you or your

insurance provider will be billed for all costs of treatment as the study does not provide compensation for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

There is the potential that the research evaluations may have caused you anxiety or worries about your health. You may need or want to investigate these health concerns further for an appropriate diagnosis. However, any procedures or tests, including the MRI scan, should be obtained separately if your doctor believes that you require those tests for your diagnosis. These additional studies and appropriate treatment, if necessary, will not be paid for by this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $50 for each completed MRI scan. You will receive $50 for each completed FDG PET scan and dopamine 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.

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.

8.3 Who could profit or financially benefit from the study results?

Researchers conducting the study, the University of Michigan, and other researchers that obtain your de-identified samples and clinical data will not profit directly from them. However, if research using your samples leads to new tests, drugs, or other commercial products as a result of knowledge gained using your samples, you will not share in any profits.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?

Your research records will be stored in a secure location to which only the investigators have access. All research records will be stored under code numbers, without attached names or other identifying information. The "key" linking these records to subject names will be stored in a separate, locked (electronic) file. The storage location for the MRI and PET brain scans will be in protected computer files that are accessible only to investigators within the University who are participating in the research project. If the radiologist orders any X-rays for MRI screening purposes, the order requisition and test results may become part of your regular medical record.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institutes of Health (NIH) which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law of harm to self or others.

The Certificate of Confidentiality will not be used to prevent disclosure for any purpose you have consented to in this informed consent document.

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)

- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, Social Security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan

"Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

9.5 Will I be contacted for other studies?

No, unless you indicate by initialing below that you may be contacted by researchers at the University of Michigan for studies for which you may eligible. If you agree to be contacted for other studies, we will keep your name and contact information in a separate password-protected database.

_____ (initials) I agree to be contacted about other research studies for which I may qualify. If I cancel my permission for this study, I will not be contacted for other studies.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Nicolaas Bohnen, MD, PhD
Mailing Address: UM Functional Neuroimaging, Cognitive, and Mobility Laboratory
24 Frank Lloyd Wright Dr., Suite B1000, Box #362, Ann Arbor MI 48105
Telephone: 734-998-8400

Study Coordinator: Miriam Bohnen
Mailing Address: UM Functional Neuroimaging, Cognitive, and Mobility Laboratory
24 Frank Lloyd Wright Dr., Suite B1000, Box #362, Ann Arbor MI 48105
Telephone: 1-877-998-1098

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies, include the appropriate calling codes.)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent for Participating in Genetic Sub-Study Testing

I understand that by signing below, I am also voluntarily agreeing to participate in the genetic testing aspects of this study. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens/data. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep my specimens/data for future research.

_____ No, I do not agree to let the study team keep my specimens/data for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____