# Assessment of Hyperphosphorylated Tau PET Binding in Primary Progressive Aphasia

NCT02736695

6Oct2024

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**Version and date:** Version 14, 10/6/2024
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**SPECIFIC AIMS**

Primary progressive aphasia (PPA) is an umbrella term that encompasses a group of neurodegenerative syndromes characterized by varying combinations of progressive speech and language problems. Three clinical variants of PPA have been described and are well recognized: the agrammatic variant characterized by grammatical errors in speech and writing and typically associated with phonetic errors in speech; the semantic variant characterized by poor naming from loss of knowledge about the meaning of words; and the logopenic variant characterized by word retrieval problems and poor sentence repetition from impairment of working memory and phonemic errors. Pathological studies of PPA patients that died with postmortem examination of their brains have demonstrated that PPA is associated with a number of different abnormal cellular proteins that do not have perfect associations with the three PPA variants. One such protein is the microtubule associated protein, tau, which is the most common abnormal protein found in the brains of patients with PPA. Tau is an important protein that has been linked to the neurodegenerative process in many diseases. Clinical trials aimed at tau have now been completed and many others are ongoing. Unfortunately, it has not been possible, until recently, to detect abnormal tau deposition in the brain during life. Hence, it has not been possible to tell which PPA patients have abnormal tau in their brains and which PPA patients do not. An imaging ligand, AV-1451 (formerly 18F-T807), was recently developed to be used with positron emission tomography (PET) scanning. AV-1451 has been shown to specifically bind to tau in humans. No neuroimaging studies have investigated tau deposition in PPA and hence the binding characteristics of AV-1451 in PPA are unknown. Understanding the binding characteristics of AV-1451 is crucial to help determine whether it can serve as a biomarker for tau deposition in the brains of patients with PPA. Recently, we performed autoradiographic and immunohistochemical analyses on the brains of autopsied patients with and without abnormal tau deposition, including patients with PPA, and have validated AV-1451 binding to abnormal tau.

The goal of this R21 is to gain an understanding of the behavior of tau PET imaging using AV-1451 in subjects with PPA and its variants. In order to do so we are requesting funds via an R21 mechanism, for two years, to perform tau PET scanning in patients with PPA. *To address our specific aims we plan to compare AV-1451 regional binding patterns in a group of 60 prospectively recruited PPA subjects (15-20 with each of the three clinical variants) to AV-1451 regional binding patterns in a group of 25 normal age and gender-matched controls. All 80 subjects will undergo the identical set of neuroimaging protocols.* Our specific aims are:

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**Aim 1:** To determine what proportion of PPA subjects and PPA variants show elevated tau PET binding compared to normal controls.
***Hypothesis*:** We hypothesize that more than 50% of subjects with PPA will show elevated tau PET binding compared to controls.

**Aim 2**: To determine whether each of the three clinical PPA variants has a signature pattern of regional tau PET binding.
***Hypothesis:*** We hypothesize that each clinical PPA variant will show elevated tau PET binding compared to controls, and that patterns of tau-PET binding will differ across the PPA variants at the group-level.

**Aim 3**: To examine subject-by-subject variability in patterns of tau PET binding to investigate distinct regional patterns of tau PET in PPA, independent of the clinically defined PPA variants, using hierarchical cluster analysis and associations between clinical features and cluster generated anatomical patterns.
***Hypothesis:*** We hypothesize that the cluster analysis will identify distinct clinico-anatomical clusters beyond the clinically defined PPA variants.

At the completion of this R21 we will have an understanding of tau PET binding in subjects with PPA. We will have generated pilot data regarding the proportion of PPA subjects that show abnormal tau PET binding, how tau PET binding in PPA variants compares to tau PET binding in normal controls and to each other, and whether regional tau PET binding is associated with clinico-anatomical profiles beyond the currently recognized profiles of the three PPA variants. Identifying new clinico-anatomical clusters could have important implications for PPA classification and treatment. Information from this R21 will be critical for future studies of tau PET in PPA and PPA variants, such as those that aim to identify a cut point to determine whether a subject

is considered tau-positive, those that will assess tau PET as a potential disease biomarker in PPA, and those that will assess how the pattern of tau deposition is related to aphasic characteristics. Ultimately, information gleaned from this R21 will be the foundation of future R01s and clinical trials that are critical for the development of future targeted treatments for PPA.

## A. APPROACH

**Overall strategy:** The main goal of this R21 is to increase understanding of AV-1451 tau PET binding in PPA/FTLD. In order to achieve this goal, tau PET imaging with the AV-1451 ligand will be performed in *100 PPA/FTLD subjects as well as 25 normal healthy controls that will be age matched to our PPA/FTLD cohort. All 100 subjects will undergo a speech and language evaluation, as well as neurological and neuropsychological testing, and a structural MRI, identical to those performed in the 25 normal controls.* All 100 subjects will also be asked to provide a blood sample to allow for future genetic studies. A subset of 10 subjects with apraxia of speech and 10 subjects without apraxia of speech will have task-based fMRI sequences performed in addition to structural MR imaging.

**Subject Recruitment**: The PPA/bvFTD subjects will be prospectively recruited from Speech-Pathology and/or Neurology, Mayo Clinic Rochester, MN. Hence, all subjects will have been seen by a speech and language pathologist or a neurologist and received a clinical diagnosis of PPA/bvFTD before recruitment into the R21. We will also consider individuals who have been diagnosed outside of Mayo Clinic by a Neurologist. We do not anticipate any problems reaching our recruitment goal since we were able to recruit 46 PPA subjects in 2014 as part of a now completed NIH-funded grant. *For the normal controls, we will leverage data that has already been collected on normal controls from our NIH funded Mayo Clinic Study of Aging (U01 AG006786). The Study of Aging recruits healthy normal subjects from Olmsted County, MN, and is currently following over 1500 subjects. Of these 1500 subjects being followed, 102 controls, ages 31-88 years old have completed the identical tau-PET protocol with AV-1451 and MRI and clinical protocols. We will select a subset of 25 age and gender match normal controls from the 102 who have already completed tau-PET and MRI for use in this R21.*

**Screening eligibility process:**

The study team will use a two-part process to evaluate eligibility. When a subject is identified as a potential participant, a study team physician or physician assistant will review EMR notes, outside records, imaging reports, etc to ensure the subject has a suspected neurodegenerative diagnosis and meets eligibility criteria. This will be documented by signing the eligibility checklist which will remain in the subject's paper study file. If the subject agrees to participate, they will be scheduled and consented by the study coordinators. At the time of consent, the study coordinator will reassess eligibility with the subject to ensure nothing has changed. The coordinator will enter a note in the EMR documenting eligibility criteria was met as well as consenting information.

**Inclusion criteria**: All enrolled subjects must be over the age of 18, speak English as their primary language, and have an informant who can provide independent evaluation of functioning. Bilingual subjects and minorities whose primary language is English will be recruited. Each PPA subject must present with a chief complaint of progressive impairment of speech or language, must fulfill diagnostic criteria for PPA. Each bvFTD subject must present with a chief complaint of behavior change and fulfill diagnostic criteria for behavioral variant Frontotemporal Dementia. All 100 subjects must consent to undergo MRI and tau-PET scanning.

**Exclusion criteria**: Any subject who is mute or whose speech is unintelligible will be excluded. All subjects with concurrent illnesses that could account for speech and language deficits, such as traumatic brain injury, strokes or developmental syndromes, and subjects meeting criteria for another neurodegenerative disease, such as amnestic Alzheimer's type dementia, dementia with Lewy bodies, progressive supranuclear palsy, and corticobasal syndrome will be excluded.

Subjects who meet criteria for PPA and have mild behavioral changes, eye movement abnormalities or mild limb apraxia but who do not meet diagnostic criteria for, progressive supranuclear palsy or corticobasal syndrome respectively, will also be excluded. Subjects will be excluded from the study if they have any of the following genetic conditions which can increase the chance of cancer: Cowden disease, Lynch syndrome, hypogammaglobulinemia, Wiskott-Aldrich syndrome, and Down's syndrome. Subjects will also be excluded if MRI is contraindicated (metal in head, cardiac pace maker, etc.), if there is severe claustrophobia, if there are

conditions that may confound brain imaging studies (e.g. structural abnormalities, including subdural hematoma or intracranial neoplasm), or if they are medically unstable or are on medications that might affect brain structure or metabolism,(e.g. chemotherapy). Subjects will be excluded if they do not have an informant, or do not consent to the research.

All women who can become pregnant must have a negative pregnancy test before the PET/CT scan.

**Neurological and neuropsychological evaluation**

Neurological and neuropsychological assessments (**Table C.1**) will be performed by a physician/physician assistant and psychometrist under the supervision of a board certified neuropsychologist. We will use education and occupation to estimate premorbid ability level. Age and education adjusted Mayo's Older Americans Normative Studies (MOANs) scores will be generated for all tests in which it is possible to do so. These data will be utilized in aim 3 where we will compare clinical features across clusters.

If the PI determines that bringing a subject back would be useful for the study data, we will offer a return visit that could happen yearly. The subject would undergo the same testing each year.

**Table C.1: Neurological, neuropsychological & speech/language evaluations**

| Evaluation measures | Explanation of measures |
|---|---|
| **Neurological battery** | |
| Montreal Cognitive Assessment[45] | General cognitive impairment scale |
| Mini-Mental State Examination[46] | Global screening measure of dementia |
| Clinical Dementia Rating Scale [47] | Cognitive indices of functional impairment |
| Frontal Assessment Battery[48] | Frontal lobe impairment |
| Frontal Behavioral Inventory[49] | Measure of behavioral dyscontrol severity |
| Movement Disorders Society sponsored revision of the UPDRS Parts I-III[50] | Assessment of non-motor and motor parkinsonism |
| Test of Upper Limb Apraxia[51] | Assessment of limb apraxia that includes pantomime and imitation tasks |
| Neuropsychiatric Inventory Questionnaire [52] | Assessment of neuropsychiatric features |
| PSP Saccadic Impairment Scale[53] | Assessment of ocular motor impairment |
| Facial recognition battery[20] | To detect loss of facial recognition |
| **Neuropsychological battery** | |
| Trail Making Test A[54] | Cognitive speed |
| Trail Making Test B[54] | Executive function |
| Wisconsin Card Sort Test [55] | Executive function |
| Digit Span and Spatial Span subtests of the Wechsler Memory Scale - III[56] | Working memory |
| Rey Auditory Verbal learning test[57] | Learning & episodic memory |
| Rey-Osterreith Complex Figure test[57, 58] | Executive & visual spatial |
| Fragmented Letters subtest of the Visual Object and Space Perception Battery[59] | Visual spatial skills |
| Cube Analysis subtest of the Visual Object and Space Perception Battery[59] | Visual perceptual skills |
| **Speech and Language evaluation** | |
| Token Test, Part V[60] | Spoken language comprehension |
| Western Aphasia Battery[61] | Language comprehension & expression; aphasia severity |
| 15-item Boston Naming Test[62] | Confrontation naming |
| Action (verb) fluency[63] | Rapid verb generation |
| Letter fluency[64] | Frontal lobe integrity |
| Northwestern Anagram Test [65] | Grammatical structure |
| Pyramids and Palm Tree Test word matching version[66] | Word knowledge |
| Peabody Picture Vocabulary test [67] | Receptive lexicon |
| Repetition of sentence subtest of the Boston Diagnostic Aphasia Examination[68] | Impaired repetition |
| Apraxia of speech rating Scale[20] | Diagnosis & description of speech apraxia |
| Non-Verbal Oral Apraxia Test | Presence & severity of non-verbal oral apraxia |
| Dysarthria assessment tasks | Presence and type of dysarthria |

**Speech and language evaluation**

Each subject will undergo a video & audio recorded speech and language evaluation (**Table C.1**) by a speech-language pathologist. These recordings can be used for internal and external research and education purposes.The results of these tests will be used to determine the PPA variants. *In addition, all subjects classified as agrammatic variant of PPA that have apraxia of speech without aphasia will be tagged as PPAOS. Clustering of these PPAOS subjects will be assessed in aim3.*

All portions of the WAB-Revised necessary to generate scores for spontaneous speech, auditory verbal comprehension, repetition, and naming and word finding will be administered to generate an Aphasia Quotient which will serve as an index of overall aphasia severity. Speech and language characteristics will be assessed during conversational and imitative speech tasks. Diagnosis of dysarthria presence and type will be based on identification of salient abnormal speech characteristics commonly associated with each dysarthria type, as described in detail in several publications. We have documented reliability of clinical diagnoses of both AOS and dysarthria in previous studies. We will also document the absence or presence and severity of phonemic paraphasic errors. Nonverbal oral apraxia will be identified based on responses to command or

imitation to two relatively rapidly presented, randomly-ordered trials of four simple non-speech oromotor tasks (cough, blow, smack lips, click tongue), with the disorder reflected in vocalization, off-target groping, false starts, and awareness of errors and attempts at self-correction. As with the neurological and neuropsychological variables, speech and language variables will be compared across clusters in aim 3.

**Neuroimaging**

**AV-1451 synthesis:** The following synthesis procedure has been tested and developed at Mayo Clinic and will be performed daily. [18F]Fluoride activity will be retained on an Accell™ Plus (QMA) cartridge and eluted to the reaction vessel using 1.5 mL of an aqueous Cryptand-K2CO3 solution. The eluted activity will be heated at 70°C under helium flow and vacuum for 4.5 minutes. The temperature will be raised to 100°C and kept for an additional minute. Helium flow will be turned off and the activity dried under vacuum for 4 minutes. A solution of AV-1622 [AV-1451 precursor, AVID Radiopharmaceuticals, Inc., 1.5mg in anhydrous DMSO (2mL)] will be added to the reaction vessel and the resulting mixture kept at 110°C for 5 minutes followed by de-protection using 1mL of 3 N HCl(aq) at 100°C for 5 minutes. After cooling to 50°C, the crude AV-1451 mixture will be neutralized with 3.5mL of 1 M NaOH(aq). The resulting mixture will be passed through an Oasis HLB cartridge. The retained crude AV-1451 will be washed with 5mL of water then eluted off the Oasis HLB cartridge using 1.5mL of acetonitrile. The crude AV-1451 will be diluted with 3mL of water and loaded onto a semi-preparative C18 high performance liquid chromatography (HPLC) column for purification using the isocratic elution 60% 10mM ammonium acetate/water:40% acetonitrile at a 4mL/minute flow rate. The total product labeling yield is 59.9% by radiation detection, and AV-1451 purity is >95% after semi-preparative C18 HPLC column purification. The HPLC fraction containing the purified AV-1451 will be collected and diluted with 30mL of water. The diluted solution will then be passed through a C18 Sep-Pak Cartridge. The retained AV-1451 will be washed with 5mL of water. AV-1451 will be eluted off the C18 cartridge using 1mL of dehydrated alcohol into 9mL of 0.9% sodium chloride injection. The final solution will be transferred into a 30mL sterile, non-pyrogenic, pre-crimped septum-sealed clear glass through a 0.22µm, sterilizing filter for human-use dose dispensing.

**Image acquisition**: *We will assess tau PET brain uptake dynamically and determine the pharmacokinetics of AV-1451 in six PPA subjects (2 of each PPA variant) to determine the optimum protocol for delayed scanning in PPA subjects. All subjects will receive a single IV administration of 10 mCi (+/- 10%) 18F-AV-1451 and PET imaging will commence immediately post injection. Dynamic PET images will be acquired of the brain over the first 40 minutes (with the scanner acquiring list mode data) followed by a 30-min rest break. The subjects will be allowed to rest outside of the scanner. A 40-minute brain PET scan (with the scanner acquiring in list mode data) will be acquired after the rest interval. Retrospective re-binning of PET data into more frequent frames (30 sec) after injection and longer frames later during acquisition (60 seconds to 5 minutes) will be performed to demonstrate dynamic uptake phases.. For the dynamic brain images, regional compartmental model transport parameters (K1, k2, k3, k4) will by estimated by nonlinear data regression using PMOD modeling package. . The optimum protocol identified through this procedure will be utilized for all subjects scanned for the grant. Data from the six PPA subjects that underwent dynamic scanning will be included in all analyses.* All subjects will also undergo a 3T MRI protocol on a GE 3T system (Signa, General Electric Healthcare) that will include 3D Magnetization Prepared Rapid Acquisition Gradient-Echo (MPRAGE). All MPRAGE scans will undergo standard corrections for intensity inhomogeneity and gradient non-linearity before analysis. A subset of patients will have task-based fMRI studies performed on a Siemens 3T system (Prisma, Siemens) with an event related design modified from clinical paradigms used for presurgical mapping of epilepsy patients. Instructions will be presented via MRI safe goggles. The paradigm consists of 5 task blocks (with articulation) alternating with 5 baseline blocks (with no articulation). During the task block, subjects will be presented with a word that they are to repeat at a predetermined cue. After a 3 second delay, the cue will be presented while image acquisition takes place using a gradient-echo echo-planar pulse sequence (EPI). After 15 seconds, the next response will be cued. In total, three articulation responses and three silent responses will be cued for each word. After all images have been acquired, the volumes acquired from 4-10 seconds after each cue will be used for the analyses, to avoid motion artifacts or lexical processing driving results. This will result in 150 task block volumes and 150 baseline block volumes for each subject.

**HUMAN SUBJECTS**

**Potential risks:** Participation in this R21 is felt to involve only a minimal risk. It is possible that anxiety may result from the neurological exam, speech and language exam, neuropsychological testing, MRI or PET studies, and this will be explained to subjects and their families. There are no alternative treatments or procedures to those proposed in the current study, but the subjects and their families will be informed that they need not participate in the study. There are no proven biologic risks associated with MRI or PET scanning. Subjects may experience short term discomfort around the site of the intravenous injection for the PET scans. We have completed thousands of PET scans to date and have not had any significant problems, side-effects or death. *Removal of blood by a needle and syringe for the dynamic scanning on six subjects poses a small risk of pain or bruising at the site of the needle stick, but this is temporary. Some people may experience fainting or dizziness, and there is also a slight risk of infection at the site of the needle stick.*

**$^{[F18]}$AV-1451 PET risks**: Drug safety studies have been completed in rats, mice, dogs and non-human primates on AV-1451 and are available in the Investigator's Brochure on File with the FDA. Testing for binding to CNS relevant receptors, potassium channels, metabolism of AV-1451 in mice, effect on human microsomes and hepatocytes, genetic toxicity, and cytotoxicity in normal and cancer cell lines has been performed. With respect to neurological assessment, the no observed effect level (NOEL) of AV-1451 in rats is at least 200 µg/kg (100x MHD, allometrically scaled), the highest dose tested. Thus, AV-1451 is not expected to induce CNS effects in humans. With respect to respiratory function, the no observed effect level (NOEL) of AV-1451 in rats is at least 200 ug/kg (100x MHD, allometrically scaled), the highest dose tested. In conclusion, no respiratory effects are expected in humans from AV-1451. With respect to cardiac function, The NOEL for males and NOAEL for females was determined to be 100x MHD (allometrically scaled) on Day 1 and 50x MHD (allometrically scaled) on Day 29. In summary, AV-1451 is not expected to prolong the QT interval or have any untoward cardiovascular effects at the intended clinical dose. AV-1451 showed the potential for genotoxicity in in vitro bacterial reverse mutation assay (Ames test) and chromosomal aberration assays. However, when potential in vivo genotoxicity of AV-1451 was evaluated in a rat micronucleus study and AV-1451 did not increase the number of micronucleated polychromatic erythrocytes at the highest achievable dose level (1600 µg/kg/day for two days). This dose is greater than 750x the intended MHD, and there is no evidence for risk to human subjects at the proposed micro dose.

In summary, single-dose toxicology studies at doses up to 150x MHD and repeat-dose studies up to 50x MHD for one month showed no clinically important effects. AV-1451 was positive in the in vitro hERG assay; however, in vivo cardiovascular assessments in dogs showed no evidence of QT prolongation. Treatment emergent adverse events were reported in a total of 3 subjects who received a dose of AV-1451. Two subjects reported headache, and one subject reported diarrhea. All events were mild in severity and not considered related to AV-1451 administration by the investigator. No serious adverse events were reported for any subject receiving AV-1451. No consistent or clinically significant changes in vital signs, laboratory values, or ECG results were observed in a completed analysis of 11 subjects.

Preliminary radiation dosimetry assessment has been performed in three dosimetry subjects. The radiotracer biodistribution among the subjects was consistent and showed rapid hepatobiliary clearance. There were three organs that received estimated doses higher than 0.05 mSv/MBq. The organ that received the largest estimated dose was the upper large intestinal wall (0.107 ± 0.009 mSv/MBq), followed by the small intestine and the liver. The Effective Dose was 0.0248 ± 0.0011 mSv/MBq. This results in an estimated Effective Dose of 9.18 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved 18F- labeled compounds such as fluorodeoxyglucose (FDG) and florbetapir F-18 injection, and consistent with the primate dosimetry studies.

We have an IND and IRB approval to perform tau PET scanning with AV-1451. We will produce this compound under the IND cross referenced to the IND held by Avid Radiopharmaceuticals for this drug (Permission granted by Avid). The Radiation Safety Committee of Mayo Clinic has also approved the protocol. The radiation statement in the consent form will accurately describe the risk of the exposure from the radiation to the volunteers. Potential volunteers who are concerned about radiation exposure risk will, therefore, be given the information they need to decide whether to participate in the study or not.

It is unknown whether AV-1451 can affect reproductive capacity or cause fetal harm when administered to a pregnant woman. Therefore, women of childbearing potential must not be pregnant or lactating at screening. All females of childbearing potential will receive a urine pregnancy test within 48 hours prior injection to confirm they are not pregnant.

**Tranquilizer risks**: In some cases a mild tranquilizer (Lorazepam 1.0mg) may be given during MRI scanning in order to make the subject feel more comfortable in the event of claustrophobia or movement in the scanner. Some subjects may feel sleepy or drowsy up to eight hours after receiving this medication. There is also a small risk of difficulty breathing. The subject will be informed of the risks before administration, and they will be advised not to drive for 8 hours after receiving this medication. If driving must occur in less than 8 hours, they will need to have a significant other drive instead. The protocol will also require that the subject has someone accompany them and remain with them during the appointment to drive them home.

10/21/20: We will be collaborating and sharing de-identified data on subjects that were enrolled and provided consent for this study. We will be working with Dr. Federica Agosta at the San Raffaele Scientific Institute, Vita-Salute San Raffaele University in Milan Italy. Our collaborators want to use the data to perform a VBM analysis on 3D T1-weighted images in order to use the atrophy maps as masks to define “target” and “off-target” networks.

Data from clinical imaging studies, including FDG PET, that was done prior to or during study participation, may be used for analysis purposes so as not to expose the patient to further radioactive materials.

3/5/21: We will be collaborating and sharing de-identified data on subjects that were enrolled and provided consent for this study. We will be working with Dr. Yolande Pijnenberg and her team at Amsterdam UMC. Our collaborators want to use the data in order to better delineate the unique clinical syndrome of rtvFTD and to establish new diagnostic criteria for the syndrome. This will be an international multi-center retrospective cross-sectional study.

6/12/2024: We will be collaborating and sharing data with Dr. Hugo Botha under his IRB 22-002430. Our subjects will be provided information via a Mayo/IRB approved flyer (MC4106-667rev1223) and asked if they would like to complete a speech recording at a future time point(s). Subjects who choose to participate will sign a separate consent form for his study. Data will be shared between projects to maximize our outcomes.

10/6/24: We will be collaborating with Dr. Iaccarino (Eli Lilly and Company) to share deidentified data as part of a collaborative project studying dementia and imaging data.