Study Title: Effects of Exercise on Glymphatic Functioning and Neurobehavioral Correlates in Parkinson's Disease
NCT04140708
March 12, 2021

Principal Investigator: Daniel O. Claassen, MD MS
Institution/Hospital: Vanderbilt University Medical Center
Funded by: Department of Defense
Study Title: Effects of Exercise on Glymphatic Functioning and Neurobehavioral Correlates in Parkinson's Disease

Version Date: March 12, 2021

This informed consent applies to Subjects with Parkinson's Disease.

Name of Subject:_____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a signed and dated copy of this consent form.

You do not have to be in this research study. You may choose not to be in this study and get other treatments without changing your healthcare, services or other rights. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study. Your medical record will contain a note saying you are in a research study. Anyone you authorize to receive your medical record will also get this note.

This study is funded by a Department of Defense grant.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have Parkinson's Disease. This study is designed to measure the change in patients diagnosed with Parkinson's disease (PD) before, during and after a 12-week exercise program. The focus of this study is the glymphatic system. The glymphatic system is a proposed waste clearance pathway within the brain. Early research suggest glymphatic function increases following exercise, which may explain the reduced symptoms sometimes seen in response to exercise in patients with PD. This study will use brain scans, cognitive tests, and physical exams to measure the response to participation in a regular community-based exercise program.

2. What will happen and how long will you be in the study?

- **Consent:** Before any study-related tests and procedures are started, you will be asked to read and sign this consent document.
- **Medical History:** A study doctor, study coordinator, or research staff will ask you to list your medical and psychiatric history, current medications, demographics (gender, age, race). If, after completing this interview, you do not fit our study criteria, you will not be asked to participate further. We will then destroy any information gathered about you immediately.
- **Questionnaires & cognitive tasks:** You will be asked to complete brief cognitive testing and answer questionnaires about mood and sleep upon your first visit and your last visit for the research study. These will be administered by Dr. Claassen or IRB-approved research staff. Dr. Claassen, a neurologist, will provide oversight and interpretation of questionnaire data. This portion of the study should take about 60 minutes.
- **Actigraph & Neurametrix:** You will be asked to wear a small, watch-like device on your non-dominant wrist during your participation. This will monitor your physical movement, to help us measure how active you are during the study, as well as how soundly you sleep. If you regularly use a personal computer, a Neurametrix software download link will be printed for you, or, sent via email. Once installed on your personal computer, this software will measure your typing speed (but **NOT** what keys you press – i.e., the software will not know what you type, only how fast you are pressing keys). This will help us monitor changes in your fine motor control. You will not notice the software, as it will run in the "background." It is programmed to uninstall itself after you complete the study.
- **Blood Draw:** You will undergo a routine neurological examination on both the baseline and follow-up days that will include a blood draw (10 mL) each time.

- **MRI scan:** You will undergo an MRI scan on the first and last day of the study, each scan will take no more than 90 minutes, normally about 60. An MRI scan is taken in a large machine that is shaped like a tunnel. This scan does not use x-rays. Instead, it uses a strong magnet and radio waves, like those used in an AM/FM radio to make pictures of your body.

  You will not be able to have this scan if you have a device in your body, such as aneurysm clips in the brain, heart pacemakers or defibrillators, and cochlear (inner ear) implants. Also, you will not be able to have this scan if you have iron-based tattoos or pieces of metal (bullet, BB, shrapnel) close to or in an important organ (such as the eye).

  Certain metal objects like watches, credit cards, hairpins, writing pens, etc. may be damaged by the machine or may be pulled away from the body when you are getting the scan. Also, metal can sometimes cause poor pictures if it is close to the part of the body being scanned. For these reasons, you will be asked to remove these objects before going into the room for the scan.

  You will hear "hammering", clicking, or squealing noises during the scan. You will be given earplugs to reduce the noise. You will also be told how to alert the staff if you need them.

  During the scan, the MRI staff is able to hear and talk to you. You will also be able to hear the staff. They will be talking to you during your scan and may ask you to hold your breath, not move, or other simple tasks. You may be asked to lie very still throughout the scan.

  In this study, the MRI scan is for research only. But, if we see something that is not normal, you will be told and asked to consult your doctor.

- **PET scan:** Subjects will undergo a PET scan on the first and last day of the study**.** This PET scan is 70 minutes long. The tracer will be introduced via a routine intravenous injection, typically in the arm.

  In this study, the PET scan is for research only. But, if we see something that is not normal, you will be told and asked to consult your doctor.

- **Community-based Exercise:** Some research has shown that that forced, intense exercise can reduce, reverse and delay Parkinson's symptoms. This study involves subjects enrolling in a community-based exercise program specifically designed for people with Parkinson's, called "Rock Steady Boxing." The program incorporates aspects of non-contact training used in boxing to improve agility, speed, muscular endurance, accuracy, balance, hand-eye coordination, footwork and overall strength. The study will offer compensation to cover up-to 2 classes per week, for the duration of the study.

3. Costs to you if you take part in this study:

There is no cost to you for participating in this study.

However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would need even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost you to take part in this study. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine care (non-research) further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine care (non-research) costs and your doctor will discuss other

treatment plans with you.

4. Side effects and risks that you can expect if you take part in this study:

Assessments

There are no known major risks with the clinical assessments (physical, cognitive, questionnaires). The blood draw will also be obtained by professionals. Some side effects from the blood draw may be redness near the site where the needle is inserted and in some rare cases people faint.

MRI

There are no known major risks with an MRI scan. But, it is possible that harmful effects could be found out in the future. During the MRI scans, some people may experience discomforts such as nausea, dizziness, flashing lights in the eyes, and a metal taste in the mouth. These discomforts are most likely to occur as a result of rapid head movement in or near the MRI machine. For this reason, the participants will be instructed to try not to move, especially the head, while inside the MRI scanner. It may bother some participants to be placed in a tight space (claustrophobia) or to hear the noise made by the magnet during the scan. Participants will be asked if they suffer from claustrophobia and warned of the potential to experience this during the MRI scan. They will also be given earplugs to reduce the noise.

If you have any metal pieces in your body, they could move during the scan and damage nearby tissues or organs. You will be carefully screened for conditions which would interfere with MRI scanning or for whom MRI scanning may involve additional risk (e.g., middle ear prosthesis, metal fragments in eyes, etc). You will not be able to have the scan if you have a device in your body such as aneurysm clips in the brain, heart pacemakers or defibrillators, and cochlear implants. Also, you will not be able to have the scan if you have any iron-based tattoos or pieces of metal (bullet, BB, shrapnel) close to or in an important organ (such as the eye). These and other risks will be identified prior to the MRI scan, as you will complete a metal screening form that is reviewed by a board-certified technician. The technician will deem whether or not it is safe for you to enter the scanner.

If you use a transdermal patch (medicated patches applied to the skin), you may need to take it off during the MRI scan. Transdermal patches slowly deliver medicines through the skin. Some patches have metal in the layer of the patch that is not in contact with the skin (the backing). You may not be able to see the metal in the backing of these patches. Patches that contain metal can overheat during an fMRI scan and cause skin burns in the immediate area of the patch. Tell the study doctor that you are using a patch and why you are using it (such as, for pain, smoking cessation, hormones). Ask your doctor for guidance about removing and disposing of the patch before having an fMRI scan and replacing it after the procedure. Tell the MRI facility that you are using a patch. You should do this when making your appointment and during the metal screening questions you are asked when you arrive for your appointment.

There are no known risks of having MRI scans without contrast while pregnant. However, there may be risks that are unknown. To minimize these risks, you will not be able to have the scan if you are pregnant. Postmenopausal women, aged 50 or older, or those who have had a hysterectomy will not be required to take a pregnancy exam. All other women of childbearing potential will be required to take the serum BHCG test to rule out pregnancy. If a woman is found to be pregnant, she will not have the scan. If sedation is used, there are risks of excessive sedation. The technologist or nurse monitors your vital signs to minimize this risk.

Due to the effects of certain drugs (dopaminergic) used to treat Parkinsonian conditions, you will be asked to abstain from taking those medications for 16 hours prior to the MRI scan. Since it is happening in the morning of your visit, this would typically mean stopping any doses around 4pm the day before your visit. This "washout" period is sometimes associated with discomfort due to a re-emergence of motor symptoms;

however, there are no permanent medical complications associated with going through this type of washout. In fact, washouts are frequently used in the course of regular medical treatment (e.g., getting certain types of scans your physician finds useful sometimes requires a washout).

PET

You are agreeing to participate in a research project that involves the use of imaging and/or nuclear medicine procedures that expose you to radiation. This section will discuss the risks associated with the procedures that are for research only. Your doctors may order additional imaging procedures as part of your normal patient care that also expose you to radiation. Those normal imaging procedures are not included in the risk discussion below. Please discuss those procedures and radiation risks with your doctors.

As part of this research study, you may be asked to have up to two PET (Positron Emission Tomography) procedures. These procedures expose you to radiation. The radiation exposure comes from the injection of a radioactive substance as well as the use of an accompanying CT (computed tomography) scan. The amount of exposure that you could receive, should you have both the prescribed procedures is approximately 15 % (or less than 1/6th) of the amount allowed annually for persons who are exposed to radiation as part of their work. Additionally, to minimize the effects of the injected radioactive substance, you are encouraged to drink plenty of fluids following the PET procedure and to empty your bladder at least every two hours for the first six hours.

There is always a risk of damage to cells or tissue from being exposed to any amount of this special type of radiation. We are all exposed to this radiation because it comes from nature. It's in rock, soil, and the atmosphere. It also comes from medical tests and treatments and nuclear power plants. Exposure to radiation adds up over time over your lifetime and may cause cancer and other health problems. But in most cases, the risk of getting cancer from being exposed to small amounts of radiation is small. Radiation exposure may cause genetic damage to future offspring. You should notify the study doctor of any other radiation exposures for research or your clinical care that you have received over the past year or plan for the next year. The radiotracer will be injected into your vein.

There is a slight risk of discomfort at the injection site, including irritation and pain. Rare problems include headache, flushing, increased blood pressure, nausea and dizziness. To protect your bladder from the effects of injected radioactive substances, you should drink plenty of fluids and empty your bladder every two hours for at least the first six hours after you have each PET/CT scan. Unknown risks may include a very rare serious allergic reaction, which must be treated promptly, and may, though rarely, lead to death. Allergic reactions may cause shock, seizures (convulsions, epilepsy, "fits"), loss of consciousness, tingling, swelling of face, lips, tongue, throat and/or vocal cords, difficulty breathing, asthma, wheezing, rash, hives and/or itching, and nausea and or vomiting.

5. Risks that are not known/Unforeseen Risks:

There may be risks from participation that are unknown at this time.

6. Compensation in case of study-related injury:

If it is determined by Vanderbilt and the Investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided at Vanderbilt to treat the injury. There are no plans for Vanderbilt or the Department of Defense to pay for any injury caused by the usual care you would normally receive for treating

your illness or the costs of any additional care. There are no plans for Vanderbilt [or the Sponsor] to give you money for the injury

7. Good effects that might result from this study:

While this study is not therapeutic in anyway, we believe this study will lay the foundation for therapies in the future. The benefits to science and humankind could potentially be life altering. Your part in this study helps those future therapies.

8. Compensation for participation:

If you are enrolled in the study you will be compensated for your participations. The compensation schedule is as follows:

Baseline assessment, first day: $160 (MRI = $60, PET = $100)
Week 2, first day of exercise classes: $190 (covers 10 classes, paid to Rock Steady Boxing)
Week 8, mid-way through exercise classes: $190 (covers 10 classes, paid to Rock Steady Boxing)
Week 12, final day: $160 (MRI = $60, PET = $100)
Note: you are free to attend more classes than compensated, though you will not be reimbursed for those additional classes.

9. Reasons why the study doctor may take you out of this study:

You may be removed from the study at any time if your participation in the study appears to be medically harmful to you, if you fail to follow directions for participating in the study, if it is discovered that you do not meet the study requirements, if the study is canceled, if you are a female subject and are pregnant, or for administrative reasons. You will be told why you are removed from the study.

10. What will happen if you decide to stop being in this study?

Being in this study is voluntary. You may refuse to be in the study or quit at any time and this will not affect the medical care you will receive at Vanderbilt. If you choose to quit, you should tell Dr. Claassen or the research staff. Dr. Claassen reserves the right to use any data gathered from you before your withdrawal of the study. However, if this data is not usable, Dr. Claassen will destroy the information.

11. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or possible injury, please feel free to contact Jason Elenberger (research coordinator) at [redacted] or the study doctor, Dr. Daniel Claassen, at [redacted]. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273 Monday – Friday during business hours.

12. Confidentiality:

Records of your participation in this study will be kept confidential except as disclosure is required by law or as described in this informed consent document (under "Confidentiality" or "Authorization to Use or Disclose Protected Health Information"). All information and results gathered during your participation will be kept in a secure place available only to the researchers involved in this study. Your confidentiality will be maintained in

this study by isolating the data being collected from your true identity. You will be assigned a code that will be used wherever possible to label stored data, rather than using your name, in order to limit subject identification. This code will be used to label all research data, including all questionnaires and MRI data. Electronic databases containing identifiable participant information will be password encoded. Image data are only accessible to study personnel on password-protected computers. Written information containing participant identifiers (informed consent, subject payment, etc.) will be stored in locked file cabinets in offices within the Department of Neurology. Dr. Claassen, his study team, and oversight agencies such as the Institutional Review Board (IRB), a group of people who are responsible for ensuring the safety and rights of study participants, will be able to inspect and copy confidential study-related records which identify you by name. As the study funder, the Department of Defense will also have access to all study-related records that may include identifiable data. Therefore, absolute confidentiality cannot be guaranteed. However, if the results of this study are published in medical journals or presented at national or international meetings, you will not be individually identified. Dr. Claassen and/or Vanderbilt may share your information, without identifiers, to others or use it for other research projects not listed in this form. Vanderbilt, Dr. Claassen and his study team will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means. It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help. Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

13. Authorization to Use/Disclose Protected Health Information:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below. As part of the study, Dr. Claassen and his study team may share the results of your study and/or non-study linked research study test results, as well as parts of your medical record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Department of Defense, the Vanderbilt University Institutional Review Board, or similar agencies in other countries. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private. The study results will be kept in your research record for at least three years after the study is finished. At that time, the research data that has not been put in your medical record will be kept for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time. Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Claassen in writing and let him know that you withdraw your consent. His mailing address is [redacted]. At that time, we will stop getting any more data about you; however, the health data we stored before you withdrew your consent may still be used for reporting and research quality.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

Date	**Signature of patient/volunteer**

Consent obtained by:

Date and Time	**Signature**
	Printed Name and Title