Cholinergic Functions and Modulation of the Cingulo-opercular Alertness Network in LBD

NCT04817891

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UNIVERSITY OF MICHIGAN CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title:

Cholinergic functions and modulation of the cingulo-opercular alertness network in LBD

Company or agency sponsoring the study:

National Institute of Health/National Institute on Aging

Names, degrees, and affiliations of the principal investigator:

Benjamin Hampstead, Ph.D., ABPP/CN, Department of Psychiatry, University of Michigan

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 a device that produces brain stimulation called High Definition Transcranial Direct Current Stimulation (HD-tDCS) in small numbers of people to learn about its effect on cognitive abilities as a treatment for LBD. This study will assess through neuropsychological tests and brain imaging whether 10 sessions of HD-tDCS improves thinking abilities in those with LBD. Your health-related information will be collected 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 include radiation exposure from the PET scan as well as possible discomfort from the HD-tDCS or fMRI scan. More detailed information will be provided later in this document.

This study may offer some benefit to you now or others in the future by potentially experiencing some improvement in your cognitive or thinking abilities by taking part. While you may not receive any personal benefits from being in this study, others may benefit from the knowledge gained from this study. In either case, we (i.e., doctors, researchers, scientists) may learn new things that will help others. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be 30 hours over 13 visits. More details on visits are below.

You can decide not to be in this study. Alternatives to joining this study include continuing your current care with your doctor.

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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:

This research study is being done to learn important information about how the brain maintains alertness in Lewy Body Dementia (LBD). Secondarily, there is evidence that cognitive abilities in those with LBD respond well to drug based treatment, therefore this study looks to learn about how cognitive abilities respond to weak electrical stimulation on brain functioning in those with LBD. We will use brain imaging to determine an individualized dosage. We will use additional brain imaging, tests, and questionnaires to determine whether these treatments changed any cognitive abilities.

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?

Inclusion criteria:

- Diagnosis of LBD with cognitive fluctuations
- 50-90 years of age
- On stable doses of cholinesterase inhibitors (i.e., at least 4 weeks)
- Participants must be MRI compatible (via the American College of Radiology guideline), criteria that also apply for High Definition transcranial Direct Current Stimulation (HD-tDCS; e.g., absence of metallic or electronic implants)

Exclusion criteria:

- Participants who cannot receive MR imaging
- Participants who cannot receive HD-tDCS (for example, but not limited to, those with a pacemaker or brain aneurysm)
- Neurological conditions such as epilepsy, stroke, multiple sclerosis, or moderate to severe brain injury
- History of severe or untreated psychiatric illness such as schizophrenia or bipolar disorder, or those with unmanaged depression or anxiety
- Sensory impairments that significantly limit one’s ability to see or hear
- A significant history of recent alcohol or drug dependence
- Previous major radiation exposure
- Pregnancy
- Evidence of large vessel stroke or mass lesion on MRI
- Use of anti-cholinergic or neuroleptic drugs
- Evidence of atypical parkinsonism on neurological exam.

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

The study will enroll a total of up to 18 participants at the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

General Procedures

You will take part in 13 visits in which you will complete memory and thinking testing, HD-tDCS, magnetic resonance imaging (MRI) and/or Functional Near Infrared Spectroscopy (fNIRS), and Positron Emission Tomography (PET) scans:

- After consenting, you will complete the neurological examination, neuropsychological testing, motor examination, and baseline outcome measures.
    - You will be asked to complete some "paper and pencil" activities, some of which are done by speaking to one another while others are done on paper. We also use a number of computerized tests, as well as certain physical tests that will assess balance and gait.
- Neuroimaging (MRI and/or fNIRS, PET) will be performed on a second visit day. The fMRI/fNIRS portion will take approximately 2 hours, and the PET scan will take approximately 4 hours.
    - Functional Magnetic Resonance Imaging (fMRI): You will lie on a bed that is moved into the scanner. Pictures of your brain will be taken to show its structure as well as its function (for example, what parts of the brain are "active" and "communicating" with each other). There are no injections required. You will be interacting with trained research assistant(s), and MRI technician(s) during these sessions. You will receive up to two MRI scans during this study.
    - We may ask you to participate in sessions that utilize Functional Near Infrared Spectroscopy (fNIRS), which is a brain monitoring technique that allows us to evaluate brain functioning via scalp sensors that use LED or lasers to detect changes in blood oxygen levels in parts of the brain. In an fNIRS session, there may be times that we ask you to "rest" (e.g., have your eyes open staring at an object) or we may ask you to do "tasks" (e.g., different memory tasks). The fNIRS can also be worn as a "backpack" which allows us to measure brain functioning during tasks (e.g., making a pot of coffee, moving through one's environment. The typical session will include: 1) Placing a cap/headgear that contain fNIRS sensors on your scalp 2) Ensuring the sensors are in good contact with your scalp (e.g., moving your hair to ensure the sensors are not blocked from the scalp) 3) "Resting" or performing tasks that involve your thinking abilities 4) Removing the fNIRS sensors.
    - Positron Emission Tomography (PET) Scans: You will be injected with a tracer that will "light up" certain things in the brain that will help the investigators better understand LBD. Three hours after the injection, you will receive the 30-minute PET scan. Similar to the fMRI, you will lie on a bed and try and be as still as you can while receiving the scan.
    - An individualized brain model of the electrical field will be created in the days following the imaging.
- You will take part in 3-5 sessions of HD-tDCS per week for a total of 10 sessions. You will have 4-5 sessions of HD-tDCS during the first week of stimulation. After the first week, we can decrease to 3-5 sessions per week. Stimulation itself will take 20 minutes, however with setup, the sessions will take approximately 60 minutes depending on set-up time.
    - At the start of each session, study staff will measure your head and place electrodes at the appropriate locations using head netting or a cap to hold the electrodes in place.

- Each holder is filled with approximately 2 teaspoons of conductive gel, the electrode placed, and then connected to the HD-tDCS unit. **For this reason, we ask that you do not wear hair products or gels on the day of stimulation as this can prevent stimulation from having an effect.**
- The study team member will then measure impedance levels and adjust electrodes (e.g., moving hair to ensure maximum scalp exposure under the electrode) as necessary.
- Stimulation will be gradually ramped up to full intensity during a 30 second period, followed by 20 minutes of stimulation at the full intensity, and finally a 30 second ramp down period.
- This ramp up/down period gradually introduces/withdraws the current and provides time for you to get used to the physical sensations of change in the electrical current.
- You will then complete a questionnaire about sensations felt during stimulation. Some of these measures let us monitor safety.

- You will undergo the final HD-tDCS session and will then complete the second fMRI scan.
- You will complete the follow-up examination (clinical examination, motor testing, and neuropsychological testing) on a separate visit day after the final HD-tDCS session and fMRI.

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

- Session 1: The initial visit will consist of a clinical examination, neuropsychological testing, motor testing, and questionnaires. It will take about **5 hours**.
- Session 2: This visit is for the fMRI (and/or fNIRS) and PET imaging. The fMRI portion will last approximately 2 hours. If applicable, the fNIRS sessions will last 60 to 120 minutes. The PET scan will last about 4 hours. Including travel time and check in, the day will last about **7 hours**.
- Session 3-11: HD-tDCS: These 9 session of HD-tDCS will take about **1 hour each**.
- Session 12: This session is the HD-tDCS and fMRI and/or fNIRS. The final HD-tDCS session will take 1 hour and the fMRI scan will take about 2 hours. If applicable, the fNIRS session will last 60 to 120 minutes. Including travel time, this session will take a total of up to 5 **hours.**
- Session 13: This is the follow up examination. This final visit will consist of a clinical examination, neuropsychological testing, motor testing and questionnaires. It will take about **5 hours**.

Study Event Table

Session	Activity	Estimated Duration	Location	Payment
Visit 1: Baseline Evaluation	Clinical/Neurological Examination Pencil and Paper Tasks Computerized Tests Motor Tests	about 5 hours	Domino's Farms, Lobby B, Suite 1200 24 Frank Lloyd Wright Dr., Ann Arbor, MI 48106	$25
Visit 2: fMRI* and PET Imaging Day	fMRI Scans*	2 hours (1 hour in the scanner)	Functional MRI Laboratory 2360 Bonisteel Blvd. Ann Arbor, MI 48109 Parking Lot: NC16	$25
	PET Scan	4 hours (30 minutes in the scanner)	PET suite – Radiology Reception – C, Floor B1 1500 E Medical Center Drive Ann Arbor MI 48109	$50
Visits 3-11: tDCS Session 1-9 (9 days over 2-3 weeks)	HD-tDCS	1.5 hours/session	RP-CNBI, 4251 Plymouth Road, Arbor Lakes Building 1 - Suite 2400, Ann Arbor, MI 48105	$90 for 9 sessions ($10/session)
Visit 12: tDCS Session 10 and fMRI* Day	HD-tDCS	about 1.5 hours	RP-CNBI, 4251 Plymouth Road, Arbor Lakes Building 1 - Suite 2400Ann Arbor, MI 48105	$10
	fMRI Scan*	about 2 hours	Functional MRI Laboratory 2360 Bonisteel Blvd. Ann Arbor, MI 48109 Parking Lot: NC16	$25
Visit 13: Follow-Up Evaluation	Clinical/Neurological Examination Pencil and Paper Task Computerized Tests Motor Tests	about 5 hours	Domino's Farms, Lobby B, Suite 1200 24 Frank Lloyd Wright Dr., Ann Arbor, MI 48106	$25
			TOTAL	**$250**

*Study PI may choose to substitute fNIRS scan for fMRI scan for visits 2 and 12; Estimated Duration: 60-120 minutes; Location: 2101 4251 Plymouth Road, Arbor Lakes Building 1 - Suite 2400, Ann Abor MI 48105; Payment: $25 per fNIRS scan.

4.3 When will my participation in the study be over?

Your participation in the study will be over once you have completed all the necessary sessions (13 visits). Of course, you are free to withdraw from the study at any time.

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, and reporting any adverse reactions you may have during the study.

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4.4 What will happen with my information used in this study?

Your collected information may be shared with National Institutes of Health/National Institute on Aging and NIH approved federal repositories such as NCRAD. This is to reduce participant burden and to prevent duplication of research staff efforts.

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

Your identifiable private information will 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 are:

Neuropsychological testing: These procedures are entirely non-invasive and painless. It is possible that you will become frustrated during these tasks or while completing questions about your mood or past emotional events. If this occurs, you may request a break from the procedure(s). If you become so upset that you cannot continue, you may ask to be withdrawn from this study.

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.

Magnetic Resonance Imaging (MRI): MRI is a very common test used by physicians. Its only known risk is that it can cause a metal implant or foreign body in the eye, brain or other organ (including pacemakers, aneurysm clips, shrapnel, metal fragments, orthopedic pins, screws, or plates, IUDs, or piercings that you cannot remove) to move, which could cause serious harm and even be fatal. It is very important to know if you have any metal in your body. If there is, you will not be allowed to undergo the MRI scan. If you are unsure whether you have metal in your body (e.g. eyes), you will undergo a standard x-ray prior to MRI scanning to ensure you are eligible for scanning. If this precaution is taken, MRI scanning is safe. A small percentage of people are unable to tolerate MRI scanning because they are claustrophobic (they become uncomfortable in the enclosed space of the scanner). If you have a history of this, you will not participate in this study. If you become uncomfortable while in the scanner, you will be removed at once. We may review your medical history with a family member or close friend to make sure you can undergo MRI.

The Food and Drug Administration (FDA) approved the scanner used in this study for diagnostic purposes. There is no evidence that it is harmful.

The following are potential risks for MRI:

- 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 during the study if needed, 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. External metal objects in contact with your skin could also heat up, causing local skin burns. We require you to remove all jewelry for this reason. 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.
- Although your MRI is for research only and will not be “read” by a radiologist, it could potentially 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. A physician is available by page to consult and review MRI images if needed by the study. All studies are conducted by experienced radiology technologists at the fMRI laboratory.
- If you believe there is any possibility of having metal in your body, an X-Ray can be performed to verify this. There will be no charge to you for this procedure.
- Due to the investigational nature of this study, there may be risks, discomforts or side effects that are not yet known.
- A copy of your MRI scan may be sent to collaborators in order to develop models that show how much electrical current actually reached your brain. Scans will include only your study identification number. They will not include any personal identifiers. Scans will be transferred using a secure process that complies with University of Michigan regulations. Our collaborators will only use these scans while they are developing the electrical current models. They will not keep any data.
- There are two potential risks to confidentiality for the MRI data.
    - First, the date that the scans were performed may be embedded in the scans. This date is considered a type of identifiable information. However, only your participant number (e.g., MM001) will be used to identify your brain scans and the appointment is scheduled under the study leaders (Dr. Bohnen or Dr. Hampstead). These steps make it very unlikely that anyone could identify you.
    - Second, it is theoretically possible that some type of biometric data (e.g., the shape of your head or brain) could somehow be used to identify you. This is also very unlikely to result in your identification. To better protect the private nature of your research information, the results from the behavioral, MRI, PET, and HD-tDCS will not be included in your medical record. These research results will be kept only in a research record. However, we may share the results of these tests

with your primary doctors (e.g. neurologists, psychiatrist, psychologist) if it is deemed necessary to improve your medical care.

Functional Near Infrared spectroscopy (fNIRS): The only known risks of fNRIS are associated with damage to the eye or skin following prolonged exposure to bright lights. The software that controls the fNRIS unit has imposed limits on the maximum allowable intensity in order to minimize risk. Because of this, there is little possibility of injury when following the safety guidelines. Additionally, the unit will be turned off should you report discomfort or significant feeling of heating/burning.

High Definition Transcranial Direct Current Stimulation (HD-tDCS): HD-tDCS is an investigational device. It has been used in thousands of individuals and laboratories all over the world. The available evidence suggests that it is safe. However, it is investigational in nature, which means that we are doing these studies to learn more about HD-tDCS.

The most common side effects associated with HD-tDCS based on the available scientific data are: Sensations under the electrode: These sensations usually stop shortly after HD-tDCS begins but can sometimes continue throughout and for a brief period after HD-tDCS.

- Mild tingling
- Light itching
- Slight burning sensation
- Discomfort

Effects reported that occur ONLY during HD-tDCS:

- Visual sensation during switching on and off the stimulation

Other effects that can occur both during and after HD-tDCS include:

- Fatigue
- Skin redness
- Headache
- Changes in concentration, memory, or other cognitive abilities. This is partially what we will be testing.

Additionally, the following rare side effects have been described in previous studies that used HD-tDCS:

- Nausea
- Nervousness
- It is also possible that the electric current can cause a burn on your skin. This is unlikely because we are using a smaller dose than what is known to cause burns and because we use gel to reduce electrical resistance that leads to burns.
- A shock-like sensation at the initiation of HD-tDCS was reported in one participant.
- Changes in the activity of the prefrontal region (front of your head) have the potential to induce sudden changes in your mood. Hypomania has been reported in a few patients receiving HD-tDCS for bipolar disorder and depression but never in normal controls. Subjects with a history of bipolar disorder may be excluded from the study. We will not be "targeting" this part of your brain, so it is unlikely that such changes would occur.

At this time, HD-tDCS has never been reported to cause a seizure in any patient population. Seizures are, however, theoretically possible and a seizure plan is in place for such an unlikely event. Importantly, the majority of the above side effects have been also reported in association with sham (fake) HD-tDCS, even with similar

rates. The table below comes from a review of HD-tDCS safety and shows the percentage of studies reporting these common sensations; Dr. Hampstead's program has validated these results using HD-tDCS. These data suggest that other factors may cause these sensations, such as your expectations or the pressure of head straps or caps.

Sensation	**Real HD-tDCS**	**Fake HD-tDCS**
Itching	39.3%	32.9%
Tingling	22.2%	18.3%
Headache	14.8%	16.2%
Burning	8.7%	16.2%
Discomfort	10.4%	13.4%

Due to the investigational nature of this study, there may be risks, discomforts or side effects that are not yet known.

The researchers will try to minimize these risks by:

- Ensuring patients are fully informed of the risks during the current session.
- Adhering to best-practice standards for cognitive/emotional testing, fMRI, and HD-tDCS.

PET/CT scanning: PET/CT scanning is associated with several risks, as follows:

Intravenous line (IV) for radiotracer injections: 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. Subjects might feel dizzy or lightheaded or may rarely even faint when the tube is put in or taken out. The risk of these side effects is minimized by using highly trained personnel.

Low-level Radiation Exposure: During the course of this study, subjects will be exposed to radiation from one radioactive drug used for PET imaging studies of the human brain, with the names [18F]FEOBV. As part of each of this PET scans, you will also have a CT scan of your head. The biological effect of radiation exposures is measured using the "effective dose", which is a measure of whole body radiation exposure. Effective dose is measured in units called 'milli-Sieverts' (mSv) of radiation exposure. The total amount of radiation you will be exposed to in this portion of the research study will result in a total effective dose less than 13.7 mSv.

The effects on your body of this radiation exposure will be added to your overall life-time radiation risk. Your life-time radiation risk includes the background radiation you are exposed to naturally like everyone else living on this planet, which is on the average 3.0 mSv per year. The radiation you will be exposed to in this study is about 3.3 times the yearly background radiation. In terms of radiation a person may get exposed to during medical care, the amount you will receive in this study will be less than 1.2 times the amount of radiation received in a CT scan of the chest, which is about 8 mSv. The Federal Government requires that the amount of radiation exposure of radiation workers does not exceed 50 mSv per year; the radiation you will be exposed to in this study is about one-fifth of that amount. Your life-time 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. The risk from radiation exposure of this amount is considered to be similar to other every day risks, such as driving a car.

No PET studies will be performed on pregnant, nursing, or potentially pregnant women, as determined by pregnancy testing within 48 hours prior to PET the scanning session. You must not plan on getting pregnant while participating in this research project.

Risks Associated with [18F]FEOBV PET scans: The use of 18F-FEOBV is considered to be generally safe and effective as approved by the University of Michigan Radioactive Drug Research Committee in accordance with Food and Drug Administration regulations (21 CFR 361.1). Adverse reactions to FEOBV have not been reported. However, the possibility exists for a rare reaction to any of the drugs or procedures to which the participant will be exposed.

Certified staff will be in attendance at all times during the study and an emergency cart will be in close proximity. Other physical risks involve possible muscle aches from lying still. 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.

Questionnaires: You will be asked to complete several questionnaires at each visit. Although each questionnaire is not stressful when answered alone, completing multiple surveys in a row may lead to a low level of mental fatigue. This study involves answering numerous questionnaires. Some of the questions may make you uncomfortable or cause a sense of unease. You may skip answering any of these questions. As the study team may not review the answers to your surveys immediately, please ask the study team for assistance if you would like a referral for receiving support.

The researchers will try to minimize these risks as described above.

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?

The goal of the study is to investigate methods for improving cognitive abilities in those who are experiencing thinking problems. Therefore, you may experience some improvement in your abilities by taking part. The results of the study may provide information that could eventually help others. While you may not receive any personal benefits from being in this study, others may benefit from the knowledge gained from this study. In either case, we (i.e., doctors, researchers, scientists) may learn new things that will help others.

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?

Cholinesterase inhibitors are the only approved drug for cognitive impairment, and there are no other alternative forms of treatment. Your participation is voluntary, and you have the right to refuse to be in this study. You can

stop at any time after giving your consent. This decision will not affect in any way your current or future medical care or any other benefits to which you are otherwise entitled. The study investigator and/or sponsor may stop you from taking part in this study at any time if they decide it is in your best interest or if you do not follow study instructions. We will give you a copy of this consent form to keep.

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?

No, you are able to leave the study at any time.

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.

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.

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.

We are taking every measure to ensure your health and safety amid the COVID-19 global pandemic. We have reduced the number of people in our office, the number of people you will work with, require personal protective equipment like masks, and have developed a thorough cleaning policy. However, COVID-19 is a general public health concern and you are at risk anytime you leave your home. Therefore, agreeing to take part in the study at this time comes with the potential risk of exposure. We will maintain a contact tracing log so that we can inform you (or our team) if someone becomes infected and are open to other suggestions about how to minimize risk.

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

You will be paid $25 per fMRI and/or fNIRS scanning (2 sessions), $25 for the Neurological examinations (2 sessions), $10 for each HD-tDCS session (10 sessions), and $50 for the PET scan as incentive, for a total of $250. You will receive payment for participation after you have completed all study visits in the form of check. Our study team tracks the number of sessions you have completed and we will use this information to determine the final amount.

In select situations, we may provide you with transportation (e.g., cab service) to and from locations for research related activities (i.e., Domino Farms, University of Michigan Arbor Lakes Building 1, fMRI scanner, PET scanner at the University of Michigan Hospital). We may also offer to reimburse you for travel in your personal car. This reimbursement would be offered only on an as-needed basis.

If necessary, we may also arrange for you to stay in a hotel room during your time in the study. In this case, you may receive reimbursement for meals and other incidental expenses at the standard per diem rate for Ann Arbor, MI (up to $59 per day) for the days you are completing research related activities. We will directly arrange and pay for hotel and/or transportation. We will not pay for any additional incidental expenses that you may incur, such as phone calls and movie rentals.

If you choose to end your participation before the scheduled time, we will do our best to arrange earlier transportation. However, we cannot guarantee that alternative accommodations can be made outside of the originally scheduled transportation.

Should you quit the study before it is finished, you will be reimbursed only for the days that you participated in the study including lodging. Our study team will track and determine the amount of reimbursement. Please keep all receipts.

You will receive your incentive (and reimbursement if applicable) as a check mailed to you after your participation is finished.

8.3 Who could profit or financially benefit 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.

We may use companies to analyze some pieces of data. For example, CorTechs Labs or Soterix Medical Inc. charge for their services, just as nearly every company does. We have no financial or other relationship with such companies and will not receive any personal financial gain from using their services.

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?

We will keep information about you strictly confidential, including any research records we create, to the extent required by law. The study staff will keep your study files locked in a file cabinet in a private office. You will be assigned a study number, which will be used on all of your data (e.g., paper tests, computerized testing, MRI and PET scans). This de-identifies your data so that others cannot identify you. We will use a study number rather than your name on study records when we can. Your name and other facts that might point to you will not appear when we present this study or publish its results.

We may also need to send your brain scans for processing to experts who will use computer-modeling programs to determine the best locations to place the electrodes or to measure the size of different brain regions. Likewise, we may use companies that analyze your MRI data. We only use your participant number in all your records, including your MRI scans. We will check to make sure that all identifiable information has been removed from the scans before such consultations/uploads are performed. This means that your brain images will not be identifiable to the experts.

If you take part in the fNIRS portion of the study, we may have the company that makes the device, NIRx, assist us with analysis of your data. We will only use your participant number in your records. We will ensure that all identifiable information has been removed before any consultation or sharing of data takes place with NIRx. We will use best practices with the transfer and storage of any information about you. As listed above, it is extremely unlikely that anyone could identify you from this data.

To better protect the private nature of your research information, the results from the neuropsychological or motor testing, MRI, fNIRS, and HD-tDCS will not be included in your medical record. Rather, a research record will be used to keep these experimental results. We will enter a note into your research record after each session. This note will briefly describe the procedures performed and any relevant observations or data. If you are participating in the study, we may share the results of these tests with your primary doctors (e.g. neurologists, psychiatrist, psychologist) if it is deemed necessary to improve your medical care and upon your request.

This research will be covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information or documents 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 or documents 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 of agency funded projects 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 an insurer, medical care provider, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not be used to prevent disclosure as required by federal, state, or local law such as child abuse and neglect, or 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
- HIV/AIDS status
- Sexually transmitted disease and/or other communicable disease status
- Genetic counseling/genetic testing records
- Health plan/health insurance records
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- 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:

- If you are interested in participating in another similar study (e.g., Lewy Body Dementia Biomarkers study HUM00120024, Differentiation of Parkinsonism HUM00195649, or the KETO study HUM00213035), your identifiable data will be shared across studies in an effort to reduce the amount of imaging and testing you will need to do.
- 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 What will happen with my research data?

It may be that you have participated in previous studies or are currently participating in one of the studies by the investigators. The research data of those studies may be combined with the research data of the current study. This will allow for a more complete analysis of Lewy Body Dementia and also reduces the burden of participants enrolled in more than one of these studies. This research data may be maintained indefinitely.

_____(initials) I understand that any existing research data from previous or current research studies that I participated in may be combined and used in the current research study.

9.6 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

Investigators:
Benjamin M. Hampstead, Ph.D., ABPP/CN
Mailing Address: Neuropsychology Section of Psychiatry,
4251 Plymouth Road, Arbor Lakes Building 1 - Suite 2400
Telephone: 734-763-9259
Email: bhampste@med.umich.edu

Nico Bohnen, M.D.
Domino Farms, Lobby B Suite 1200
Frank Lloyd Wright Drive
Telephone: 734-998-8400 Ann Arbor, MI 48106
Email: nbohnen@med.umich.edu

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 a signed and dated copy of:

- 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/Assent 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/Assent to Collect for Unspecified Future Research

In an effort to lower duplication of research we ask that you consider giving permission for us to utilize your research data collected in this study for future research.

If you agree, the researchers would use the identifiable results of imaging MRI and PET scans, and all the neuropsychological, questionnaires and motor data collected as part of this study for future research. Do you agree to us retaining your identifiable data after the study has been completed for these purposes?

Please initial your choice:

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

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

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Instructions revised 4-11-2020
DO NOT CHANGE THIS FIELD—IRBMED USE ONLY

Legally Authorized Representative

Subject Name:_____

Parent/Legally Authorized Representative:

Printed Legal Name: _____

Signature: _____

Address: _____

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

Relationship to subject: ☐ Parent ☐ Spouse ☐ Child ☐ Sibling ☐ Legal guardian ☐ Other

If "Other," explain: _____

Reason subject is unable to consent: _____

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): _____

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Instructions revised 4-11-2020
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