Protocol Addendum AV-45 ^{18}F-AV-1451 PET

IND: 79, 511 & IND: 119863

Rationale for Master Protocol Addendum:

Due to an additional funding source Veteran subjects currently enrolled in the *Effects of traumatic brain injury and posttraumatic stress disorder on Alzheimer's disease in Veterans using ADNI* (DOD ADNI) as well as civilian subjects currently enrolled in the National Institute on Aging (NIA) funded grant entitled: *The Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2)* will be asked if they would like to participate in a sub-study/addendum which determines the effects of prior TBI and ongoing PTSD on brain tau, and the longitudinal change of brain tau, measured with the tau specific ligand ^{18}F-AV-1451([F-18] T807) and positron emission tomography (PET scanning). Patient participation in this addendum is voluntary; patients do not have to participate in this addendum to participate in either of the master protocols above. The choice not to participate in the ^{18}F-AV-1451 PET addendum will not be considered a protocol violation for either protocol.

Measurements of brain tau including longitudinal change of tau, using PET are a highly innovative approach to determining the causes of cognitive impairment. Considerable evidence suggests, while brain Aβ might precipitate cognitive decline in aging, the actual severity of the decline is more closely linked to deposition of brain tau. Furthermore, tau is deposited in cases of single TBI and patients with chronic traumatic encephalopathy (CTE). Together, these findings suggest that TBI might exacerbate Aβ-related deposition of tau and that the tau will be strongly linked to cognitive decline. Furthermore, PTSD is a common comorbidity of TBI and may be a risk factor for cognitive decline and Alzheimer's disease (AD) and that the tau will be strongly linked to cognitive decline. Therefore, the U.S. Army Medical Research and Materiel Command and the Telemedicine and Advanced Technology Research Center (TATRC) of the Department of Defense has funded a new grant, the *Effects of traumatic brain injury and post-traumatic stress disorder and Alzheimer's disease on brain Tau in Vietnam Veterans using ADNI*.

- The sample of Veteran subjects and all other procedures are identical to the DOD ADNI grant.
- The sample of civilian subjects and all other procedures are identical to the ADNI2 grant.

However, because not all of the DOD ADNI and/or ADNI2 clinic sites may be able to add the Tau scan to their clinic procedures, the Tau protocol will be added as an addendum to each of the current protocols.

Study Aims for Adding ^{18}F-AV-1451 PET:

The overall goal of this addendum is to determine the effects of prior traumatic brain injury (TBI), and ongoing post-traumatic stress disorder (PTSD) on brain tau, and the longitudinal change of brain tau, measured with the tau specific ligand ^{18}F-AV-1451 and positron emission tomography (PET) scanning.

This study will test the hypotheses that:

- The distribution of brain tau will correspond to the previously reported Braak & Braak staging;
- The brain tau in older subjects is associated with cognitive impairment and increased in the presence of brain amyloid β (Aβ) deposition (measured by Aβ PET);
- A prior history of TBI is associated with increased brain tau relative to Aβ deposition, after controlling for age and Apoe4 gene status;
- Longitudinal changes of brain tau correlate with Aβ PET, cognition, and history of TBI.

Ethical Review and Informed Consent:

Study sites participating in this addendum will be expected to obtain ethical approval of the TAU PET addendum via an ethical review board (ERB). Patient participation is voluntary, and patients do not have to participate in this addendum to participate in the DOD ADNI or ADNI2 studies. The choice not to participate in this addendum will not be considered a protocol violation for either study. The investigator at each clinic site will provide the ADCS with documentation of ERB approval of the addendum and the related informed consent form before 18F-AV-1451 PET procedures can be implemented at the participating study sites.

Study Design:

Approximately 450 baseline tau PET scans and up to 450 longitudinal scans with the ^{18}F-AV-1451 ligand will be conducted on 450 subjects who are currently enrolled in one of two funded studies:

- A DOD funded grant entitled: *Effects of traumatic brain injury and post-traumatic stress disorder on Alzheimer's disease in Vietnam Veterans using ADNI (DOD ADNI) / with and without MCI.*
- A National Institute on Aging (NIA) funded grant entitled: *The Alzheimer's Disease Neuroimaging Initiative (ADNI2)*

The 450 subjects will be divided into 9 groups of approximately 50 subjects each for a baseline scan and up to 450 subjects will be re-scanned after approximately 12 months. The nine groups are listed below:

- Six groups of Vietnam Veterans will be drawn from subjects enrolled in the DOD ADNI study.
    - Three groups of Vietnam Veterans **who meet criteria for normal cognition** with history of:
        - PTSD only
        - TBI only and/or both TBI and PTSD
        - Controls (no history of TBI and/or PTSD)
    - Three groups of Vietnam Veterans who **meet criteria for mild cognitive impairment (MCI)** with a history of:
        - PTSD only
        - TBI only and/or both TBI and PTSD,
        - Controls (no history of TBI and/or PTSD)

- Three groups of civilian subjects (who are not Vietnam Veterans) and who have no history of TBI and/or PTSD will be drawn from subjects enrolled in ADNI2. These subjects will meet criteria for one of the three groups listed below:
    - Normal cognition,
    - MCI
    - Dementia due to AD

This project will use ^{18}F-AV-1451 provided by Avid Radiopharmaceuticals, Inc. Avid will be responsible for submitting this addendum under their IND. All data will be analyzed with the data acquired by both studies. All subjects studied in this proposal will have been previously enrolled in one of the two studies described above. An attempt will be made to ensure that subjects have all or most of the longitudinal clinical, cognitive, MRI, Aβ PET, lumbar puncture with CSF analysis of tau and Aβ, and genetics. The PET scans will be transferred to the Laboratory of Neuroimaging at University of Southern California (USC), quality controlled at the University of Michigan, and analyzed at University of California (UC) Berkeley and UC San Francisco (UCSF). The project will be coordinated by the PI and his staff, as well as the Alzheimer's Disease Cooperative Study (ADCS) group at UC San Diego (UCSD), which coordinates all clinical activities for the two studies, will oversee the regulatory approvals and receive all data into the ADNI data base. All data will be made publicly available to all scientists in the world using the existing ADNI website supported by the Laboratory of Neuroimaging at University of Southern California.

Sample Size:

Utilizing the same subject groups in each of the main DOD and NIH ADNI studies, for those subjects that consent to the Tau scan, the goal is to conduct 50 baseline ^{18}F-AV-1451 ligand scans in each group and up to 50 longitudinal scans within each group (see below). Subjects will receive their initial (baseline) ^{18}F-AV-1451 PET scan at their next scheduled visit. Longitudinal scans will occur approximately 12 months after their initial scan.

All DOD ADNI Vietnam Veteran subjects enrolled in the baseline procedures will be asked to complete a baseline Tau scan as well as a longitudinal scan.

ADNI2 subjects will be selected for the ^{18}F-AV-1451 scan based on the following:

- **Site location**: Subjects will be eligible to participate in the addendum if their enrolling site is in a location in which the ^{18}F-AV-1451 ligand is available.
- **Date of ADNI visit**: Subjects will be eligible for participation in the addendum as they come in for their scheduled ADNI-2 visit.
- **Clinical status**: Controls, Subjects with MCI, or Subjects who converted to a diagnosis of AD during ADNI-2 will be eligible; and
- **Florbetapir SUVR**: Subjects with and without evidence of amyloid deposition will be identified based on review of Florbetapir SUVR and will be invited to participate.

9 Cohorts

Vietnam Veterans with Normal Cognition:

- Vietnam Veterans with TBI and/or PTSD and **without** MCI:
  - n=50 baseline
  - n=up to 50 longitudinal
- Vietnam Veterans with PTSD only and **without** MCI:
  - n=50 baseline
  - n=up to 50 longitudinal
- Vietnam Veteran Controls with no history of TBI and/or PTSD and **without** MCI:
  - n=50 baseline
  - n=up to 50 longitudinal

Vietnam Veterans who meet criteria for Mild Cognitive Impairment:

- Vietnam Veterans with TBI and/or PTSD
  - n=50 baseline
  - n=up to 50 longitudinal
- Vietnam Veterans with PTSD only
  - n=50 baseline
  - n=up to 50 longitudinal
- Vietnam Veterans with no history of TBI/PTSD
  - n=50 baseline
  - n= up to 50 longitudinal

Civilian Population:

- ADNI subjects who meet criteria for normal cognition,
  - n=50 baseline
  - n= up to 50 longitudinal
- ADNI subjects who meet criteria for MCI
  - n=50 baseline
  - n=up to 50 longitudinal
- ADNI subjects who meet criteria for AD Dementia
  - n=50 baseline
  - n=up to 50 longitudinal

Inclusion and Exclusion Criteria:

After giving informed consent, approximately 450 participants will be entered in this protocol addendum.

***Inclusion Criterion**:*

- Participants will have met all eligibility criteria for enrollment into either the main DOD-ADNI or the main ADNI2 protocols.

***Exclusion Criterion**:*

A participant will be excluded from participation in this addendum if he or she meets any of the criteria below:

- Has any condition that, in the investigator's opinion, could increase risk to the participant, limit the participant's ability to tolerate the experimental procedures, or interfere with collection/analysis of the data (for example, participants with severe chronic back pain might not be able to lie still during the scanning procedures).
- Has abnormal findings on the physical examination, or laboratory screening tests that suggest the patient might have a condition that could, in the opinion of the investigator, affect his or her response to the radiopharmaceutical and related testing procedures.
- Is deemed likely to be unable to perform all addendum imaging procedures for any reason.
- Has a history of risk factors for Torsades de Pointes or is taking medications known to prolong QT interval.
- Has ECG obtained during screening that, in the opinion of the investigator, is clinically significant with regard to the subject's participation in the study. Bazett's corrected QT (QTcB) interval must be evaluated and must not exceed >458 msec in males or >474 msec in females.
- Has hypersensitivity to ^{18}F-AV-1451 or any of its excipients.

Discontinuations

Discontinuation from the Protocol Addendum

- Participants may discontinue participation in this protocol addendum for any reason; this will not affect their participation in either the DOD-ADNI or ADNI2 study (depending on which they are currently enrolled).
- Participants who exhibit hypersensitivity to ^{18}F-AV-1451 or any of its excipients are to be discontinued from this protocol addendum and are <u>not</u> to have another ^{18}F-AV-1451 dose administered;
- Females of child-bearing potential who have a positive urine pregnancy test (HCG) will be discontinued from this protocol addendum and are <u>not</u> to have another ^{18}F-AV-1451 dose administered.

- ^{18}F-AV-1451 was positive in the in vitro hERG (human ether-à-go-go-related gene) assay, with an IC_{50} of 0.610 µM. This represents at least a 42 fold safety margin compared to the theoretical maximum plasma concentration that could be associated with the maximum human dose of 20µg in 5.2 L of blood. Additionally, in vivo cardiovascular assessments in dogs showed no evidence of QT prolongation. Nonetheless, a participant will be discontinued from the protocol addendum if it becomes necessary for the patient to start taking a medication known to prolong QT interval prior to performance of the baseline ^{18}F-AV-1451 scan.

***Discontinuation or Holding of ^{18}F-AV-1451 dose**:*

The dose of ^{18}F-AV-1451 will be discontinued or held for the following reasons:

- Following baseline, a participant is not to receive the next scheduled ^{18}F-AV-1451 dose should it become necessary for the patient to start taking a medication known to prolong QT interval and the patient is continuing to take the medication at the time of the scheduled ^{18}F-AV-1451 scan;
- If, however, a participant receives a course of a QT-prolonging medication that is finished prior to a scheduled ^{18}F-AV-1451 scan, the advisability of administering the next scheduled dose of ^{18}F-AV-1451 and performance of the ^{18}F-AV-1451 scan or holding the dose of ^{18}F-AV-1451 should be considered by the investigator in consultation with the sponsor.

Addendum Design and Schedule:

- Approximately 450 participants will participate in the ^{18}F-AV-1451 PET addendum.
- ECG with results reviewed prior to 18F-AV-1451 dose administration.
- Approximately 450 subjects (50 from each cohort) who have consented to the Addendum will complete a Tau PET scan with F18-AV-1451 PET scan at their next scheduled visit for DOD-ADNI and/or ADNI-2. For newly enrolled subjects enrolling in the DOD-ADNI study, the Tau PET scan will be performed at the baseline visit. Florbetapir scans and the F18-AV-1451scans must be at least 16 hours apart; there is no maximum time limit to obtain the two scans.
- Up to 450 subjects (50 from each cohort) will be asked to do a follow-up Tau PET scan. The follow-up scan will be conducted 12 months after their initial scan.
- In the case of early discontinuation from the DOD-ADNI or ADNI-2 studies, the final ^{18}F-AV-1451 PET scan will be obtained at the time of the early discontinuation visit if at least 3 months have passed since the most recent ^{18}F-AV-1451 scan.
- Site investigators, patients, and caregivers will not be informed of the results of the 18F-AV-1451 PET scan results as they relate to the study; however, any findings that may be of potential medical concern will be provided for appropriate follow-up.
- Females of childbearing potential are to have a urine pregnancy test (HCG) on the day of the ^{18}F-AV-1451 PET imaging session, before ^{18}F-AV-1451 dose administration.
- ^{18}F-AV-1451 PET scans should be performed at least 16 hours apart from the ^{18}F-florbetapir PET scans due to the half-life of fluorine 18.
- Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in an operations manual.

Prior to Imaging Day:

An ECG will be conducted on a separate day prior to the day of imaging to determine, in the opinion of the investigator, anything clinically significant with regard to the subject's participation in the study. (The read results must be reviewed prior to the day of dose administration). Bazett's corrected QT (QTcB) interval must be evaluated and must not exceed >458 msec in males or >474 msec in females.

Imaging Day:

The following assessments will be performed at the ^{18}F-AV-1451 PET imaging sessions:

- A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or regional equivalent) designated by the site principal investigator, must assess or evaluate the subject prior to administration of ^{18}F-AV-1451 Injection to determine if they are still suitable to undergo the scan. If a designee performs this activity, a physician must be available to provide medical consultation;
- ECG with results reviewed prior to 18F-AV-1451 dose administration
- For women of childbearing potential, a negative urine pregnancy test must be obtained on the day of ^{18}F-AV-1451 dose administration;
- Subjects will receive a single IV bolus injection of approximately (370 MBq) 10 mCi of ^{18}F-AV-1451 Injection followed by a saline flush. At approximately 75 minutes following injection, a continuous 30 minute brain scan (6 frames of 5 minute duration) will be performed after a CT or transmission scan for attenuation correction;
- The injection site will be observed for evidence of inflammation or damage to the surrounding tissue where the dose was injected;
- The subject will be requested to void after completion of the PET scan;
- Adverse events (AEs) will be continuously monitored during the ^{18}F-AV-1451 imaging session; Subjects who experience an AE will not be discharged from the imaging center until the event has resolved or stabilized; and
- A physician or a licensed/credentialed medical professional (i.e., a PET technologist, imaging center nurse or a regional equivalent) designated by the site principal investigator must assess or evaluate the subject prior to discharge from the imaging center to evaluate the subject's readiness for discharge. If a designee performs this activity, a physician must be available to provide medical consultation.
- A follow-up phone call to the subject will be conducted between 2 or 3 business days of the imaging day, but not before 48 hours post-injection, to confirm subject well-being and to collect information about any new adverse events.

Time Commitment

- An additional 2-3 hours for the Addendum Tau scan will be added to the protocol for the initial and baseline scans.

RISK:

^{18}F -AV-1451 Safety

The primary risk related to ^{18}F-AV-1451 is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion, and cumulatively, are provided in the table below.

	Effective Dose (mSv) for Baseline scan*	Effective dose (mSv) for scan 12 Months post baseline	Total Effective dose (mSv) for both scans
18F-AV-1451 Scan (10 mCi i.v.)	9.32	9.32	18.64
18F-Forbetapir Scan (10 mCi i.v.) **	7.43	N/A	7.43

**Dose shown includes radiation exposure from the radiotracer and also assumes a non-clinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is done on a PET/CT scanner. A clinical CT scan is not needed during the PET scan session and because it will add additional radiation exposure is not recommended.*

***Florbetapir scan is performed under the main DOD and NIH ADNI studies.*

In addition to radiation risk, the tau ligand ^{18}F-AV-1451 is an experimental compound in the early stages of clinical evaluation, and risks from the agent are not fully known. Details on the clinical information to date regarding ^{18}F-AV-1451 exposure and risks will be provided in the informed consent form (ICF). More information about the known and expected benefits, risks, and reasonably anticipated AEs of ^{18}F-AV-1451 may be found in the Investigator's Brochure (IB).

Adverse Events

18F-AV-1451 is an imaging agent that will be used at relatively low (tracer) doses (maximum mass dose of nonradioactive AV-1451 is 20 μg). It is recommended that subjects receiving 18F-AV-1451 be followed by means of appropriate safety measurements throughout the course of study participation. In the event of a study related adverse event, subjects should not be discharged until the event has resolved or stabilized.

In exploratory studies that dosed a total of 35 subjects with 18F-AV-1451, two subjects reported headache, one subject reported diarrhea, and one subject reported musculoskeletal discomfort. Because events reported during these studies could be related in part to the PET scan apparatus and procedures, careful attention should be taken to make the subject aware of the planned procedures and to maximize subject comfort in the scanner. No consistent and clinically significant pattern of changes in vital signs, ECG, or laboratory changes was observed in a completed analysis of 11 subjects enrolled in one study. All events were mild in severity and not considered related to 18F-AV-1451 administration by the investigator. No serious adverse events were reported for any subject receiving 18F-AV-1451.

A Serious adverse event (SAE) spontaneously reported to have occurred within 48 hours of ^{18}F-AV-1451 administration will be reported, regardless of the investigator's opinion of causation. Thereafter, reporting of SAEs to Eli Lilly is not required for events that occur outside of this time period unless the investigator feels the events were related to either ^{18}F-AV-1451 or the drug delivery system, or a protocol procedure.

Analyses for Addendum Hypotheses

Hypothesis 1: The primary outcome variables for this hypothesis are the Braak & Braak stage ROI ^{18}F-AV-1451 uptakes (3 outcome variables per person). Because there are repeated measures (across the Braak & Braak stages), repeated measures regression models will be used to test the primary hypothesis. The first set of analyses will focus on the ADNI non-veterans to understand differences by diagnostic group. In this model, diagnostic group and Braak & Braak stage (and their interaction) will be considered as primary predictors, each coded in a hierarchical manner so that coefficients directly test particular contrasts of interest. For example, in Braak I-II, do those with dementia due to AD have higher ^{18}F-AV-1451 uptake than cognitive normal and do MCI have higher ^{18}F-AV-1451 uptake than cognitively normal individuals? Further, is there a larger difference in ^{18}F-AV-1451 uptake at Braak III-IV between MCI and cognitively normal (or dementia due to AD and cognitive normal) than at Braak I-II or similarly a larger difference at Braak V-VI than at Braak III-IV? The hypothesis will be supported if differences between diagnostic groups are larger particularly at the later Braak stages. The next set of analyses will use the MCI and cognitively normal veterans with TBI, PTSD, or neither from the DOD proposals to understand differences between MCI and cognitively normal in veterans, as well as the impact of TBI or PTSD in veterans on ^{18}F-AV-1451 uptake. In these repeated measures models, diagnosis (MCI vs. cognitively normal), TBI (vs. no PTSD or TBI), and PTSD (vs. no TBI or PTSD) and the interactions between diagnosis and TBI or PTSD will be considered. Finally, a global model will be assessed across all individuals from the two funded DOD proposals and the ADNI study of non-veterans to primarily compare the veteran groups to the non-veteran groups. All of these models can further include age, sex, and Apoe4 status. All model assumptions will be checked and transformations or generalized estimating equation approaches for non-normal repeated measures data will be considered if necessary.

Hypothesis 2: For the first part of the hypothesis, episodic memory will be the primary outcome (other cognitive functions will be explored later). Linear regression models will be used to assess the association between ^{18}F-AV-1451 uptake and cognitive function. The primary independent variable will be a global measure of ^{18}F-AV-1451 uptake, although additional analyses will consider the Braak & Braak stage ROIs to see if there are regional differences in the association with cognitive function. Similar to the

repeated measures models for Hypothesis 1, these models will include potential confounders including age, education, and Apoe4 status. Model assumptions of normality of the residuals, constant variance, and linearity will be checked and transformations or non-linear models will be considered if needed. The first part of the hypothesis will be supported if higher ^{18}F-AV-1451 uptake is associated with worse cognitive function. For the second part of the hypothesis, ^{18}F-AV-1451 uptake will be considered the primary outcome variable while Aβ deposition measured by florbetapir SUVR will be considered the primary independent variable. When considering global ^{18}F-AV-1451 uptake, linear regression models will be the analytic method. When considering the Braak & Braak stage ROIs, repeated measures regression models similar to those described in Hypothesis 1 will be used.

Hypothesis 3: The analysis for this hypothesis will build on the model that was used for the second part of Hypothesis 2. Previous history of TBI and its interaction with Aβ deposition will be included in the model (in addition to Aβ deposition and confounders such as age and Apoe4 status) to see if those with a previous history of TBI and Aβ deposition have even higher ^{18}F-AV-1451 uptake than those without a previous history of TBI. The hypothesis will be supported if the interaction between history of TBI and Aβ deposition is statistically significant and positive.

Longitudinal hypotheses: Change in tau, as measured by differences between the time 2 and time 1 images will be the primary outcome when assessing associations with Aβ deposition or history of TBI. Aβ deposition (florbetapir SUVR) will first be considered as a continuous variable, though secondary analyses will compare change in tau in those that are Aβ positive versus Aβ negative. Linear regression, similar to that described above for Hypothesis 2, will be used to assess associations or differences between groups while adjusting for potential confounders of age and Apoe4 status. Finally, to assess associations between change in tau and change in episodic memory, the primary analytic strategy will use an extension of the repeated-measures, random effects models called simultaneous modeling, which utilizes the repeated-measures of both tau and episodic memory simultaneously in the same model. This technique allows for different observation times for the different outcomes, different predictors for each outcome (such as age, education, or Apoe4 status), and estimates of the between- and within-person variability. Model validation will be carried out using analytic and graphical techniques to check the core assumptions about linearity, homoscedasticity, multivariate normality, and independence of the within-person residuals beyond the person specific random effects. Hypotheses will be supported if there is a significant correlation between change in tau and change in episodic memory. Alternative strategies, if the simultaneous models do not converge, include linear regression models that use change in episodic memory as an outcome and change in tau as a predictor.

Power considerations: For Hypothesis 1, assuming 50 individuals per group, we will have 80% power to detect a difference as small as 0.57 standard deviations assuming alpha=0.05 and a two-sided test. If we reduce alpha to 0.01, we will still have 80% power to detect a difference as small as 0.69 standard deviations. Recent studies from AIBL [351] and ADNI [344] found effect sizes ranging from 0.71 to 2.2 when performing similar comparisons with Aβ deposition with the smallest effect size between MCI and NL subjects in ADNI; we expect tau to have similar effect sizes when comparing groups, so we should have ample power to detect effects. For Hypothesis 2, using all 450 subjects across all of the studies, we will have 80% power to detect a correlation as small as 0.13, assuming alpha=0.05 (0.16 with alpha=0.01) between ^{18}F-AV-1451 uptake and cognition or Aβ deposition and ^{18}F-AV-1451 uptake. If other variables account for 10-20% of the variability in the outcome, we will still have 80% power to detect an

association accounting for as little as 1.4-1.6% of the variability (2.0- 2.3% with alpha=0.01). For Hypothesis 3, we will have 80% power to detect a difference in correlation as small as 0.30 (0.36 with alpha=0.01) assuming the correlation in the group without a previous history of TBI is at least 0.1. For the longitudinal hypotheses involving correlations, we will have 80% power to detect a correlation as small as 0.21 (0.25 with alpha=0.01) between change in tau and Aβ deposition or change in cognition, assuming 180 individuals. If other variables account for 10-20% of the variability in change the outcome, we will still have 80% power to detect an association accounting for 3.4-3.8% of the variability (5.0-5.6% with alpha=0.01) attributable to change in tau. When comparing those with and without a history of TBI, we will have 80% power to detect a difference as small as 0.91 standard deviations (1.13 standard deviations with alpha=0.01).

Exploratory Multimodality Tau-PET and MRI analysis: This project will generate the first voxel-based NFT distribution maps in vivo, enabling correlation of tau with neurodegeneration, quantified as atrophy from T1-MRI, WM fiber integrity indices from DW-MRI, network dysfunction from tf-fMRI, and WMH and hemorrhages/micro bleeds from FLAIR and GRE. We hypothesize that co-varying tau burden across MTL brain regions may reveal a pattern of neurodegeneration that is characteristic to normal cognition and MCI. We further hypothesize that the rate of tau progression will correlate with progression of neurodegeneration. The subjects with past history of TBI will have greater degree and spread of the tau-associated neurodegeneration than people without TBI history. As an exploratory analysis, we will use a voxel-based multivariate statistical analysis technique, parallel independent component analysis (ICA) [352], to investigate the differential linkage between MRI measures of brain structure and function and F-18 ^{18}F-AV-1451 PET SUVR distribution in different cohorts. The method aims to identify co-varying patterns of each modality (MRI versus ^{18}F-AV-1451 PET), and the relationships between them, simultaneously. Compared to voxelwise univariate and other multivariate analysis methods, the primary advantage of parallel ICA is the ability to identify associations between image modalities across spatially separated brain regions, without selecting regions a-priori.

References:

Investigators Brochure, 18F- AV-1451 ([F-18] T807) Injection for Brain Tau Imaging, 2014.