Amyloidopathy, Cholinopathy, Dopamine Responsiveness and Freezing of Gait in PD

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Statistical Analysis Plan

In this proposal, the investigators present data suggesting that L-DOPA refractory freezing of gait (FoG) is associated with comorbid cholinopathy and amyloidopathy in Parkinson's disease.

The investigators propose to test the novel **hypothesis** that comorbid amyloidopathy may be a possible mechanistic factor underlying the poor response of FoG to dopaminergic therapy in advancing PD. In contrast, isolated cholinopathy (without amyloidopathy) would be expected to be associated with preserved dopamine responsiveness of FoG.

For this purpose, the investigators propose to perform detailed motor, including FoG, testing in PD patients "on" and "off" their dopaminergic medications and relate this to dopaminergic 11C- DTBZ, vesicular acetylcholine transporter 18F-FEOBV and amyloid 11C-PIB brain PET imaging in PD subjects with and without FoG.

Our statistical approach is to run a series of hierarchical ordinal logistic regression models, predicting freezing type (L-DOPA responsive, diminished L-DOPA responsiveness, and L-DOPA non-responsive) from dopaminergic (DTBZ), cholinergic (FEOVB), and amyloid (PIB) PET distribution volume ratio (DVR) of the striatum. The null model includes in it striatal DTBZ only. The FEOVB model adds a term for striatal cholinergic innervation. The interaction model, that most directly tests our comorbidity hypothesis adds an interaction term between FEOVB and PIB PET. Goodness of fit for the FEOVB model is compared against the null model, and the interaction model is compared against the FEOVB model.

Furthermore, based on recent clinical observations that serotoninergic drugs, like the popular anti-depressant SSRI drugs, are associated with significantly lower build-up of beta-amyloid plaques in the elderly population, and based on the investigators' subsequent observation of an intriguing inverse relationship between -amyloid plaque deposition and striatal serotoninergic terminal in PD, the investigators propose to perform an exploratory sub-study to test an exploratory hypothesis that PD subjects with FoG will exhibit not only higher striatal -amyloid but also lower striatal serotoninergic innervation (as determined by 11C-DASB serotonin PET imaging) compared to PD subjects without FoG. Due to a large number of participants taking anti-depressant drugs the number of participants with additional 11C-DASB PET scans was too small to perform a statistical analysis

Protocol Synopsis

Freezing of gait (FoG) becomes more prevalent in advanced Parkinson's disease (PD) and afflicts approximately half of all patients with PD. With disease progression, FoG usually becomes a major contributor to loss of mobility, falls, and decreased quality of life. Elucidation of possible mechanisms underlying dopamine non-responsiveness of gait disturbances in PD, therefore, has high clinical importance.

The premise of this project is that our preliminary data show that 'uncomplicated' PD—when still in a stage of predominant nigrostriatal dopaminergic denervation—does not have to be a very disabling disease per se. As a matter of fact, we found that gait speed in patients with predominant nigrostriatal degeneration is not significantly slower from healthy non-PD control subjects. However, our preliminary data show also that the emergence of non-dopaminergic extra-nigral pathologies in PD may result in significant disability due to FoG. If the association of amyloidopathy and dopamine refractoriness of FoG can be confirmed then this would provide a window for targeted interventions as these at risk-individuals could receive anti-amyloid targeted therapies that might prevent or improve disability in PD. A particular advantage of PD is that the low but symptomatic level of amyloidopathy provides a unique window of opportunity to intervene relatively early in the amyloid cascade. Serotonergic drugs that are already on the market may deserve further study as potential novel anti-amyloid investigational therapeutics, especially when administered very early in the disease course and well before the development of motor complications in PD. Such early and targeted anti-amyloid investigational therapy will critically depend on appropriate biomarker identification of subjects who are at risk of b-amyloid deposition.

The overarching goal of this study is to investigate the relationship between FoG and extranigral pathologies in PD and to test the hypothesis that comorbid amyloidopathy is a mechanistic factor underlying the poor response of FoG to dopaminergic therapy in advancing PD whereas FoG in cholinopathy alone is associated with preserved dopamine responsiveness. To achieve the goals of this project, patients with PD with and without FoG will undergo detailed FoG and gait motor testing in PD patients "on" and "off" their dopaminergic medication. Findings will be related to β-amyloid 11C-PIB, vesicular acetylcholine transporter 18FFEOBV, VMAT2 11C-DTBZ and, in a subset, SERT 11C-DASB brain PET imaging data. Interested subjects may also participate in an additional biomechanical/EMG of FoG and ocular function studies, to be performed on another day.

UNIVERSITY OF MICHIGAN

CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title:

Amyloidopathy, cholinopathy, dopamine responsiveness and freezing of gait in PD

1.2 Company or agency sponsoring the study:

U.S. Department of Veterans Affairs—Merit Review Award

1.3 Names, degrees, and affiliations of the researchers conducting the study:

Principal Investigator: Nicolaas Bohnen, MD, PhD, PI, Professor, Department of Radiology, University of Michigan

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Advancing Parkinson's disease is associated with disabling balance and gait problems, including freezing of gait in about half of patients. Freezing of gait is when you feel as though your feet are being glued to the floor and therefore, experience difficulties making movements. Several changes occur in the brains of Parkinson's disease patients. The hallmark change is a loss of a neurotransmitter ("chemical messenger" between brain cells) called dopamine. To alleviate Parkinson's disease symptoms, doctors prescribe dopamine replacement therapy, for example Sinemet (levodopa). Although effective for some of the symptoms, it typically does not sufficiently alleviate balance and gait problems, such as freezing of gait. This study focuses on other changes in the brain that occur in Parkinson's disease that may contribute to freezing of gait. In particular, we will be looking at other neurotransmitters, called acetylcholine and serotonin, as well as the presence of amyloid plaques (buildups of proteins between nerve cells that negatively affect the function of these cells). In previous studies, we have shown that a loss of acetylcholine and/or the presence of these amyloid plaques are related to incidences of freezing of gait. Also, serotonin appears to be related to amyloid plaques, and perhaps freezing of gait. In this study, we will take a closer look at these findings.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

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?

People with Parkinson's disease can participate in this study. All participants need to be over the age of 50 years. Participants should be willing and able to comply with study requirements. Men and women may participate. Subjects with other neurological, psychiatric, or unstable medical conditions may be excluded. Subjects taking some medications that might interfere with the research may also be excluded. In addition, subjects 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 having a pacemaker, having metal fragment in their body, or severe claustrophobia, or any contraindication of PET imaging such as previous participation in research procedures involving ionizing radiation may not be eligible to participate in this study

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

A total of 80 people with Parkinson's disease are expected to participate in this study.

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. To obtain an accurate assessment that is not affected by dopaminergic medications, some of the motor testing and the neurologic examination rating will be performed in a dopaminergic "off" state; i.e. you will be asked to withhold taking certain dopaminergic medications, such as Sinemet (levodopa) or Mirapex (pramipexole) on the morning of your testing at our testing site at Domino's Farms. You also need to withhold your dopaminergic medications prior to one of the PET scans as well.

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 medication, screen your cognitive abilities, and take a blood and/or saliva sample. We will also ask questions to see if you're eligible to undergo MRI and PET scans. In addition, we will ask you some general demographic and clinical information. Muscle strength will also be assessed with a hand held device and/or the side plank test.

Bone density and body mass assessment: Your bone density and body mass will be quantified using a technique called 'dual X-ray absorptiometry' or more commonly referred to as a DXA scan.

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.

Motor tests: Fine movements of the hands, fingers and feet will be examined by finger and foot tapping devices and a pegboard examination (a timed test where subjects put pegs in holes). We will place small sensors at your wrists, ankles, and around your chest 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. All of these assessments will be performed while you are "off" your dopaminergic medications (see above). After motor testing has completed you can take your anti-parkinsonian medication. Approximately one hour after taking your medication, selected elements of this test battery will be repeated.

Freezing of gait provocation protocol: The way that you move will be assessed during walking, turning, stopping, and rising from a chair. These tasks are meant to provoke freezing of gait. As mentioned above, freezing of gait is when you feel as though your feet are being glued to the floor and therefore, you may experience difficulties making movements. During the tasks, you will wear the same small sensors at your wrists, ankles, and around your chest to measure your body movements. In addition, a video of you performing the freezing of gait protocol will be recorded and reviewed by movement disorders specialist(s) to identify incidences of freezing of gait.

Please initial below whether you agree to have a video of you performing the freezing of gait protocol recorded.

_____(initials) I discussed the video recording of me performing the freezing of gait protocol that will be used for research purposes and **agree** to participate in the video recording.

_____(initials) I discussed the video recording of me performing the freezing of gait protocol that will be used for research purposes and **do not agree** to participate in the video recording.

Neuropsychological and neurobehavioral tests: The neuropsychological tests are designed to get an overall estimate of your ability to plan and make decisions ('executive functioning'), memory, concentration, and ability to react fast. These functions will be measured with a series of standard pencil and paper tests or computer tests. We will also ask you questions about your mood. Other questions are about sleep and fatigue.

MRI scan: MRI scans allow the investigators to visualize the brain in great 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 a FDA-approved MRI scanner at the Department of Radiology at the University of Michigan Hospital.

PET scans: The PET scans will allow the investigators to "see" the specific marker of acetylcholine and dopamine neurotransmission and amyloid plaques in the brain. To establish this, in three separate sessions, a radiotracer will be injected into your vein through an IV (intravenous catheter 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 tracer will be injected as you lie on a table, which will move into a hollow machine resembling an X-ray CT (or CAT) scanner. Images of your brain will be obtained over a period of time. 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. For the dopaminergic PET scan, you will be asked to withhold taking your dopaminergic medications, such as Sinemet (levodopa) or Mirapex (pramipexole) on the morning of your testing.

We will ask some subjects to undergo an additional PET scan, which will allow the investigators to "see" the specific marker of serotonin neurotransmission in the brain.

Please initial below whether you agree to undergo an additional (optional) PET scan.

_____(initials) I discussed participating in the PET session and **agree** to participate.

_____(initials) I discussed participating in the PET session and **do not agree** to participate.

Genetic testing: We are interested in investigating whether some genes may affect the clinical disease presentation or the brain. To this end, we are collecting saliva or a blood 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. All samples will be stored or transferred with only a code attached. Research teams will analyze the genetic samples for known variants in the DNA sequence. Once analysis is performed we will break the links between the DNA and your name. Therefore, no one will be able to connect any genetic information we learn about you with your identity. We will not be sharing the genotype results with you.

Diary study: You will be asked to fill out a monthly diary to document any falls or near falls you might have experienced, the circumstances and possible consequences of the falls. You will be asked to send a completed diary by mail to the investigators for each month during a 6-month period. We will contact you on a regular basis to check to see how you are doing.

Assessment of daily life activity: You will be asked to wear an activity monitor for a week 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 were 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 session: If you can make the time commitment, you may be asked to return to the laboratory (on a different day) to repeat the freezing of gait provocation protocol and a few walking tasks so that we can measure your muscle activity during these tasks. In addition to the sensors worn to measure how you move, we will place additional sensors on the skin over various muscles of your lower-body to measure how your muscles activate. A video of you performing the freezing of gait protocol will be recorded and reviewed by movement disorders specialist(s) to identify incidences of freezing of gait. This session also includes a test during which you will be wearing video goggles that measure your eye movements while following a dot.

Please initial below whether you agree to participate in the optional session.

_____(initials) I discussed participating in the optional session, which includes the video recording of me performing the freezing of gait protocol only that will be used for research purposes, and **agree** to participate.

_____(initials) I discussed participating in the optional session, which includes the video recording of me performing the freezing of gait protocol only that will be used for research purposes, and **do not agree** to participate.

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 in Ann Arbor. PET and MRI imaging will take place at the University of Michigan Health System hospital. The clinical and behavioral part of the study, including the DXA scan, will require 6-8 hours of testing at the Domino's Farms laboratory. If all the study procedures cannot be completed in one visit, you may be asked to return to complete the procedures or, if possible, to conduct them by phone. The brain imaging part of this study at the University of Michigan Health System hospital will be performed over two or three days, depending on scheduling availability and unforeseen circumstances. The dopamine PET scan will take approximately one hour. The acetylcholine PET scan will take approximately 30 minutes of imaging but there will be a waiting time between the injection of the tracer and the imaging (approximately 3-4 hours) during which time you can do other things. The amyloid scan will take approximately 80 minutes. If you participate in the additional PET scan (serotonin) study, the serotonin scan will take approximately 80 minutes. Scans may finish earlier although you may also be required to be present for a longer time. The MRI scan will take approximately 75 minutes. The fall diary portion of this study will last for six months. For the actigraphy portion of the study, you will be asked to wear the activity monitor for a week. If you participate in the additional freezing of gait provocation protocol with muscle activity assessment, as well as the eye movement test, you will be asked to return to the Functional Neuroimaging, Cognitive and Mobility Laboratory located at Domino's Farms for a session of approximately two hours.

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 the VA Ann Arbor Healthcare System.

With appropriate permissions, your samples 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 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 PET and 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, 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.

In most patients, temporary withdrawal can be accomplished safely on an outpatient basis and may result in inconvenient reduction in functional abilities, but not result in inability to conduct essential activity of daily living. There is an infrequent chance that you may develop "freezing" symptoms, which is caused by stiffening of your muscles making movements more difficult. You may require additional assistance from your caretaker during this time.

Any risk of adverse effects will be minimized by careful supervision of the research staff during the morning after the overnight withdrawal of the dopaminergic medications. You will be instructed to resume taking your dopaminergic medications after the completion of the testing. If the withdrawal of medication is intolerable, you may resume taking medication and withdraw from this study at any time.

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.

There is an infrequent risk that the blood sample method may cause minor bruising at the injection site. There is a very rare risk for infection. There is a rare risk that you may feel dizzy, lightheaded, or faint after the blood draw.

Blood will be drawn by a certified and experienced research technician who is also trained in blood borne pathogens control. Aseptic techniques will be used in accordance with University of Michigan guidelines. You can lie down if you feel dizzy, lightheaded or faint after the blood draw.

There is a likely risk of experiencing some pressure when pushing against the handheld dynamometer for the muscle strength assessment.

The pressure will disappear if you release the dynamometer.

Risks associated with the DXA scan are described below under the header “PET scans”.

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.

Given that the freezing of gait provocation protocol is meant to provoke freezing (i.e., stiffening of your muscles making movements more difficult) during walking and turning tasks, it is likely that you may experience such freezing.

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 of breach of confidentiality, which may affect privacy, self-esteem, social standing, employability, and insurability, with regard to the video of you performing the freezing of gait protocol.

Section 9.1 will provide more detailed information on how we protect your privacy. The original video recorded on video camera will be stored in a locked cabinet in the investigator’s locked office. After review by investigators, the video will be transferred to a secure server, which is only accessible to personnel involved in the study. The original copy on the recording device will be deleted.

There is a very rare risk that the sensors to measure overall movement and balance and those to measure muscle activity 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.

If you agree to participate in the optional session (i.e., freezing of gait provocation protocol; eye movement measurement), there is an infrequent risk that the EMG sensors that you will wear during this session will cause a skin irritation due to the skin preparation procedures (i.e., shaving very small area in location of sensor placement, if excessive hair prevents proper adhesion of sensor to skin; light abrasion (to remove dead skin cells) and cleaning of skin with an alcohol pad to lower skin impedance, and therefore increase the signal quality), the sensors' gel, and the adhesive on the sensors and tape used to secure the wires leading to the sensors.

If you develop a skin irritation, EMG will not be used in future testing sessions.

If you agree to participate in the optional session (i.e., freezing of gait provocation protocol; eye movement measurement), 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 will be exposed to radiation from the DXA scan, the PET/CT transmission scans and the PET tracers [^{11}C]DTBZ, [^{18}F]FEOBV, [^{11}C]PIB, and in a subset of subjects the additional [^{11}C]-DASB PET scan.

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. Radiation you will be exposed to from this research project will be approximately 11.6 mSv for the DTBZ, FEOBV and PIB 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 18.5 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 three tracers and the DXA scan (0.0159 mSv) combined is less than 2/5th of this amount. Persons who will also complete the additional DASB PET scan will receive a total of 15.5 mSv radiation, and in the rare event one of the scans will need to be repeated, a total maximum exposure of 22.3 mSv. This is slightly more than 2/5th of the allowed annual amount for radiation workers.

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 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 neurotransmission in the brain and 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*

Fall diary study:

There is a very rare risk that confidentiality will be breached when the diary, fall-event information sheet, or the activity questionnaire are returned to us by mail.

You will be asked not to write your name on neither the envelope nor on any of these test materials. We will write a code on the test materials that will allow us to connect these test materials with your name. This code is securely monitored and behind lock and key, only accessible by the principal investigator of this study (see also 9.1).

Assessment of daily life activity:

There is a very rare risk of the movement monitor (Actigraph) detaching, which may result in a trip during the daily life monitoring of overall movement (actigraphy). It should be noted that the Actigraph only measures overall movement. It does not 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.

You will receive instruction for proper attachment of the Actigraph.

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. Participation in this study may provide important new insights into better treatment options of Parkinson's disease. This may ultimately result in development of pharmaceuticals for these diseases.

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. OTHER OPTIONS

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. Taking part in the research is not a treatment for Parkinson's disease.

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" (below).

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.

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 researchers' number listed in section 10.1.

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.

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 and PET 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.

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.

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 will have to arrange for treatment on your own, as the study will not provide medical treatment or provide any compensation to you. You or your insurance provider will be billed for all costs of treatment for sickness or injury caused by the study. It is possible that your insurance will not cover these costs.

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

You will receive $350 for completion of the brain imaging procedures ($100 per completed PET scan and $50 for the MRI scan). You will receive an additional $100 if you complete the additional PET scan (SERT ^{11}C-DASB). Payment for completion of the detailed clinical, neuropsychological, and motor testing will be $100. Upon completion of the diary study, you will receive $25. Upon return of the ActiGraph, you will receive $25. If you participate in the EMG and VNG study, you will receive an additional $50. Compensation for your time and effort after full study completion may total a maximum of $650.

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. 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. You will need to provide receipts to the study team before expenses can be reimbursed. We will reimburse to a maximum of $200 for lodging. 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?

Neither the researchers conducting the study nor the University of Michigan will have financial profit from the study results.

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 your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

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 locations 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 or a urine pregnancy test is ordered, the order requisition and test results may become part of your regular medical record. Your research records will also be stored at the US Department of Veterans Affairs (VA) since this is a VA-sponsored study, and thus required.

9.2 What information 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. Information 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
- Billing information
- Demographic information
- Personal information
- Other information

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 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.

At the conclusion of the study, your research records may be used for future research purposes.

A description of this study will be available on www.ClinicalTrials.gov, a database of publicly and privately supported clinical studies of human participants. 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.

9.3 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. If I do participate in another study, data obtained in this study may also be used for that study.

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

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).

9.5 When does my permission 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).

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
Study Coordinator: Christine Minderovic
Mailing Address: UM Functional Neuroimaging, Cognitive, and Mobility Laboratory
24 Frank Lloyd Wright Drive
Suite B1000, Box #362
Ann Arbor, MI 48105
Telephone: 734-998-8400

You may also express a 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: US Country Code: 001)
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.

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.

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.

Legal Name: _____

Title: _____

Signature: _____

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