Official Title:	Neuroenergetic Adaptations in Alzheimer's Disease: Implications on Amyloid Burden and Cognition.
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NYU Langone MEDICAL CENTER

Research Subject Informed Consent Form

Title of Study:	Neuroenergetic Adaptations in Alzheimer's disease: Implication on Amyloid Burden and Cognition S1801919
Short Title:	PhosphoRus, Proton imaging and Amyloid BuRdEn (PREPARE)
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1. About volunteering for this research study

You are being invited to take part in a research study. Your participation is voluntary which means you can choose whether or not you want to take part in this study. People who agree to take part in research studies are called "subjects" or "research subjects". These words are used throughout this consent form. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. You may also decide to discuss this study and this form with your family, friends, or doctor. If you have any questions about the study or about this form, please ask us. If you decide to take part in this study, you must sign this form. We will give you a copy of this form signed by you for you to keep. A study informant that knows you well will be required for participation in this study.

2. What is the purpose of this study?

Normal cells primarily produce energy with the help of the mitochondria. These "small organs", also known as the "powerhouses of the cell", turn the sugars, fats and proteins that we eat into forms of chemical energy that the body can use to carry on living. This process is called oxidative phosphorylation. In addition to the help from the mitochondria and oxidative phosphorylation, most cells can produce energy by lactic acid fermentation. Although this process is less energy efficient, it is a faster process and is used by the brain, muscle, and other organs under specific circumstances and energy demands, even in the presence of abundant oxygen. Another name for this process is aerobic glycolysis. Aerobic glycolysis and oxidative phosphorylation are the two major mechanisms involved in brain energetics.

One consequence of Alzheimer's disease (AD) is known to be the deposition of amyloid plaques and neurofibrillary tangles. The cause of this deposition of proteins is unknown. Some scientists argue that an increase in oxidative phosphorylation activity and a lack of ability to shift to aerobic glycolysis are the underlying source of these changes.

The purpose of this study is to test whether there is a correlation between neuroenergetic levels of aerobic glycolysis/oxidative phosphorylation and risk for Alzheimer's disease. We will study these neuroenergetic adaptations in a group of 15 elderly participants between 60 and 85 years old, with amnestic mild cognitive impairment (aMCI) and 30 cognitively normal controls (NL) recruited from the NYU Alzheimer's disease Research Center (ADRC) or the Health Brain Aging and Sleep Center (HBASC). Multimodal (MR/PET) and multinuclear (31P/1H) neuroimaging will allow us to gain access to a uniquely comprehensive and highly consistent view of neuroenergetic adaptations in both the clinical and preclinical stages of Alzheimer's disease.

3. How long will I be in the study? How many other people will be in the study?

The study will be over the course of 1 month, although we will provide flexible visit options and can last up to 6 months. We expect that 60 participants will be screened, 50 will be enrolled, and 45 will complete the study evaluations.

Study Procedures

Your participation will involve a maximum of two visits. The first visit will include the clinical evaluation and cognitive testing which will be done remotely via phone, video call or WebEx The clinical evaluation and cognitive tests will be obtained from your previous visit to the ADC. The second visit will consist of the MRI/PET scans. Each of these visits will take approximately 3-4 hours.

4. What will I be asked to do in the study?

Visit 1

This visit will occur at the HBASC or ADRC *or remotely via WebEx, Zoom call or video call*

- You will sign the consent form via email or in person.
- We will record your demographic information (age, sex, etc.)
- All your physical, neurological, and psychiatric examination as well as your medical history including medications you take and surgeries you have had will be obtained from your records from your previous visit to the ADRC or HBASC
- We will ask you about your family history including whether you have had relatives who have AD and their ages.
- All Psychometric testing that you completed from the ADRC or HBASC will be obtained from your records: A combination of standardized oral and paper and pencil tests that you previously completed will be obtained to assess areas of memory, perception, attention, concentration, language, reasoning, comprehension, problem solving skills, etc.

Visit 2

This visit will occur at the Center for Biomedical Imaging (660 1st Avenue at E. 38th Street).

- You will have an amyloid PET-MR scan of your brain at the Center for Biomedical Imaging. PET/MR scans combine two types of imaging methods: Positron Emissions Tomography (PET) and Magnetic Resonance Imaging (MRI). PET uses radioactive tracers to produce images that can inform us how a particular compound is used by tissue or for identifying unique cell-types, such as amyloid, in this study. MRI uses magnetic fields and radio waves to produce images that can inform us about structures and function of tissue in the body. Combining both techniques provides more useful information while reducing the amount of radiation exposure compared to a standard PET scan or PET/CT. The PET/MR scan will be immediately followed by a 30 minute 3T MR spectroscopy scan. Women will be asked to take a urine pregnancy test prior to the exam.
- A small amount of tracer, either ^{11}C-Pittsburgh compound-B (PiB) or florbetaben (FBB) will be injected into a vein in your arm before the scan begins and a 60-min amyloid PET-MR scan will be performed after injection. The wait time between the injection and the scan is 45-90 minutes for FBB and 35 minutes for PiB.Although PiB and FBB have been extensively studied for the past 10 years, the tracers are considered investigational because they are not Food and Drug Administration (FDA) approved for use outside of a research study, such as this one.
- Since the scanner makes a loud tapping noise while it acquires the image, you will be offered earplugs. After the platform moves you inside the MRI tube, you will be able to speak through an intercom to the technician performing the exam. Inside the scanner, you will be lying on your back facing up.

Your head will be held in place by foam pads. A blanket will cover your legs to keep you from getting chilly, and a foam pad will be beneath your knees for your comfort. In your hand, you will hold an emergency squeeze-ball. Squeezing this ball will allow you to alert the technician and the doctor that you want to communicate with them.

To do more powerful research, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. Researchers can then study the combined information to learn even more about health and disease.

5. What are the possible risks or discomforts?

Risk of taking part in this Study

Amyloid PET-MR *using* ^{11}C- *Pittsburgh compound B* (PiB) or *F-18 Florbetabem* (FBB):

During this study, you will have exposure to radiation from PET tracer Pittsburgh compound B (PiB) or florbetaben (FBB). This radiation exposure is not necessary for your medical care and

is for research purposes only. This range is within the limits set by the FDA for individuals participating in basic research studies. The lower dose (the PiB scan) is comparable to 0.84 years of natural environmental radiation in the US (3.1 mSv per year). The higher dose (the FBB scan) is comparable to 1.8 years of natural environmental radiation in the US (3.1 mSv per year).The organ receiving the highest dose in this study is the gallbladder for PiB and the urinary bladder wall for FBB

This radiation exposure is not necessary for your medical care and is for research purposes only. Radiation has been shown to cause cancer from exposures that are significantly higher than the additional radiation dose you will receive by participating in this study. According to the ICRP, NCRP and HPS, the increased risk of health effects, such as cancer, from radiation doses of this amount is either too small to be observed or nonexistent.

The NYULH Radiation Safety Committee has reviewed and approved the use of diagnostic radiation in this research study. Please inform your researcher if you have been exposed to radiation as a result of any other research studies. If you participate in future studies that involve the use of radiation, you should discuss the guidelines for radiation exposure with the researchers performing those studies.

Pregnant women cannot be exposed to radiation. Women must have a negative pregnancy test before they can have a PET scan.

In order to better see internal structures of your body during the imaging study, there is the injection of a tracer. Infrequently, the needle (catheter) may slip of out the vein. In these cases. the injected tracer goes into the tissues and causes local pain. Some risks include: minor pain or soreness, lightheadedness and/or minor bruising at the site of the catheter insertions, and less commonly, the formation of a small clot or swelling of the vein and bleeding. This is usually treated with appropriate compresses.

Magnetic Resonance Imaging (MRI):

MRI uses a strong magnetic field to create images of the body. Because of the strong magnetic field, there are risks. These risks are detailed in this section.

One possible risk is burns to the skin. There is an increased risk of burns from devices that conduct electrical energy. These devices can include metallic objects, pulse oximeters, EKG leads, or skin tattoos. These devices can be either in or on the patient in order for a skin burn to occur. The FDA has found that 70% of all reported injuries from MRIs were burns to the skin.

To reduce this risk, all patients who are scanned in this study must complete thorough screening to ensure that no conductive materials are present in or on the patient’s body. Additionally, the power limits of the magnet will be adjusted as necessary.

Another possible risk is that a metal object could be pulled into the scanner and hit you. You could be physically injured as a result.

To reduce this risk, everyone near the magnet will remove all metal from their clothing or pockets when in the scanning environment. The door to the scan room will remain closed during the exam for your safety.

There are no known risks or adverse effects resulting directly from exposure to MRI. However, subjects who have a pacemaker or metal objects in their body such as shrapnel or metal in the eye should not have the scan performed. If you have any question about metal implants or metal fragments in the body, you should inform the technologist or investigators before entering the magnet room.

Fear of Confined Spaces: Some people may feel confined and experience anxiety in the MR scanner. If you are unable to tolerate being in the scanner, we can stop the scan immediately at any time.

Noise Levels: The MR scanner produces tapping sounds during operation, which may reach very loud levels. To minimize any discomfort from this noise, you will be given disposable earplugs to reduce the noise levels but will still allow voice communication with the scanner operator.

MRI system failure (quench): In extremely rare cases, a magnet can lose its magnetism, in which case cooling fluids may be released noisily through escape valves and may collect in gas form in the scan room. The gas is not harmful in itself as long as fresh air is available. In this very remote event, you will immediately be brought out of the magnet room.

Neurostimulation and heating: Some subjects may experience muscle twitches or tingling sensations and/or a slight increase in body temperature during some types of scan activity. These are very unlikely under current MR guidelines.

6. Can I be in the study if I am pregnant or breastfeeding?

Because taking part in this study may harm an embryo, fetus, or breastfeeding baby, you should not become pregnant, breastfeed a baby, or father a child while participating in this study. Other risks may not yet be known.

If you are currently pregnant, you will not be able participate in the study. You should not become pregnant while you are participating in this study. If you are able to become pregnant, you will be required to use a medically accepted method of birth control while you participate in the study:

- Hormonal methods like birth control pills, patches, vaginal rings or implants,
- Barrier methods such as condoms or a diaphragm used with spermicide (a foam, cream or gel that kills sperm),
- Intrauterine device (IUD),
- Abstinence (no sex).

If you become or you think you have become pregnant during the study, you must tell the principal investigator right away and must tell your obstetrician or other health care provider caring for you during your pregnancy that you took part in this study. If you become pregnant, you will have to stop taking part in the study for safety reasons. The principal investigator may ask you to provide information about the outcome of your pregnancy and the health of your baby.

Note to Men
Because the effect of participating in this study on sperm are unknown, you will be required to use a medically accepted method of birth control while you participate in the study, using one of the applicable methods described above.

7. What if new information becomes available?

During the course of this study we may find more information that could be important to you. This includes information that might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

Incidental Findings
In some cases, an imaging scan of a healthy volunteer will reveal the presence of a previously undetected abnormality with (or without) a clinical significance. Every scan performed in this study is saved and handled under the standard PHI confidentiality restrictions and regulations employed for patients' information. Each scan is additionally reviewed by a radiologist, who might then detect an abnormality. If clinically useful information is uncovered, either the Principal Investigator or another clinician on the study will speak to you in person or on the telephone regarding the new information. A copy of the original image report will also be provided to you in person and you will be encouraged to follow up on the discovery with your treating physician outside of the study.

8. What are the possible benefits of the study?

We do not expect the majority of participants to benefit directly from the research other than by financial remuneration for their time and effort. The potential benefits to society are considerable if this study reveals new information about mitochondrial dysfunction and conversion from oxidative phosphorylation to aerobic glycolysis in AD.

9. What other choices do I have if I do not participate?

You are free to choose not to participate in the study.

10. Will I be paid for being in this study?

You will be paid $300 for completing the PET/MR. If you chose to leave or are withdrawn for any reason before finishing the entire study; you will be paid for each completed procedure described above.

You will receive a ClinCard (similar to a credit/debit card) of $300 during your second visit for completing visit one and two. Under special circumstances, travel costs to and from the study site may be reimbursed. In order to be paid, you must give travel receipts to the study staff.

You are required to track all payments made to you by NYU Langone for your participation in any research for this calendar year. You must let us know immediately if/when the total research payments presently equal or is likely to exceed $600.00 total (not including travel reimbursements) for this calendar year. If your total payments (for one or more studies) reach $600.00, please advise the research coordinator of this study.

If you decide to withdraw from the study before completing the PET/MR scan, you will be paid $50 for your time via a ClinCard.

11. Will I have to pay for anything?

All study-related costs are being paid for by a grant from the National Institutes of Health (NIH). You or your insurance company will not be charged or held responsible for the costs of tests and procedures you receive specifically for this study.

12. What happens if I am injured from being in the study?

For medical emergencies contact 911. If you think you have been injured as a result of taking part in this research study, tell the principal investigator as soon as possible. The principal investigator's name and phone number are listed at the top of page 1 of this consent form. We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for NYU Langone Medical Center or NYU School of Medicine to provide compensation for a study injury. You do not give up your legal rights by signing this form.

13. When is the study over? Can I leave the Study before it ends?

This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped or your participation ended at any time by your physician, the study sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The principal investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The study sponsor, the principal investigator, the Food and Drug Administration (FDA) or other body responsible for monitoring the safety of the study has decided to stop the study.

If you decide to participate, you are free to leave the study at anytime. Leaving the study will not interfere with your future care, payment for your health care or your eligibility for health care benefits.

14. How will you protect my confidentiality?

Your medical information is protected health information, or "PHI", and is protected by federal and state laws, such as the Health Insurance Portability and Accountability Act, or HIPAA. This includes information in your research record as well as information in your medical record at NYU Langone Health. In compliance with NYU Langone Health policies and procedures and with HIPAA, only those individuals with a job purpose can access this information.

Medical information created by this research study may become part of your medical record. We may include your research information in your medical record for several reasons, including for the billing of services provided in connection with the study, to securely document any medical services you receive, and so that other members of the NYU Langone Health community who may treat you have access to important information about your health.

You have a right to access information in your medical record. In some cases, when necessary to protect the integrity of the research, you will not be allowed to see or copy certain information relating to the study while the study is in progress, but you will have the right to see and copy the information once the study is over in accordance with NYU Langone Health policies and applicable law.

Certificate of Confidentiality
To help us further protect your confidentiality, this research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). The NIH has issued a Certificate of Confidentiality for this research. This adds special protection for the research information (data, documents, or biospecimens) that may identify you.

Research information protected by this Certificate of Confidentiality cannot be disclosed to anyone else who is not connected with the research, without your consent. With this Certificate of Confidentiality, the researchers may not disclose or use research information 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, without your consent. However, disclosure, without your consent, is still necessary if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases).
The Certificate of Confidentiality cannot be used to refuse a request for information from appropriate government agencies responsible for project oversight.

The Certificate of Confidentiality does not prevent you from releasing information about yourself and your involvement in this research, including for your medical treatment. Federal regulations may also allow for the use or sharing of information for other scientific research.

By agreeing to be in this research and signing below, you are giving your consent to share research information with others at NYU Langone Health. This means that your research information, including lab results, x-rays, MRIs, information about the investigational drug used in this study, may be included in your NYU Langone Health electronic medical record.

15. HIPAA Authorization

As noted in the Confidentiality section above, federal law requires us, and our affiliated researchers, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions. We are asking for your permission (authorization) to use and share your health information with others in connection with this study- in other words, for purposes of this research, including conducting and overseeing the study.

Your treatment outside of this study, payment for your health care, and your health care benefits will not be affected even if you do not authorize the use and disclosure of your information for this study.

What information may be used or shared with others in connection with this study?
All information in your research record for this study may be used and shared with those individuals listed in this section. Additionally, information in your medical record that the research team believes may be important to the study may be accessed by those listed here. This includes, for example, results from your physical examinations, laboratory tests, procedures, questionnaires, and diaries. In addition, PiB/FBB scans will be shared with the referring cohorts from the NYU ADRC and HBASC.

Who may use and share information in connection with this study?
The following individuals may use, share, or receive your information for this research study:

- The research team, including the Principal Investigator, study coordinators, and personnel responsible for the support or oversight of the study.
- The NYU Alzheimer's disease Research Center (ADRC) (Wisniewski T,PI)
- The NYU Helathy Brain Aging and Sleep (HBASC) Center (Osorio R, PI)
- The study sponsor: NIH/NIA
- Governmental agencies responsible for research oversight (e.g., the Food and Drug Administration or FDA).
- Health care providers who provide services to you in connection with this study, and laboratories or other individuals who analyze your health information in connection with this study.

Your information may be re-disclosed or used for other purposes if the person who receives your information is not required by law to protect the privacy of the information.

What if I do not want to give permission to use and share my information for this study?
Signing this form is voluntary. You do not have to give us permission to use and share your information, but if you do not, you will not be able to participate in this study.

Can I change my mind and withdraw permission to use or share my information?
Yes, you may withdraw or take back your permission to use and share your health information at any time for this research study. If you withdraw your permission, we will not be able to take back information that has already been used or shared with others. To withdraw your permission, send a written notice to the principal investigator for the study noted at the top of page 1 of this form. If you withdraw your permission, you will not be able to stay in this study.

How long may my information be used or shared?
Your permission to use or share your personal health information for this study will never expire unless you withdraw it.

16. The Institutional Review Board (IRB) and how it protects you

The IRB reviews all human research studies – including this study. The IRB follows Federal Government rules and guidelines designed to protect the rights and welfare of the people taking part in the research studies. The IRB also reviews research to make sure the risks for all studies are as small as possible. The NYU IRB Office number is (212) 263-4110. The NYU School of Medicine's IRB is made up of:

- Doctors, nurses, non-scientists, and people from the Community

17. Who can I call with questions, or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on top of the page 1 of this consent form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Institutional Review Board (IRB) at (212) 263-4110. 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.

When you sign this form, you are agreeing to take part in this research study as described to you. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer.

Name of Subject (Print)	Signature of Subject	Date

Name of Person Obtaining Consent (Print)	Signature of Person Obtaining Consent	Date

STUDY PARTNER/INFORMANT INFORMATION (OPTIONAL):

In addition to obtaining information from you directly, it is important that we also obtain information about your history and symptoms from a close relative or friend. Ideally, this individual should accompany you during at least one of your visits to the Center, although they can be contacted by telephone if accompanying you is not feasible. Please check “yes” or “no” below, to indicate whether you authorize us to obtain information from the close relative or friend that you designate.

□ Yes: Name of study partner: _____

Contact Information: _____

□ No