Study Protocol and Statistical Analysis Plan

Study Title: FDDNP-PET Imaging in Persons at risk for Chronic Traumatic Encephalopathy

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Specific Aims:
The proposed project will focus on application of small molecule radiolabeled probes of tau neurofibrillary tangles (NFTs) for in vivo positron emission tomography (PET) imaging of brain pathology for early detection and treatment monitoring of Chronic Traumatic Encephalopathy (CTE) and related neurodegenerative diseases (dementias and cognitive impairment).

We plan to test the following hypothesis: PET imaging with small molecule probes, in the form of novel fluorescent dyes with radioactive labels, will demonstrate distinct cerebral patterns of binding in subjects with CTE. These cerebral patterns will differentiate from those of age-matched persons who are cognitively intact or from the patients with other neurodegenerative diseases.

The binding patterns will match the disease specific pattern of brain pathology characteristic for CTE (or other dementias, when studied). CTE distinguishes itself from other dementias by its clear tauopathy: NFTs and neuritic threads. In addition, brains of CTE subjects show white matter changes and inflammation.

In order to assess in vivo deposition of CTE's tauopathy, we propose to use PET imaging with [F-18]FDDNP, a molecular imaging probe for PET, with high in vitro binding affinity to NFTs and of the fibrillar tau deposits as shown with fluorescent microscopy with non-radioactive FDDNP. The analysis of [F-18]FDDNP will allow us to evaluate the specificity and sensitivity of this imaging probe for detection of the brain pathology and utilization of these methods for detection of early deposition and for monitoring of any therapeutic intervention aimed at stopping or reducing the deposition of neuropathologic aggregates.

Simple blood-based biomarkers that correlate biochemical changes to clinical or cognitive status, when used in conjunction with genetic risk status, may increase the power of predicting who will decline in an asymptomatic population. An additional aspect of this protocol is to obtain blood based biomarker information to identify differences in markers of CTE sufferers. Better characterizing the relationship between various biochemical markers and disease status may allow us to improve our understanding of CTE causes, enhance our ability to diagnose early, and may lead to more effective treatments in the future. We propose investigating several blood-based biomarkers related to inflammation, (Interleukin (IL)-1, I-309, IL-6, IL-13, and superoxide dismutase 3; SOD3) in diseased (clinical diagnosis of AD) and healthy APOE e3 and APOE e4 carrying individuals to better characterize inflammation levels in these genetic groups.

In addition to the above hypotheses, neuropathological data from autopsy follow-up will be used to determine correlations between regional plaque and tangle deposition patterns and PET signals. We will create PET cortical surface maps for [F-18]FDDNP-PET between subjects with Traumatic Brain Injury and controls compared with region of interest analysis in transaxial PET images. MRI scans will be available for diffusion tensor imaging (DTI), and we will use these DTI measures to confirm our anticipated findings of greater white matter integrity in controls compared with AD patients.

Background and Significance:
Emerging evidence indicates that repetitive, mild traumatic brain injury (MTBI) may have long lasting effects following exposure during contact sports or military activities. As a result of the recent military conflicts, 95% of U.S. veterans have returned from the war returning from the war in Iraq and Afghanistan with head injuries resulting from non-penetrating mechanisms.

The syndrome of Chronic Traumatic Encephalopathy (CTE) has been established by WVU researchers in 25 contact-sport athletes, including one military veteran previously diagnosed as having Post Traumatic Stress Disorder. CTE was first diagnosed in 2005 by the neuropathologist Bennet Omalu, M.D. (Raghupathi, Graham & McIntosh, 2000; Omalu et al. 2005; 2006). In addition, studies of retired NFL players have found a high incidence of dementia, Alzheimer's disease, mild cognitive impairment, and depression in these patients. The only correlative risk factor was the presence of three or more significant concussions or MTBI's during their NFL playing career (Guskiewicz et al., 2005; 2007).

Chronic Traumatic Encephalopathy consists of a characteristic neurobehavioral syndrome manifested by failed relationships, marriages, and businesses, emotional disturbances, depression, alcohol and substance abuse, and suicide attempts and completions. It typically begins after a latency period of several years following single or repeated Traumatic Brain Injuries (TBIs). A history of cerebral concussion may or may not be present. The clinical syndrome usually terminates in suicide (Bailes & Cantu, 2001; Omalu et al., 2010; 2010b). The neuroanatomical correlate consists of a tauopathy, the abnormal staining indicative of tau protein deposition in neuronal cell bodies and their axonal and dendritic connections. These representative changes of neurofibrillary tangles (NFTs) and neuritic threads (NTs) are characteristic of CTE, and distinguish it from other forms of dementia. In addition, white matter changes and inflammation are also seen in these brain specimens (Omalu et al., 2010b).

Chronic Traumatic Encephalopathy has a classical distribution that differs than other forms of dementia, and sub-typing based on location and distribution is reflected in the recent Omalu-Bailes classification (Omalu et al., 2010b). The areas of involvement are the temporal and frontal cortices, in addition to the mesencephalon and upper pons, locus cereuleus, and substantia nigra. This distribution, along with the history of multiple exposures to MTBI, the age distribution, and anatomical patterns further distinguishes this condition from Alzheimer's disease and other forms of dementia. In addition, 70% of athletes diagnosed postmortem with CTE are positive for apolipoprotein A3 (Omalu et al., 2010b).

Currently, the only method to diagnose CTE is through post-mortem brain examination, utilizing special immuno-staining techniques for tau protein deposits in NFTs and NTs. The ability to image tau protein collections in vivo in the form of NFTs would provide tremendous benefit for clinical management, treatment, and possibly prevention if a pre-morbid diagnosis could be confirmed. The implications for the sports communities, military organizations, and the general population, all of whom have potential exposure to MTBI, are tremendous.

UCLA scientists have developed the only currently available in vivo method to measure NFTs and of the fibrillar tau deposits in the brain. This discovery was led by Dr. Jorge

Barrio (Molecular and Medical Pharmacology), Dr. Gary Small (UCLA Center on Aging, Aging and Memory Research Center at the Semel Institute at UCLA), and others, working in the UCLA PET scan program. They sought a way to directly measure the physical evidence of Alzheimer's disease – the abnormal amyloid brain protein deposits including amyloid plaques and tau NFTs– in the living patient. A key to the discovery was the realization that the internal environments of these abnormal proteins were hydrophobic, that is, less friendly to water than to fat. Dr. Jorge Barrio synthesized a new group of compounds that thrived in these hydrophobic environments, and these molecules passed easily from the blood stream to brain tissues.

In initial autopsy studies, the UCLA group found that one of these new compounds (called FDDNP – UCLA Patent Ref. No. 1998-507-1) clearly displayed the well-defined amyloid proteins characteristic of the disease. They then injected a radioactive form of the compound into the veins of living Alzheimer's patients, and the PET scan accurately measured the concentration of the compound in the patient's brain. This allowed them to see for the first time, increased signals coming from living human brains in areas that contained dense collections of the abnormal proteins. .

The chemical marker essentially seeks out and temporarily attaches itself to the abnormal amyloid, thus providing a clear PET scan signal in the areas of the brain where Alzheimer's strikes. In healthy people without Alzheimer's, these brain regions produce little or no signal. However, in people with the disease, the signal is so strong and accurate that it actually correlates with each individual's degree of memory impairment. The UCLA group has also found that people who are at risk for Alzheimer's disease (mild cognitive impairment) have an amyloid-PET pattern intermediate between normal people and patients with Alzheimer's and that [F-18]FDDNP binding is influenced by APOE-4 status (Small et al., 2009; 2010). Therefore, this technology will likely assist in early detection of the disease so that prevention treatments might be used prior to significant cognitive decline. It will also be useful in detecting and developing treatments for other conditions. Patients with dementias that have different treatment approaches (e.g., frontotemporal) have an [F-18]FDDNP-PET pattern distinct from Alzheimer's, as do patients with cognitive impairment associated with prion disease(Kepe et al., 2010).

Research Design and Methods:
Subjects in all portions of the study will have the procedures outlined below.
The following procedures are performed solely for research purposes.

Potential subjects will be recruited from a variety of sources including:

1. Referrals from our co-investigators, and other colleagues;
2. Referral from previously enrolled research subjects;
3. Self-referral from word of mouth in the community or from media surrounding our pilot study (Small et al., 2013);
4. Referrals from healthcare providers, the NFL Network, NFL Player's Association and other sports associations and leagues.
5. Referrals from TauMark, licensee of the FDDNP tracer.

Potential participants will be screened via telephone by a staff member to determine eligibility. Subjects who meet eligibility criteria will be enrolled. Oral consent will be required to perform the telephone screen.

Study Procedures

A. Screening and Clinical Evaluation (1 hr)
B. Informed Consent (30 min)
C. Routine Laboratory Blood Draw, DNA Blood Sample and EKG (1 hr)
D. [F-18]FDDNP-PET/CT scan (1 hr)
E. Neuropsychological Evaluation (3 hrs)
F. MRI or Computed Tomography (CT) Scan (1 hr)
    a. Only subjects who are not eligible for MRI scans will undergo CT scanning.

A. Screening and Clinical Evaluation: The screening and evaluation are performed in a private office on the UCLA medical campus. The medical evaluation includes a psychosocial history and medical record review by one of the study physicians, as well as a neuropsychiatric evaluation. If there is doubt that a player's diagnosis is consistent with CTE, one of the study neurologists will provide a second opinion and conduct a neurological evaluation. Other measures recorded are as follows:

1. Hachinski Ischemic Scale - completed by physician
2. Clinical Dementia Rating Scale - completed by physician
3. Blessed Dementia Scale - completed by SRA under physician's supervision
4. Cornell Scale for Depression in Dementia - completed by SRA under physician's supervision
5. Katz Scale - completed by SRA under physician's supervision
6. Family History Questionnaire - completed by SRA
7. Framingham Stroke Risk Factor Prediction Chart - completed by SRA
8. STOP-BANG Questionnaire for Sleep Apnea - completed by SRA
9. Pittsburg Sleep Quality Index - completed by SRA

B. Informed Consent:

- If the potential subject meets inclusion criteria following screening and clinical evaluation, the subject will be consented and enrolled into the study.

Autopsy Consent:
Patients seen as part of the study may choose (or their families may choose for them) to sign UCLA form #30903 (rev 5/07), "UCLA Healthcare Report of Death and Permission for Postmortem Examination" authorizing a clinical autopsy to be conducted at UCLA. The autopsy program is administered through the UCLA Decedent Affairs office.

C. Laboratory Assessment (Blood Draw): Subjects are taken to the Clinical and Translational Research Center (CTRC) or to the Clinical Translational Research Laboratory (CTRL) for routine lab work and collection of a DNA blood sample. Subjects must be fasting 8-9 hours priori to the labs, for accuracy on the cholesterol lab test. The following tests are performed:

1. CBC & PLT & DIFF
2. Free T4 Index
3. Vitamin B12 Serum
4. Chem Panel
5. Uric Acid
6. TSH
7. Cholesterol

8. RPR with FTA Confirmation
9. Blood collection for DNA Analysis
10. Vital Signs, Height and Weight, and an Electrocardiogram

D. [F-18]FDDNP-PET Scan or PET/CT Scan: Subjects will undergo the [F-18]FDDNP-PET/CT scan at the UCLA Nuclear Medicine Clinic, the Ronald Reagan Medical Center Neurosurgery Center (6th Floor), or the UCLA Brain Mapping Center. While in the scanner in a dimmed room, all subjects receive a 10 mCi intravenous injection of F-18]FDDNP. During the scanning, each subject is asked to lie still. The procedure will take 1 hour of the subject's time.

Scanning is performed on a CTI/Siemens 831-08 tomograph (Siemens Corp, Hoffman Estates, 111) in three-dimensional acquisition mode (inter-plane septa removed), using double the previous standard axial sampling (Cherry et al, 1991, 1992). Imaging commences immediately after administration of the radiolabeled dye and lasts for 65 minutes, with > 2 million counts per plane.

Female subjects of child-bearing age will be required to provide a urine sample prior to undergoing the FDDNP PET scan. The urine pregnancy test will be done at the Nuclear Medicine Clinic, the Ronald Reagan Medical Center Neurosurgery Center (6th Floor), or the UCLA Brain Mapping Center. Pregnant women will be withdrawn from the study.

E. Neuropsychological Evaluation: The neuropsychological test battery includes:

A. INTERVIEW

B. MOOD SCREENING

- Hamilton Rating Scale Depression (17 item)
- Hamilton Anxiety Scale
- Suicide Behavior Questionnaire - Revised
- Pfeffer Functional Activities Questionnaire (FAQ)
- Geriatric Depression Scale (GDS)
- Mini-mental Status Exam (MMSE) (10 min)

C. NEUROPSYCHOLOGICAL MEASURES

- Test of Premorbid Functioning (i.e. revised version of Wechsler Test of Adult Reading)
- WAIS-IV Digit Span
- Boston Naming Test
- WMS-IV Logical Memory—Immediate
- WAIS-IV Block Design
- Benton Facial Recognition Test (short form)
- WAIS-IV Similarities
- Buschke Selective Reminding Test
- Trails A
- Trails B
- Rey-Osterrieth Complex Figure Test
- Verbal Fluency—CFL or FAS (4 min)
- Animal Naming (2 min)
- Baron-Cohen Emotional Recognition Tests
- Advanced Clinical solutions Social Perception Subtests

- Malingering test: Nonverbal Medical Symptom Validity Test

Patients are tested in a private office. Healthy and motivated subjects can generally complete the battery in a three-hour period, including time for periodic rest breaks.

F. MRI Scan or CT Scan:

A 3 Tesla Siemens Trio with a 12 channel receive head array will be used. 2-fold parallel acceleration will be used for all image acquisitions. Specific image acquisitions will be as follows:

3-D T1-weighted Anatomic Imaging (8 min): MP-RAGE imaging will be obtained at a spatial resolution of 1x1x1 mm^3 using ADNI compliant image acquisition parameters.

DTI (14 min): High angular resolution diffusion imaging (HARDI) will be obtained using a vendor supplied single-shot spin-echo echo-planar imaging (SE-EPI) pulse sequence that incorporates a twice-refocused spin echo acquisition to reduce eddy current induced spatial distortions. Sixty-four diffusion weighted image (DWI) volumes will be collected using a b-factor of 1000 sec mm^{-2} and uniform directional sampling. Ten image volumes will be collected with a near zero b-factor with all other acquisition parameters held identical to those used for the b = 1000 DWIs. Each 3D DWI volume will consist of 75 contiguous 2-mm thick axial slices having 2.0 x 2.0 mm^2 in-plane resolution.

SWI (5 min): Susceptibility Weighted Imaging will be performed using the vendor supplied pulse sequence (gradient recalled echo imaging with TR/TE/FA = 30/20/15, 1.0 x 1.0 x 2.0 mm^3 spatial resolution).

FLAIR (4 min): Fluid attenuated inversion recovery imaging will be performed using a vendor supplied turbo spin-echo pulse sequence with TR/TE/TI = 9000/80/2500 and spatial resolution = 1.0 x 1.0 x 2.0 mm^3.

Image Quality Review: FLAIR images will be reviewed for incidental findings such as mass lesions or brain infection that are unrelated to the study goals. Subjects showing such findings will be replaced by new recruitments. All other images will be reviewed for incidental findings and/or artifacts, such as head motion during the DTI image acquisition. If artifacts are present, the subject will be invited to return for a replacement study or be replaced by a new recruitment.

Image Preprocessing: For each set of individual subject images the following procedures will be performed. MP-RAGE images will be intensity-normalized, skull stripped and segmented for tissue type (GM, WM, CSF and background (BG)) using standard automated procedures (e.g. FSL, SPM, MIPAV software). Any head injury related white matter lesions (i.e. DAI, microhemorrhage etc) that are misassigned by the segmentation procedure will be manually corrected. FDDNP labeled GM regions are sometimes also mislabeled by automatic segmentation programs. These segmentation errors will also be checked for and manually corrected if necessary. MP-RAGE, FLAIR, and SWI image volumes will be aligned to the DTI image volumes by reading spatial parameters stored in the DICOM headers for each image type and then calculating and applying the optimal re-alignment matrix that will align these images with the DTI-related images. Alignments done in this way are very accurate but can be adversely affected by scan subject movement. If evidence of movement is present, hard body intensity-based

alignment will be used to correct the alignment. FDDNP images will be aligned to the skull stripped MP-RAGE intensity images using hard body intensity-based alignment after spatial rescale to match voxel size. Then FDDNP images will then be aligned to the DTI space using the same realignment matrix that is used for the MP-RAGE images. Tissue segment images will be aligned to the DTI space using this same procedure (e.g., **Fig. 1** shows alignment of DTI and FDDNP images). This approach to within-study alignment reduces the possibility of alignment errors that result from EPI-related surface distortions in the DTI images and makes optimal use of the DTI resolution. Eddy current distortions will be corrected for each DWI and B0 image individually using software that corrects for distortion in the phase encode direction only. Principal diffusivities (λ1, λ2, λ3 (eigenvalues)), mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), fiber orientation (eigenvector) images, and fractional anisotropy (FA) images will be computed using the standard approach (Basser, 1995). Automated streamline tractography will then be used to identify all detectable WM tracts (DTIStudio or FSL software). This process will result in the following aligned 3D images for each subject: MP-RAGE intensity, GM, WM, CSF, FDDNP, SWI magnitude, SWI phase, FLAIR, λ1, λ2, λ3, MD, FA, and an array of Streamline Tract (ST) images.

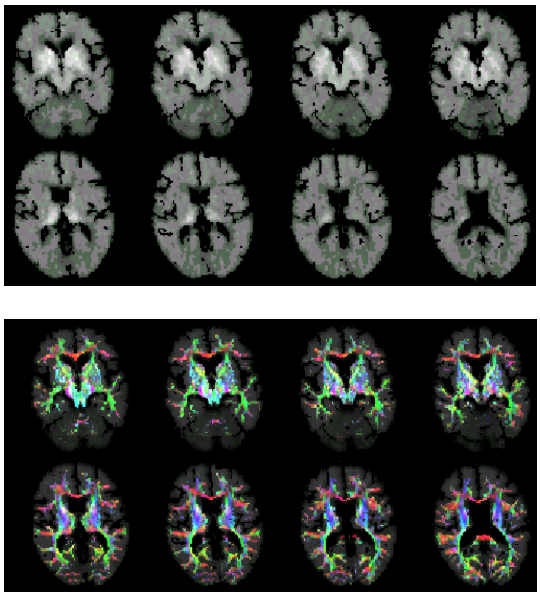

Fig. 1. Example of alignment of FDDNP and DTI images on a patient with MCI with basal ganglia and thalamus FDDNP labeling. The top panel shows 8 slices from a 3D FDDNP image volume that has been aligned to the DTI target space. The bottom panel shows the DTI color map data for this subject overlaid onto the same FDDNP images.

Location of scanner and procedure for research subjects:
Subjects will undergo a structural/functional scans using the 3-Tesla MRI scanner in the Staglin IMHRO Center for Cognitive Neuroscience at UCLA. Alternatively, subjects may undergo scanning at the UCLA Department of Radiology or at the UCLA Brain Mapping Center, using a 1.5 or 3 Tesla MRI scanner. Subject will lie on a narrow bed in a closed screened room. The sound of the MRI scanner can be loud and special earplugs will be given to subjects to minimize the noise. During the MRI, subjects may be asked to perform sensory, mental or movement tasks. Subjects will need to remain motionless for periods of up to 30 minutes (although most procedures will be much shorter). The MRI scan will take approximately one hour.

Subjects who cannot undergo MRI scanning will undergo one Diagnostic Brain Computed Tomography scan in the UCLA Department of Nuclear Medicine or the Department Radiology.

G. Benzodiazepine Medication for Anxiety

Subjects who anticipate becoming anxious or claustrophobic during brain imaging procedures may request benzodiazepine medication during the PET/CT, MRI and CT scans. One of the study physicians will evaluate requests individually and if warranted, prescribe one of the following medications:

- Alprazolam 0.5-2 mg
- Lorazepam 0.5-4 mg
- Clonazepam 0.25-2 mg
- Diazepam 5-20 mg

Data Analysis of Records from Database IRB# 12-001391

Research records from control subjects will be retrieved from the Longevity Center Research Database and compared to TBI participants' research records.

Data is stored in an MS Access table-based relational database, which resides on a 64-bit SSL encrypted server to provide security for transmission of any sensitive or confidential data. The computerized database will be protected through the use of entry codes available only to authorized personnel. An identification (ID) number is assigned to each subject; only the ID numbers and not subjects' names are used in data files. The key that matches the participant names and ID numbers remains in a file cabinet accessible only to authorized personnel. Subjects' identities are not disclosed by publication or any other means. Comparison subjects will be identified only through their subject ID. Data used in this study will not contain comparison subjects' identifying information other than age.

Between-group analyses have been described in section 6.0 "Statistics and Data Analysis."

Data Collection and Analysis

Time required of subjects, per visit or contact, and in total for the study:

The study duration is 4-6 weeks. The total time per subject will not exceed twelve hours.

Statistics and Data Analysis:

The study examines FDDNP binding signals at baseline in persons with a history of Traumatic Brain Injury with and without signs of cognitive and mood changes congruent with Chronic Traumatic Encephalopathy (CTE) presentation. We expect to show greater FDDNP binding in the regions of interest with age-matched controls. Data for age-matched controls will be obtained through previously collected data from Database IRB# 12-00391. The study's hypotheses will be examined by using nonparametric Wilcoxon tests, with global, frontal and medial temporal FDDNP signals as the dependent variables and group (CTE vs. control) as the classification variable. We will also estimate regression models within the CTE group and examine whether more impaired neurocognitive performance is associated with greater FDDNP binding signals, especially in the medial temporal region. Again, rank-based analyses will be conducted

due to the small sample size. Data will also be compared to neuropathological data obtained at autopsy.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Agreement to participate in study
2. A history of Traumatic Brain Injury resulting from, but not limited to, any of the following: sports, accidents, violence, and military combat.
3. Age 18 or older
4. No significant cerebrovascular disease – modified Ischemic Score of ≤ 8 (Rosen et al, 1980)
5. Adequate visual and auditory acuity to allow neuropsychological testing.

Exclusion Criteria:

1. Preexisting major neurologic or other physical illness that could confound results (e.g., multiple sclerosis, diabetes, cancer)
2. Unstable cardiac disease
3. Uncontrolled hypertension (systolic BP > 170 or diastolic BP > 100)
4. Current major psychiatric disorders such as mania or schizophrenia, which might interfere with completing study procedures (APA, 2000)
5. Subjects taking ibuprofen or naproxen will be asked to stop taking the medication for five days before the PET scan since these medicines may affect FDDNP-PET scan results. Other anti-inflammatory medicines, such as diclofenac or aspirin, can be substituted during that period. If the subject cannot temporarily discontinue the medicine, that subject will be excluded from the study.
6. Use of any investigational drugs within the previous month or longer (depending on drug half-life)
7. Pregnant and nursing subjects will be excluded.

POTENTIAL RISKS AND DISCOMFORTS (as described to subjects)

1. SCREENING

You may feel uncomfortable answering some of the screening questions. You do not have to answer any questions you do not wish to answer and you may stop at any time. Your participation in the screening is voluntary. A decision whether or not to participate in the screening will not affect your relationship with UCLA. You will not directly benefit from the screening.

Your answers will be confidential. No one will know the answers except for the research team. If you decide to answer the questions of the screening interview, it will determine your eligibility for the research. If you qualify for the study, you will be asked to read through and sign an informed consent. Your answers will be kept with your other research generated records. If you do not qualify for the study, your answers will be destroyed.

2. BLOOD DRAW FOR ROUTINE BLOOD ANALYSIS AND DNA SAMPLE

The risks include problems associated with blood drawing. This is a routine procedure performed under standard and sterile medical conditions. The potential side effects of

removing blood may include momentary discomfort during the puncture, lightheadedness, faintness, and soreness and discoloration of the area for several days. In very rare instances, either bleeding or infection can develop at the venipuncture site. There is no more discomfort encountered than when blood samples are taken during periodic medical examinations or when blood is donated at a blood bank.

3. BLOOD DRAW FOR GENETIC ANALYSIS

The data collected for genetic analysis will not be kept in your medical record and will remain strictly confidential. The potential side effects of genetic analysis of blood may, however, involve certain psychological and social risks in the advent of inadvertent disclosure. These risks include:

a. Broad sharing of phenotype and genomic data (e.g. genotype, DNA sequence, expression profiles, etc.);
b. Computer security breaches;
c. Other unanticipated distributions arising from maintaining data in an electronic format;
d. Privacy breaches (both those known and those unforeseen at this time);
e. Uncertainty of findings related to genetic risk for a given disease or trait;
f. Risks to relatives or identifiable populations or groups;
g. Physical risks (such as those associated with collecting blood or other tissues samples).

Effective November 2009, federal legislation (The Genetic Information Nondiscrimination Act, or GINA) was passed to provide baseline protection against discrimination in employment and health insurances decisions across the nation.

4. NEUROPSYCHOLOGICAL EVALUATION

You may experience feelings of failure, frustration, or anxiety induced by neuropsychological testing. The psychologist administering the tests is experienced in assessing persons and will convey a relaxed and confident attitude. You have the right to refuse to answer any questions that you may not wish to answer. If you do have the above reaction to the evaluation, it should go away at the completion of the test. If you finish the test and feel anxious, then you can talk to the psychologist who administered the test.

In the event that you tell the research staff that you are thinking about killing yourself or you answer yes to a question about having thoughts about suicide, the investigator will ask you more questions about these thoughts. Depending on your answers to these questions, the research staff may:

a. Provide you with referrals for treatment;
b. Work with you to contact your personal physician, trusted family member, or therapist to discuss your thoughts of harming yourself;
c. Work with you on a plan that may include getting you to a hospital for safety.

5. PET/CT SCAN and CT SCAN SRADIATION EXPOSURE

You are exposed to radiation on a daily basis, both from natural (sun and earth) and manmade sources. The estimated radiation dose that you will receive as a volunteer for this type of research has been compared to the limits allowed for a radiation worker. This

limit is low and is not expected to be harmful. The person obtaining your consent can answer any questions you have, and provide detailed written information about the amount of radiation resulting from this study.

PARTICIPATING IN OTHER RESEARCH STUDIES INVOLVING RADIATION:
If within one year, you have participated, are participating, or are considering participating in another research study that involves radiation (PET scan, SPEC scan, DEXA scan, CT scan, radiation therapy, chemotherapy, etc.), please let a member of the research personnel know immediately.

Research personnel may ask you to sign a medical release form to access your medical history in order to determine whether it is safe for you to partake in the study. The investigator/or associates will ensure through accurate record keeping, that the total amount of radioactivity administered for research purposes will remain small and is not expected to cause any adverse effects.

Estimated Radiation Doses for One FDDNP-PET/CT Scan:
If the PET/CT scan is performed, the total estimated radiation dose to the whole body would be 153 millirem, or 3% of the 5,000 millirem annual whole body limit allowed adult radiation workers. The total estimated radiation dose to the primary critical organ (gallbladder) would be 544 millirem, or 1% of the 50,000 millirem annual limit radiation workers. The total estimated radiation dose to the secondary critical organ (liver) would be 497 millirem, or 1% of the 50,000 millirem annual limit allowed radiation workers.

Estimated Radiation Dose for One Helical CT Scan of the Head:
If the CT scan is performed, the total estimated radiation dose to the whole body would be 220 millirem, or 4% of the 5,000 millirem annual whole body limit allowed adult radiation workers.

6. MAGNETIC RESONANCE IMAGING (MRI)
You may experience anxiety and/or claustrophobia from being in an enclosed space. You can ask to be taken out of the scanner at any time. Earplugs will be given during the MRI procedure.

The magnetism of the machine attracts certain metals; therefore, people with these metals within their bodies (such as pacemakers, infusion pumps, aneurysm clips, metal prostheses, joints, rods, or plates) will be excluded from the study. The “metal” in dental fillings is less responsive to magnetism and is therefore allowed. The MRI technician will ask you if you have any metals within your body. **You will be expected to notify the investigator conducting the study of any metal in your body, other than dental fillings.**

There are no other known side effects resulting from exposure to the MRI scan. However, there may be risks that are currently unforeseeable. In the studies performed so far, there have been no significant risks reported in animals or humans for similar exposures.

7. BENZODIAZEPINE MEDICATION FOR ANXIETY (This section may not apply to you)

Benzodiazepines in general tend to be very well tolerated. Some common side effects include temporary drowsiness, dizziness and increased saliva production. The doctor will make sure to go over your medical history to make sure that this medication is safe for you.

This study may include unforeseen risks.

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