Project Summary/Abstract: Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer's disease (AD) in Veterans using ADNI. Principal Investigator: Michael W. Weiner MD

Key Words: Alzheimer's disease, traumatic brain injury, post traumatic stress disorder, PET, MRI

Background: The overall long-term goal is to prevent AD. In order to accomplish this, a population at risk must be identified. AD affects almost 50% of the US population over 85 yrs. Evidence suggests that both traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) increase risk for cognitive decline, AD, and dementia. However, no prospective studies using imaging and biomarkers, which directly measure changes in the brain and AD pathology, have been performed to study the effects of TBI and PTSD. This proposed study will provide novel data to test the stated hypotheses. Furthermore the results will ultimately help design and power an AD prevention trial (using a suitably chosen intervention such as lifestyle modifications or pharmaco-therapy) which could be performed using at-risk Veterans as subjects. Thus, this project could be a first step leading to the prevention of AD.

Objective/Hypothesis: Combat associated TBI and/or PTSD increase the risk for AD, and decrease cognitive reserve, determined with imaging/biomarkers, in Veteran subjects, after accounting for age and APOE genotype.

Specific Aims: 1) Using military and VA records, identify Vietnam War Veterans with well documented history of moderate/severe TBI or evidence of ongoing PTSD, and comparable Veteran controls. Subjects meeting criteria for mild cognitive impairment and dementia will be excluded. 2) Contact the subjects, screen them, and enroll them in the study. Perform Structured Diagnostic Interview for DSM-IV and the Clinician Administered PTSD Scale (CAPS) by telephone prior to referral to ADNI clinics. 3) Subjects will be referred to and enrolled in the existing network of the Alzheimer's Disease Neuroimaging Initiative (ADNI). 4) Baseline measurements of cognition, function, blood and cerebrospinal fluid analyses, MRI (structural, diffusion tensor, and resting state BOLD fMRI) and amyloid PET imaging with Florbetapir and 1 yr follow-up measurements will be obtained. 5) Analyze the data to test the primary and secondary hypotheses as stated, as well as exploratory analyses.

Study Design and rationale: Subject groups: 1) 65 TBI without PTSD; 2) 65 PTSD without TBI; 3) 65 controls without TBI or PTSD, comparable in age, gender, and education to groups 1 and 2. Subjects with mild cognitive impairment (MCI) or dementia will be excluded. The rationale for this approach is that it is already established that 50-60 % of subjects with MCI have AD pathology in their brain, and it may be difficult to detect added effects of a history of TBI or ongoing PTSD in MCI or demented subjects. The objective will be to detect an increase in AD markers (measured with PET, MRI and CSF biomarkers, as well as cognitive testing) associated with history of TBI or ongoing PTSD. After screening, subjects will be studied at baseline with: clinical examination, cognitive tests, amyloid PET using F18 Florbetapir,l MRI, lumbar puncture for cerebrospinal fluid, markers of tau, P tau amyloid beta, and blood for genetics. After 1 year the clinical/cognitive battery and MRI will be repeated.

Relevance: AD is the most common cause of dementia. TBI and PTSD are common problems resulting from military service, and both may be associated with increased risk of cognitive decline and dementia due to AD or other causes. The results will have major implications for identifying subjects at increased risk for AD, a possible need for early detection of AD in military Veterans with histories of TBI and PTSD, and a possible need to employ prevention and treatment measures to avoid accelerated development of AD in US military Veterans. This study is a first step towards a larger, more comprehensive study of dementia risk factors in Veterans. The result will lead to a design and statistical powering of a prevention trial. Therefore, this project could be first step towards the prevention of AD in Veterans, and in the general population.

Abbreviations: Alzheimer's disease (AD), Alzheimer's Disease Neuroimaging Initiative (ADNI), amyloid β (Aβ), cerebrospinal fluid (CSF), chronic traumatic encephalopathy (CTE), diffusion tensor imaging (DTI), lumbar puncture (LP), magnetic resonance imaging (MRI), mild cognitive impairment (MCI), Pittsburgh compound B (PIB), positron emission tomography (PET), post-traumatic stress disorder (PTSD), traumatic brain injury (TBI)

Project Narrative

I.The Statement of Work:

1. First Year: 1) Hire necessary staff to perform the work. Write research protocols and informed consent documents for all performance sites, including documents for local IRB and DOD IRB. 2) Establish contacts with individuals in DOD, and VA Compensation and Pension program who can provide names, medical records, Armed Forces Qualifying Exam scores, medical records and other information concerning Vietnam era Veterans with documented traumatic brain injury, PTSD, and other Veteran control subjects. 3) Obtain approval from all relevant IRBs and VA Privacy Office, so that recruitment and enrollment can begin. 4) Send mailings to large numbers of Veterans age 60-80 currently receiving compensation for TBI and PTSD occurred during Vietnam War and Veteran controls who are neuropsychiatrically healthy. 5) Between 6-12 months after funding begin recruitment and enrollment of subjects. All subjects will be identified by DOD and VA records and contacted by mail, followed by telephone contact for screening, consenting, and comprehensive psychiatric assessment. 6) All subjects will be subsequently referred to a nearby ADNI site for medical/cognitive evaluation, lumbar puncture, blood testing, MRI, and amyloid PET (F18 Florbetapir) scanning. 7) All data uploaded by internet to the ADNI data center. 8) All data will be publically released without embargo, similar to all ADNI data.

2. Second Year: 1) Continue and complete enrollment and baseline and begin 1 year follow-up examination. 2) For follow-up, all subjects will have repeat psychiatric assessment by telephone and return to the ADNI sites for repeat medical/cognitive evaluation, blood testing, and MRI. Due to budget restrictions there will be no follow-up Florbetapir scans. All raw and analyzed data will be uploaded to the ADNI data center. 3) The biostatistical core will begin data analyses on cross sectional results.

3. Third Year: 1) Complete the 1 yr follow-up. 2) Data analysis/hypothesis testing by the biostatistical core continues and uses 1 yr longitudinal data. 3) The biostatistical core together with the PI and study investigators completes analysis of data leading to abstracts and publications. 4) ADNI publications committee monitors all proposed publication submissions from the grant investigators and outside investigators, to insure that the funding organizations and ADNI are properly credited. 5) Final report submitted to DOD

II. Body of Proposal:

1. Background:

1.1. Alzheimer's Disease (AD): AD is the most common form of dementia, which affects almost 50% of the entire US population over the age of 85 years. Clinical signs and symptoms of AD include cognitive impairments, especially memory as well as emotional disturbances. AD is characterized by brain pathology consisting of extracellular plaques containing amyloid β (Aβ), tangles of phosphorylated tau protein inside neurons, synapse loss (which begins in the entorhinal cortex and hippocampus in the medial temporal lobe) and neuronal loss, leading to dementia. It is generally recognized that age and family history are the major risk factors for the development of AD. Evidence also exists that several factors including occupation, education, and intellectual/social activity affect cognitive decline and incidence of AD, leading to the concept of "cognitive reserve" [1]. Although acetylcholine-esterase inhibitors and memantine are approved for treatment of AD, these produce modest symptomatic improvement, but do not slow the progression of AD. Currently a large number of treatment trials are underway. Most use immunotherapy (vaccines or monoclonal antibodies) or secretase inhibitors (to reduce synthesis of Aβ), but none have been successful. Most treatment trials are conducted using patients with dementia due to AD, although an increasing number are enrolling subjects with mild cognitive impairment (MCI) who have evidence of AD pathology (using imaging/biomarkers). A long-term goal of the field will be to prevent the development of cognitive impairment or dementia by treatment of normal subjects. Previous attempts at prevention trials with Ginkgo Biloba [2] or non-steroidal anti-inflammatory drugs [3,4] have failed.

1.2. Imaging and Biomarkers: The Alzheimer's Disease Neuroimaging Initiative (ADNI)

1.2.1. Imaging and biomarkers of AD: Although the diagnosis of AD dementia and MCI are made by clinical information and neuropsychological tests, there has been increasing use of magnetic resonance imaging (MRI) and positron emission tomography (PET), as well as analysis of proteins in cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) for diagnosis, early detection, and monitoring of the progression of AD. The literature in this field is huge but in brief: AD is associated with 1) low CSF Aβ, and elevated tau; 2) high uptake of the Aβ [5] imaging agent [^{11}C]PIB (Pittsburgh compound B), a ligand which sticks to Aβ neuritic plaques, and

other more recently developed [^{18}F]-labeled amyloid PET ligands, including [^{18}F] Florbetapir which will be used in this study; and 3) reduced volume of entorhinal cortex, hippocampus and cortical thinning of the temporal and parietal cortices. Furthermore, many subjects with MCI show similar patterns, and these biomarkers predict more rapid decline and conversion to AD. About 20-30% of normal subjects in their early 70s also appear to have imaging/biomarker evidence of AD, consistent with previous pathological studies. The recognition of the importance of biomarkers in the AD field, and the need for standardization and validation, led to the ADNI.

1.2.2. ADNI: ADNI (PI M.Weiner) [6-8], is a large multisite project funded by the National Institute on Aging (NIA) of the NIH, the Alzheimer's Association and other nonprofit groups, and private industry (more than 20 corporate partners) through the Foundation for NIH (FNIH). The overall goal of ADNI is validation of imaging and biomarkers for AD clinical trials. ADNI was initially funded for $60 million for 5 years, enrolled more than 800 subjects (200 controls, 400 MCI, and 200 AD subjects) in 57 sites throughout the US and Canada, and performed standardized longitudinal, clinical and cognitive [9,10], MRI [11], FDG-PET and PIB-PET [12], blood/cerebrospinal fluid biomarker [13], and genetics measurements [14,15]. All data is centrally data-based and has been available to the scientific community without embargo at UCLA/LONI/ADNI. More than 200 peer-reviewed publications have sprung from ADNI including special journal issues [16]. ADNI methods are used in many AD trials, and ADNI results were used to define the newly proposed research criteria for AD [17]. ADNI sparked similar studies in Australia [18,19], Japan [20,21], Europe [22], Taiwan, Korea, and China (known as World Wide ADNI [23]). ADNI subsequently received $24 million in ARRA funds (for additional data analysis and to enroll 200 subjects with early MCI), and has recently been refunded by NIA and its partners for an additional $69 million for the next 5 years in order to follow those subjects originally enrolled and to enroll an additional 600 subjects. The current ADNI uses clinical/cognitive tests, LP for CSF, 3T MRI F18 Florbetapir PET [24-27] and FDG PET on all subjects. We propose to use the ADNI sites, ADNI methods, and the ADNI data collection and analysis infrastructure for this proposed project concerning TBI and PTSD as risk factors for AD. However, since ADNI is focused on studying controls, MCI, and AD subjects using memory and aging clinics in neurology and psychiatry departments, additional methods will be developed for this project to identify, screen, enroll, and evaluate Veterans with past history of TBI and current PTSD (see Methods).

1.3. Traumatic Brain Injury (TBI)

1.3.1. Definition and Pathophysiology: TBI is defined as traumatically induced physiological disruption of brain function, as manifested by either loss of consciousness, memory impairment, alteration of mental state, and/or focal neurological deficits. TBI has many effects on the brain including focal injuries such as cerebral contusions, lacerations and epidural, subdural, intracerebral or intraventricular hemorrhage. Diffuse injuries include hypoxia/ischemia, vascular damage, and diffuse macro/microstructural axonal injury.

1.3.2. TBI as a risk factor for AD:

1.3.2.1. Human studies: After age, family history, and APOE4 genotype [28], the risk factor which appears to have the strongest linkage to AD is a history of TBI (reviewed in [29]). Specifically, TBI was found to be risk factor in many [30-61] but not all [41] epidemiological studies (reviewed in [29,62] and [28]). Some studies have suggested that a history of TBI is associated with earlier onset of AD [29,31,34,41,46,48,62,63]. Others but not all have shown an interaction with APOE 4 [33,34,43,45,64-72]. Aβ plaques and intra-axonal Aβ deposits were found in approximately one third of TBI subjects who died sometime after the TBI insult (who did not have preexisting AD, Down syndrome, or clinical dementia) [73-81]. A biopsy study of TBI survivors confirmed Aβ pathology [82,83]. Following TBI, young subjects age 15-21 years have had Aβ pathology, suggesting that TBI is causal [76,80].

Repetitive mild TBI is associated with the development of Chronic Traumatic Encephalopathy (CTE), a progressive tauopathy and TDP-43 proteinopathy that may also result in a late-life dementia [84]. CTE is distinguished from AD by the relative lack of Aß containing neuritic plaques [84]. Nevertheless, the link between CTE and AD is not clear and thus will obtain a complete history of all TBI incidents reported by the subjects.

A comprehensive consensus analysis of the literature concluded that there was some evidence for a relationship between TBI in males and future development of AD (summary Odds Ratio was 2.29 with a range of 1.47 to 3.58). One study [61], which showed a significantly increased risk of developing AD following TBI, used information provided by the US Department of Defense to identify and prospectively enroll subjects with non

penetrating head injury during WWII and Korea, and non head injured controls. Dr. Plassman, the first author of that study has joined this project. The Vietnam Head Injury study [86] is a federally funded project which follows Vietnam Veterans with penetrating head injuries. Dr. Grafman, who has led that study for many years, has also joined the current project. We intend to take a similar approach and have already been encouraged by DOD and VA officials concerning the feasibility and mechanisms of identifying appropriate subjects with a documented history of TBI and PTSD (see Methods).

1.3.2.2. Animal Studies of TBI and AD pathophysiology: There is an extensive animal model literature showing pathological effects of TBI on the brain and the increased expression of Aβ reviewed in [87]. A pig model of traumatic axonal injury shows Aβ pathology [87]. In both human and pig studies, there was co-accumulation of amyloid precursor protein (APP), presenilin-1, BACE1 and caspase-3 immunoreactivity at sites of axonal injury with intra-axonal Aβ deposits [79,81,87,88]. TBI in animal models, may additionally upregulate BACE expression [89] and caspase activation may further increase Aβ production by stabilizing BACE [90]. Taken together with the human data reviewed above, there is extensive evidence to support the view that TBI is a risk factor for AD. However, there is no study that used recently developed imaging and biomarker technology which directly assesses the presence of AD pathology in the brain (particularly amyloid protein) in subjects with a prior history of TBI. This is one major objective of this proposal.

1.4. Post Traumatic Stress Disorder

1.4.1. Definition and pathophysiology: Posttraumatic stress disorder (PTSD) is an anxiety disorder that develops in some individuals following exposure to traumatic stress [91]. Diagnostic symptoms include flashbacks or nightmares, avoidance of stimuli, increased arousal, anger, and hypervigilance. In addition to experiencing symptoms of intrusion, avoidance, and hyperarousal following exposure to trauma, individuals with PTSD are at increased risk of co-morbid psychiatric disorders including depression, alcohol and drug abuse, panic disorder, and agoraphobia [92-96]. Remission of PTSD symptoms once established can be very slow: 50% of men and 33% of women who met diagnostic criteria for PTSD in the first year after returning from Vietnam continued to meet the full diagnostic criteria nearly two decades after their Vietnam service [94]. The prevalence of combat-related PTSD in US military Veterans since the Vietnam War ranged from approximately 10% to 15% [94,97]. Furthermore, the magnitude of the public health impact of PTSD is highlighted by epidemiologic findings in the general population. Breslau and colleagues [98] reported a lifetime exposure rate to traumatic life events of 39.1% in a sample of 1007 young adults in an urban HMO, with a lifetime prevalence of 9.2% for PTSD in this sample. Resnick et al. [99] estimated a lifetime prevalence of 12.3% for PTSD in a nationally representative sample of women. Kessler et al. [96] estimated a 7.8% lifetime lower bound prevalence for PTSD in a representative national sample of 5877 persons aged 15 to 54. Estimates of the lifetime prevalence of trauma exposure in the Kessler study were 60.7% for men and 51.2% for women. These data emphasize the prevalence and importance of PTSD in veterans and civilians.

1.4.2. PTSD as a risk factor for AD: There is evidence to suggest that PTSD may be associated with cognitive impairments and increased risk for AD and dementia.

1.4.2.1. Human studies: PTSD substantially increases risk for age-related diseases, including cardiovascular, autoimmune, neurodegenerative diseases, and early mortality [100-104]. Recently, a study of the national VA clinical database shows that Veterans with PTSD are twice as likely to develop dementia compared to Veterans without PTSD even when controlling for known risk factors for dementia [104]. The mechanisms accounting for brain volume loss, cognitive impairment, and increased risk for dementia in PTSD are not known. At present, no study has examined if PTSD is associated with increased deposition of amyloid β. There are several lines of evidence to suggest that PTSD might be associated with increased risk for AD. First, PTSD is associated with cognitive impairments, especially memory. Therefore, there may be reduced "cognitive reserve" in PTSD subjects making them more vulnerable to the effects of AD pathology. Specifically, PTSD is associated with impaired verbal memory [105,106]. Working memory deficits related to PTSD have been observed in samples of combat Veterans [105,107,108], rape survivors [109], and refugees exposed to war and political violence [110]. There are also many reports of verbal declarative memory deficits related to PTSD, in samples of adult patients with PTSD related to combat [105,107,108,111-115]. Second, PTSD is associated with brain alterations in the hippocampus (including work from by the PI [103,116-119]), anterior cingulate [118], and prefrontal structures (reviewed in [120]). Our group has found atrophy in the CA3/dentate gyrus subfield [103]. We have also reported reduced hippocampal N-acetyl aspartate [116-118], a neuronal marker.

We have reported that ongoing PTSD is associated with greater hippocampal atrophy [103,119] while improvement of symptoms is associated with less progressive atrophy [119]. However, one twin study suggests that hippocampal atrophy may increase susceptibility to PTSD and may not result from PTSD [121]. Atrophy of medial temporal lobe structures, especially in the entorhinal cortex and hippocampus [122], occurs in AD, and hippocampal atrophy also predicts future cognitive decline and conversion of MCI to dementia. Thus, hippocampal atrophy in older subjects with PTSD could represent either: 1) evidence of early AD pathology, 2) evidence of damage which could increase risk for development of AD pathology and/or 3) reduced synaptic mass indicating reduced cognitive reserve, leaving the subject more susceptible to the effects of AD. Third, PTSD is also associated with a variety of other behaviors, pathologies, and co morbidities including: smoking, hypertension, hyperlipidemia, diabetes, obesity, and inflammation; which are all independently associated with increased risk of dementia including AD and vascular dementia, reviewed in [123], and may reduce cognitive reserve. Therefore the presence of these comorbidities may also increase the risk for AD in human subjects with PTSD [124]. Finally, major depression which often occurs in subjects with PTSD [125,126](and TBI [127,128]) is associated with reduced hippocampal volume [132-134] and increased risk for AD [129-131]. We will examine the effects of depression on outcome variables.

1.4.2.2. Animal studies linking stress to brain injury and AD pathology: Many animal studies have demonstrated that psychological stress causes hippocampal damage [135-138] and/or impaired neurogenesis, mediated by high levels of glucocorticoids [139-141]. Sapolsky and coworkers have published many papers on hippocampal damage associated with major depression [142] and glucocorticoids [143], [144], [145].

Psychological trauma [146-150] and PTSD [151] are associated with increases in acute and chronic inflammation. Studies in animals and humans [152] show a link between psychological trauma and oxidative stress [153] through several mechanisms [154-156]. Psychological trauma is also associated with vascular dysfunction [157-159]. Psychological stress is associated with increased risk of cerebral ischemia; in humans, early life trauma is associated with increased risk of stroke [160], and psychological distress in adults is associated with increased fatal ischemic stroke [161]. In animals, psychological stress, produced by prolonged restraint, causes increased Aβ in transgenic mice brains [162-168]. High blood levels of glucocorticoids, which occur during acute stress, increase brain amyloid accumulation [169,170]. Stress and corticotropin releasing factor [171] increase AD-like tau phosphorylation [172]. Chronic sleep disturbances, which are a prominent feature of both PTSD and TBI, have been shown to be associated with Aβ plaque formation in APP transgenic mice [168]. Therefore, animal studies add weight to the hypothesis that exposure to psychological trauma and/or PTSD may be associated with increased risk for developing AD in humans. This could be either by producing damage in brain structures that reduces cognitive reserve, and/or by accelerating rate of Aβ deposition and tau phosphorylation.

1.4.3. Summary: PTSD as a risk factor for AD: Taken together, there is a body of evidence from human and animal studies suggesting that PTSD may be a risk factor for cognitive impairments, brain atrophy, and comorbidities. These risk factors may either accelerate the rate of AD pathology and/or reduce brain reserve so that when such pathology develops, the symptoms are expressed at an earlier stage of the disease, compared with subjects with normal brain reserve. At present, no study has prospectively (or even retrospectively) examined if PTSD is associated with biomarker evidence for AD including increased deposition of Aβ by amyloid PET, reduced CSF Aβ, increased CSF tau, and brain atrophy in human subjects; this is one of the primary hypotheses of the proposed study.

1.5. Rationale and limitations for this study design: This is a 3-group study including: 1) Subjects with past history of military-associated TBI from military records and VA Compensation/Pension records without PTSD; 2) Subjects with ongoing PTSD without TBI from the same sources; 3) Controls comparable in age, gender, education, socioeconomic status, and APOE4 status to groups 1 and 2 identified from the same sources. Subjects with MCI, using well accepted criteria used in ADNI or dementia will be excluded. The rationale for excluding subjects with cognitive impairments and dementia is that it is already established that 50-60% of subjects with MCI have AD pathology in their brain, evidenced as positive C-11 PIB scans [173-175] or low CSF Aβ [5,176,177]. Subjects with AD dementia are at least 90% positive on C-11 PIB. Given the already high prevalence of AD biomarkers in MCI and AD subjects, it might very well be difficult to detect added effects of a history of TBI or ongoing PTSD. The rationale of the proposed study design is that there will be greater statistical power to detect the effects of TBI and PTSD on brain AD pathology in subjects without MCI

(because of the relatively low prevalence of brain amyloid pathology in this group) than in subjects with MCI or dementia (who have high prevalence of AD pathology, and thus there might be a "ceiling effect"). Furthermore, several groups (personal communication from Dr C. Rowe, M. Mintun) have found that the effects of APOE4 and age on amyloid PET positivity are more significant in cognitively normal subjects compared with MCI or AD patients. Therefore, we will study subjects with normal cognition who are expected to have an age-associated prevalence of brain AD pathology of 10-30% [19,178,179].

One potential limitation of this study design is that TBI and PTSD may be associated with much greater incidence of MCI and dementia, and by excluding such subjects from our study we may be biasing the sample. Furthermore, it will not be possible to distinguish MCI resulting from AD pathology and MCI resulting from TBI or other factors by telephone interview. However, APOE4 is a major risk factor for AD (a stronger risk factor than history of TBI), but the presence of APOE4 does not result in such rapid conversion to MCI, that control subjects age 60-80 are not easily available for study. Therefore, the risk of cohort bias appears to be small. Nevertheless, as subjects are contacted by mail and screened by phone, we will carefully track those subjects who are excluded because of MCI. If we find much higher rates of excludes in the TBI and PTSD group we will document this. Depending on the results, we may seek additional funding to expand this study to include MCI subjects.

Our major hypothesis is that history of TBI or presence of ongoing PTSD will increase the prevalence of brain AD pathology (measured by amyloid PET, CSF Aβ and tau, medial temporal lobe atrophy) after accounting for effects of age and APOE. In addition, we will examine the possibility that TBI or PTSD reduces brain reserve, causing greater downstream effects including hippocampal atrophy and cognitive impairment even after accounting for brain amyloid. One possibility is that TBI is associated with chronic traumatic encephalopathy (CTE) which is distinguished from AD by the relative lack of Aß containing neuritic plaques (fewer than 50% of individuals with CTE have Aß plaques and if present, occur in low density), and by atrophy of the medial temporal lobe, diencephalon, and mammillary bodies only in late stages of disease [84]. CTE would be manifest as a form of "reduced brain reserve". We would expect that CTE would be differentiated from AD by: 1) the relative lack of neuritic plaques and therefore PIB negativity; 2) the absence of low CSF Aß; 3) elevated CSF tau and p-tau; and 4) the lack of hippocampal atrophy. We will explore for these effects.

Another limitation of this study is that we are seeking TBI subjects without PTSD and PTSD subjects without TBI, and we are not including a group with both, and not testing for an interaction between them. This study design is choosen to maximize statistical power to detect the main effects of PTSD and TBI. In the future, especially if we find evidence for significant main effects, we will seek additional funding to expand this study to a full 2x2 design with power to detect an interaction between PTSD and TBI, and to detect interactions with age and APOE4.

Finally, TBI may increase risk for other neurodegenerative diseases such as Parkinson's disease (PD). With additional resources, this study could be extended to detect preclinical or early PD.

In conclusion, this study is designed to provide maximum power to detect main effects of TBI and PTSD on AD pathology measured with imaging and biomarkers. It is expected that the results will lead to additional studies that would replicate and extend these findings.

2. Objectives/Hypotheses: The overall long-term goal of our field is to prevent AD in combat Veterans. This project is an important step in that direction because it will identify risk factors for development of AD in military Veterans and will provide information and a network of sites for design, statistical powering, and performance of clinical treatment and prevention trials in the future.

2.1. Hypotheses: The primary hypotheses to be tested (all data analyses will be covaried for age, gender, and APOE4 genotype) are that Veterans without MCI or dementia with a history of moderate to severe TBI during military service, as well as Veterans with ongoing PTSD, have increased evidence for AD pathophysiological markers, when compared with Veteran controls (without TBI or PTSD and matched for age, APOE4 status and accounting for other comorbidities) manifested as the following dependent variables: 1) greater uptake on Florbetapir amyloid PET scans; 2) lower CSF amyloid beta levels; 3) increased CSF tau/P tau levels; 4) greater brain atrophy in hippocampus, entorhinal cortex, and parietal/temporal cortices; 5) greater longitudinal rates of brain atrophy in hippocampus, entorhinal cortex and parietal/temporal cortices; 6) reduced cognitive function, especially delayed memory; and 7) greater rate of change of cognitive function.

The second major hypothesis to be tested is that TBI and/or PTSD reduce brain reserve, causing greater

cognitive impairment after accounting for age, educational status, pre-war cognitive function as assessed with the Armed Forces Qualifying Exam score during basic training, brain amyloid load or hippocampal volume. Greater cognitive impairments at a given level of brain Aβ or brain volume in the TBI or PTSD group compared with controls would support the hypothesis of reduced cognitive reserve.

The third hypothesis will be that TBI, when compared to controls, is associated with changes in brain regions previously reported to be associated with TBI [180-182]. White matter regions frequently noted to have reduced microstructural integrity due to TBI on DTI include the anterior corona radiata, uncinate fasciculus, corpus callosum, forceps minor, forceps major, sagittal stratum, corticospinal tract, inferior fronto-occipital fasciculus and cingulum bundle [180-182]. We will also replicate previous findings of reduced hippocampal volume in PTSD compared to controls, [103,116-119].

The fourth hypothesis is that there will be significant correlations between severity of TBI (from hospital records) and severity of PTSD (CAPS score) on the above-listed outcomes, i.e. a dose response effect.

Exploratory analyses will be performed to examine other questions, although after correction for multiple comparisons, the statistical significance of these will be low, requiring future replication. Nevertheless, we will compare the patterns (using voxel based methods) of amyloid deposition (from Florbetapir uptake) and brain atrophy among TBI, PTSD, and control subjects, and with the patterns from non-Veteran subjects in ADNI. These results of these studies may provide insight into the question of whether or not TBI and PTSD alter the pattern of amyloid distribution or brain atrophy. The relationship between cortical areas with amyloid plaque (from Florbetapir) and underlying white matter integrity as assessed with DTI will also be studied to determine if axonal injury resulting from TBI was associated with greater amyloid accumulation, or whether regions of brain with axonal damage have less amyloid accumulation due to disconnection and reduced brain activity.

3. Technical Objectives: The technical objectives will include identifying the subjects in DOD and VA databases, and setting up centralized methods for evaluating medical records, and contacting the subjects by telephone. Dr. Neylan has already established staff who perform standardized SCID/CAPS by telephone. All other methods, including standardized PET, MRI, and CSF measurements, are already standardized by ADNI and in place at 57 ADNI sites.

4. Project Milestones:

First Year: 1) Write research protocols and informed consent documents for all performance sites, including documents for local IRB and DOD IRB. 2) Successfully make contacts with individuals in DOD and VA Compensation and Pension who can provide names, medical records, Armed Forces Qualifying Exam scores, and other information concerning Vietnam era Veterans with documented traumatic brain injury, and other Veteran control subjects. 3) Obtain IRB approval from all relevant IRBs so that recruitment and enrollment can begin. 4) During the second half of this year, begin recruitment and enrollment of subjects. 5) Subjects are screened and consented by telephone. This is followed by a Structured Clinical Interview for DSM-IV (SCID) and the Clinician Administered PTSD Scale (CAPS) also done by telephone. 6) After SCID/CAPS subjects will be referred to ADNI sites for medical/cognitive evaluation, lumbar puncture, blood testing, MRI, and PET scanning. All data uploaded by internet to the ADNI data center. 7) All data will be publically released without embargo, similar to all ADNI.

Second Year: 1) Continue and complete enrollment. 2) Analyze baseline data. 3) Subjects return to the ADNI sites and begin 1 yr follow-up examination and repeat MRI. All data uploaded to the ADNI data center.

Third Year: 1) Complete all follow-up studies. 2) Complete analysis of all data. 3) Data analysis will be performed by the biostatistical core together with study investigators, leading to abstracts and publications. 4) Final report submitted to DOD.

5. Military Significance: TBI and PTSD are highly prevalent consequences of military service and combat. For example one recent study of 2525 soldiers who spent 1 year serving in Iraq [183], 5% reported injuries with loss of consciousness, and 10% reported injuries with altered mental status. Of those reporting loss of consciousness, 44% had PTSD. Medical attention has largely been focused on the acute treatment of these conditions, but the long-term consequences may even be greater than the immediate morbidity in terms of human suffering, economic cost and pain to the families. Therefore a study to determine the extent to which TBI and PTSD are risk factors for the development of dementia due to AD or other factors has huge military significance. The results of this study are expected to lead directly to greater efforts to detect AD in military Veterans and to the development of appropriate treatment and prevention studies, ultimately leading to the

prevention of cognitive decline, AD, and dementia in Veterans and in the general population.

6. Public Purpose: AD is the most common cause of dementia in the population affecting about 50% of elders over 85 years of age. TBI from accidents and sports, and PTSD from civilian traumatic events are common, and these conditions may be risk factors for AD and dementia in the general population. Therefore, similar to the military significance, the results of this study are expected to lead directly to greater efforts to detect AD in the general population and to the development of appropriate treatment and prevention studies, ultimately leading to the prevention of AD in the general population.

7. Methods

7.1. Overall Strategy: In order to test the hypotheses, subjects age 60-80, without regard to gender, with documented history of TBI without PTSD, patients with ongoing PTSD without TBI, and Veteran control subjects will be identified from VA Compensation and Pension records of subjects who receive disability payments for TBI and PTSD. We will examine the records similar to methods used by Plassman et al [61] We have already been informed by VA Compensation and Pension Officials that they see "no obstacle" to our obtaining these records, once we obtain funding, IRB approval, and approval from the VA Privacy Office (who has also indicated that "in principle" there will be no obstacle to this). Subjects will be contacted by mail, screened by mail and telephone, consented by mail/telephone, evaluated with SCID/CAPS by telephone, and then referred to the ADNI sites near where they live for the ADNI clinical/cognitive battery, lumbar puncture, blood draw, MRI/Florbetapir PET scans at baseline. After one year they will again have a SCID/CAPS assessment by telephone, the clinical/cognitive assessment at the ADNI site, and follow-up MRI

Subjects with ongoing PTSD, Control subjects without TBI or PTSD will be selected from the same databases (e.g. Veterans who are service connected for non-combat related injuries who do not have PTSD or TBI) and will have the identical studies. Controls will be recruited to match the PTSD and TBI groups for age, gender, and education. The subjects will be contacted by letter and then by telephone, where the scope of the project will be explained a brief screening interview performed, and informed consent will be obtained, subsequently documented in writing. Using a trained group of telephone interviewers, based in San Francisco, a Structured Interview for DSM IV (SCID) and other measurements of trauma exposure will be obtained by telephone. After 1 year the PTSD subjects will have a repeat CAPS assessment. All subjects will be assigned a code number, and all data will be de-identified. All clinical cognitive demographic data will be uploaded to the clinical database at the ADCS at UC San Diego. All MRI and PET scans will be uploaded to the UCLA/LONI/ADNI site. Similar to the ADNI project, the entire clinical database and all scans will be available to all qualified scientists, without embargo. The project will be conducted by the PI and Core Leaders of ADNI (described in Budget Justification), guided by a TBI Workgroup (Chair J. Grafman, P. Mukerjee, B. Plassman, E. Peskind) and a PTSD Workgroup (Chair T. Neylan, C. Marmar, R. Pitman, M. Stein, M. Raskind, M. Friedman).

7.2. Detailed Clinical Methods (Overseen by M. Weiner, T. Neylan at UCSF, P.Aisen UCSD, R. Petersen Mayo Clinic): Men and women Veterans who served in Vietnam age 60-80 will be included in this study. Staff at the VA San Francisco will identify the TBI, PTSD subjects with a documented combat MOS (military occupation specialty, meaning they served in combat), who received a combat action badge (ribbon for Marines), purple heart, Bronze Star or other decoration related to combat. Controls will also be selected from VA and DOD medical records. All subjects will be initially contacted by mail with telephone follow-up. The PI has already had contact with several individuals in DOD records and VA Compensation and Pension offices. He has been reassured that, assuming that funding and IRB approval are obtained, there will be "no obstacle" to access to required records, including personal contact information (name, address, telephone) which is available since the subjects are receiving disability payments. In the event that there is difficulty in identifying suitable numbers of healthy controls from the VA records, advertisements in publications aimed at Veterans will be used. However, given the hundreds of thousands of Vietnam Veterans who are service connected for TBI and PTSD, and the large geographic distribution of the many ADNI sites, enrollment of the projected sample should be feasible within the 18 month projected period. Suitable subjects who live within a 1-hour drive of one of the participating ADNI sites will be contacted initially by mail, and then by telephone for a short screening interview to determine level of interest, whether major exclusions exist, and to obtain informed consent (verbal and written). All subjects in each of the 3 groups will have the identical assessments. The San Francisco site will manage the initial contacts with subjects by mail and telephone, collection of telephone interviews and self-

report data. All patient data and telephone calls will be logged into a currently existing electronic capture system, modified for the study. All case report forms (CRFS) will be uploaded to the ADCS database. All de-identified data will be available at the ACDS database, displayed at the LONI website without embargo. Upon completion of the mail/telephone assessments, eligible subjects will be referred to the ADNI sites, and ADCS will coordinate all data capture. In addition to information concerning TBI and PTSD, all available medical information from the Veteran's military health records and VA health records will be captured and used for exploratory analysis. Information obtained on education level, a proxy for socio-economic status (SES)[184], health and cognitive status, including the Armed Forces Qualifying Exam taken during basic training (AFQE, if available) will be captured and entered into an electronic capture system which is linked to the ADCS database, to determine if cognitive status prior to combat is predictive of AD or PTSD. The TBI, PTSD, and controls subjects will be matched by age, gender, and education by first enrolling some TBI subjects (the most difficult to enroll) and monitoring the matching variables. As PTSD and controls are enrolled, the matching variables will be tracked, and PTSD/control subjects will be contacted and enrolled in order to keep the 3 subject groups matched on these variables.

7.2.1. Identification, inclusion criteria, and recruitment of TBI subjects: Subjects with documented history of moderate-severe non penetrating TBI which occurred during military service in Vietnam will be identified from the Department of Defense or VA records. Methods for assessing and scoring the medical records will be similar to those used by Plassman et al. (Brenda Plassman is a consultant on this grant) and Koenig et al. (Jordan Grafman, the senior author on Koenig et al., is the Chair of the TBI Workgroup) will be employed. TBI will be defined as: Loss of consciousness for >30 minutes, post-traumatic amnesia >24 hours, alteration of consciousness or mental state >24 hours, traumatic intracranial abnormalities detected on imaging. TBI subjects with a CAPS score of >30 and who have PTSD symptoms of recurring recollections of the traumatic event/flashback/nightmares of the traumatic event, and hyperarousal will be excluded.

7.2.2. Identification, inclusion criteria and recruiting of PTSD subjects: The Veterans Benefits Administration Annual Benefits Report for 2010 reports that there are 268,865 Vietnam Vets in the USA rated as disabled (receiving VA compensation) due to PTSD. Therefore, we have confidence that a sufficient sample of subjects will be available to recruit for this study. Subjects will be identified using records of Vietnam Veterans with service-connected disabilities for PTSD provided to us by VA Compensation and Pension. Subjects who meet DSM IV criteria for current chronic PTSD (identified by records, and verified by our telephone assessments), and who are judged to be suitable for this study will be recruited. Inclusion criteria for chronic full syndromal PTSD related to Vietnam-related trauma will be defined by the Clinician Administered PTSD Scale (CAPS, [185]) and a minimum CAPS score of 50 as determined by telephone assessment.

7.2.3. Identification, screening, recruitment and assessment of control Veteran subjects: No controls will be enrolled until approximately 25% of the TBI and PTSD subjects are enrolled. Controls will have served in Vietnam, have no documented or self report history of mild/moderate/severe TBI, and no history of PTSD. All exclusionary criteria applied to TBI and PTSD will be applied to the controls.

7.2.4. Common Assessment Battery by Telephone for all subjects (Overseen by M Weiner and T Neylan):

7.2.4.1. Uniform Exclusion Criteria and Assessment battery for all subjects: All subjects including the TBI, PTSD and control subjects will have the identical set of telephone screenings and assessments, including SCID/CAPS performed by the San Francisco site. Several studies [186,187] have shown that telephone administration of behavioral interventions and mental health assessments are valid, reliable, and equivalent to face-to-face administrations [188-191]. Dr Neylan's team at the San Francisco VA has considerable expertise from previous and ongoing studies using the telephone to conduct all aspects of survey and clinical trial research. All participants entering the study will participate in an audiotaped telephone diagnostic interview conducted by clinical evaluators. First, a brief telephone screen will be used to determine willingness to participate, to determine presence of an informant, and to rule out subjects with cognitive impairments, dementia, or other significant exclusionary neurological or psychiatric disorders.

Once completed, qualified subjects will be referred to the ADNI sites for the ADNI clinical/cognitive battery and imaging/biomarker studies.

7.2.4.2. Exclusion Criteria for all subjects: 1) History of psychosis or bipolar affective disorder; 2) History of alcohol or substance abuse/dependence within the past 5 years; 3) For subjects not in the TBI group, any history of head trauma associated with injury-onset cognitive complaints or loss of consciousness for 10 minutes; 4)

For subjects not in the PTSD group, presence of PTSD by DSM-IV criteria, or a CAPS score greater than 30; 5) MRI-related exclusions: metal implants, claustrophobia; 6) Contraindications for lumbar puncture PET scan, or other procedures in this study; 7) Any major medical condition must be stable for at least 4 months prior to enrollment. These include but are not limited to clinically significant hepatic, renal, pulmonary, metabolic or endocrine disease, cancer, HIV infection and AIDS; patients who have received an investigational medication within the last 30 days; patients who have received a radiopharmaceutical for imaging or therapy within the past 7 days prior to the imaging session for this study. Prohibited medications: regular use of benzodiazepines during daytime hours. Patients who have ever participated in an experimental study with an amyloid targeting therapy (e.g., immunotherapy, secretase inhibitor, selective amyloid lowering agents) must not be enrolled unless it can be demonstrated that the patient received only placebo in the course of the trial. Seizure disorder or any systemic illness affecting brain function during the past 5 years will be exclusionary.

Measures obtained on all subjects by Evaluators on the Telephone: The following assessments range from

1. Structure interview to document history of traumatic brain injury including military associated injury, as well as all other episodes.

2. Structured Clinical Interview for DSM-IV, Non-Patient edition (SCID-NP, [192]): The SCID-NP is a structured diagnostic interview protocol for the determination of DSM-IV diagnoses.

3. Clinician Administered PTSD Scale (CAPS, [185]): The CAPS provides both a dimensional and categorical measure of PTSD. CAPS will determine lifetime and current PTSD. The CAPS measures frequency and magnitude of PTSD-related symptoms. Possible scores range from 0 to 136. In a recent review of studies utilizing the CAPS, Weathers and colleagues [193] propose the following severity score ranges for interpreting the CAPS, which are as follows: 0-19 = Asymptomatic/few symptoms; 20-39 = Mild PTSD/subthreshold; 40-59 = Moderate PTSD/threshold; 60-79 = Severe PTSD symptomatology; > 80 = Extreme PTSD. Subjects must have a history of lifetime PTSD by categorical criteria and a lifetime CAPS score of greater than 50.

4. Life Stressor Checklist - Revised (LSC-R): Structured clinical interview for lifetime exposure to stressful life events [194]. This structured clinical interview for lifetime exposure to stressful life events will be used to characterize the type of trauma exposure and age of occurrence(s) of different traumas in all subjects. We have modified the instrument to produce analogous scores of severity and frequency (0 to 6) as the CTI. Duration of exposure is calculated in years from age at onset to cessation of any type of event that includes direct threat to life or physical integrity.

Self Report Measures: (Mailed to subjects: Collected at time of Neurocognitive testing at the ADNI sites)

1. Symptom Check-List-90-Revised (SCL-90-R, [195]): The SCL-90-R is a standard self-report measure of general psychopathology. Scored for nine primary dimensions and three summary indices, the SCL-90-R manual reports extensive reliability and validity of data.

2. Pittsburgh Sleep Quality Index [196]: This self-report measure provides a subjective assessment of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances (including nightmares), use of sedative-hypnotics, and daytime energy. This widely-used index will be used in exploratory analyses to examine the effect of sleep quality on specific brain regions (e.g. CA3/dentate [197] and cognitive performance).

3. Smoking: Lifetime smoking will be assessed using two measures: 1) Smoking status [198] is a two-question categorical measure employed by the Centers for Disease Control and Prevention National Health Interview Survey, and categorizes individuals into one of three groups: (a) “Never smokers”, adults 18 or over who have smoked fewer than 100 cigarettes in their lifetime; (b) “Former smokers”, adults who have smoked at least 100 cigarettes in their lifetime but are not smoking at time of interview; and (c) “Current smokers”, adults who have smoked at least 100 cigarettes over their lifetime and who are still smoking at time of interview; 2) Number of pack years [199] is a two-question continuous measure of smoking that utilizes the number of cigarettes per day multiplied by the number of years of smoking to calculate pack years of smoking.

4. Alcohol use and non-alcohol substance use: Alcohol and non-alcohol substance use will be assessed using portions of the Addiction Severity Index Lite (ASI-Lite) [200,201]. The ASI-Lite Composite Score for Alcohol Use will provide past month alcohol use severity and the ASI-Lite number of years of alcohol use will provide a marker of lifetime alcohol use. The ASI-Lite Composite Score for Drug Use will provide past month non-alcohol substance use severity, and the ASI-Lite number of years of drug use will provide a marker of lifetime non-alcohol substance use. The ASI-Lite is a valid and reliable standardized research interview to assess the

occurrence and severity of alcohol and non-alcohol substance abuse. The ASI-Lite includes questions about the frequency, duration, and severity of problems over the subject's lifetime and in the past 30 days.

5. SF-12 Health Survey (SF-12) [202] is a brief inventory measuring functional status in 6 domains and measuring global daily functioning. Published normative age-adjusted means for each domain and a global functioning score were derived from US residents. We will calculate a mean global functioning score to examine differences in global functioning across the 4 groups for secondary analyses.

6. Combat Exposure Scale (CES) [203]: This is a brief but reliable and valid 7-item Combat Exposure Scale to quantify the subjective report of wartime traumatic stressors experienced by combatants in the Vietnam War. The 7 items are differentially weighted; scores range from 0-41. In the report presenting psychometric properties, α was .85, and test-retest reliability was .97 over a one week interval.

7.2.5. Clinical/cognitive measurements collected at the ADNI sites (Overseen by ADNI Clinical Core leaders P. Aisen and R. Petersen): Upon arrival at the ADNI sites, all subjects will have the complete standardized ADNI assessment which is too lengthy to be completely described in detail in this application. The subjects will be screened and tested for conditions which might affect cognition including B12 and TSH. The subjects will be asked about the presence of all medical conditions and use of medications. Subjects with medical conditions or taking medications which are judged to affect cognition will be excluded. When the Site MDs and study coordinators have questions about this, they contact the central ADNI clinical core, and these issues are adjudicated (usually by Dr. Petersen, Aisen or Weiner).

7.2.5.1. Excluding subjects with disqualifying metal in the body: Because MRI will be performed at 3 Tesla, all subjects will be assessed at the ADNI sites for the presence of disqualifying metal objects in the body. All participants will be assessed using a standardized checklist of body parts including head, neck, chest, abdomen and pelvis, arms and legs. A thorough physical exam will be performed at the ADNI sites, and any scars which might indicate entry wounds (where metal may be located) will be noted. All participants will also be assessed using a portable magnetic screening wand that detects ferromagnetic objects. Examination for tattoos which would exclude subjects from brain MRI will be performed.

7.2.5.2. Cognitive, Behavioral, Functional, and Global Assessments: The tests and scales chosen for use in this protocol represent the ADNI battery to take fullest advantage of the APOE genotype, amyloid and AD trajectories of decline as a reference for interpretation of the data from this study. ADNI measures were themselves selected because: (1) they represent the domains of interest in the aging population at risk for AD; (2) they will adequately sample cognitive domains of interest in subjects who are cognitively normal (CN), have MCI or AD; (3) they can measure change over two to three years in these patient populations; (4) subjects enrolled will not demonstrate floor or ceiling effects; (5) they are reasonably efficient and can meet the practical demands of the ADNI as well as this proposed study. The measures are briefly described below.

7.2.5.2.1. Montreal Cognitive Assessment (MoCA) [204]**:** The Montreal Cognitive Assessment test (MoCA) is a brief cognitive assessment designed to detect subjects at the MCI stage of cognitive dysfunction.

7.2.5.2.2. Everyday Cognition (ECog) [205]**:** For a functional assessment, we have selected the Measurement of Everyday Cognition (ECog). This instrument is an informant-rated questionnaire developed to assess functional impairment of a very mild nature as can be seen in MCI. Results of ECog suggest that it is a useful tool for the measurement of general and domain-specific everyday functions in the elderly. The performance of the ECog will be followed to determine its ability to differentiate among the three cognitive groups.

7.2.5.2.3. Mini-Mental State Exam (MMSE) [206]**:** The MMSE is a fully structured screening instrument frequently used for Alzheimer's disease drug studies. The scale evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two overlapping pentagons.

7.2.5.2.4. Alzheimer's Disease Assessment Scale-Cognitive (ADAS-COG) 13 [207]**:** The ADAS-COG is a structured scale that evaluates memory (word recall, word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, and ability to remember test instructions are also obtained. The test is scored in terms of errors, with higher scores reflecting poorer performance. Scores can range from 0 (best) to 70 (worse). Delayed Word Recall and Number Cancellation will be conducted in addition to the eleven standard ADAS-Cog Items.

7.2.5.2.5. Logical Memory Test I and II (Delayed Paragraph Recall) [208]**:** The Logical Memory test that will be used is a modification of the episodic memory measure from the Wechsler Memory Scale-Revised (WMS-R) [208]. In this modified version, free recall of one short story (Story A) that consists of 25 bits of information will be elicited immediately after it is read aloud to the subject and again after a thirty-minute delay. The total bits of information from the story that are recalled immediately (maximum score = 25) and after the delay interval (maximum score = 25) are recorded. A retention or "savings" score can be computed by dividing the score achieved during delayed recall by the score achieved during immediate recall.

7.2.5.2.6. Boston Naming Test [209]**:** This measure of visual confrontation naming requires the subject to name objects depicted in outline drawings. In our modification of the full BNT, only 30 items are presented (the odd-numbered items from the full 60-item test). The drawings are graded in difficulty, with the easiest drawings presented first. If a subject encounters difficulty in naming an object, a stimulus cue and/or a phonemic cue is provided.

7.2.5.2.7. Category Fluency Test [210]**:** This is a measure of verbal fluency in which the subject is asked to generate examples from the semantic categories (animals) in successive one-minute trials. The primary performance measure is the number of correct, unique examples generated. Perseveration (repetitions of a correct item) and intrusion (non-category items) errors are also noted.

7.2.5.2.8. Clock Drawing Test [211]**:** In this visuoperceptual constructional task, the subject is given a blank sheet of 8 ½" x 11" paper and instructed to "Draw a clock, put in all of the numbers, and set the hands for 10 after 11." After that task is completed, the "copy" condition ensues in which the subject attempts to copy a drawing of a clock with the hands set at ten past eleven. A quantitative score (maximum total score = 10) is derived for each drawing by adding the scores of three separate features. The Clock Drawing Test is effective for discriminating between subjects with AD and normal elderly individuals [212].

7.2.5.2.9. American National Adult Reading Test (ANART): [213] The ANART is a method for estimating premorbid verbal intelligence (VIQ) in demented patients based upon their ability to read words aloud, a skill that is thought to remain relatively preserved until the later stages of Alzheimer's disease [213]. The test requires patients to read and correctly pronounce 50 "irregular" words that do not follow common rules of phonography and orthography.

7.2.5.2.10. The Auditory Verbal Learning Test will be used to assess memory function in normal subjects and has been used extensively in all ADNI protocols [214]. This test has an extensive normative database and has been used in many Alzheimer's Clinics and population-based studies of aging [215]. Since it is a more difficult memory test than others, it is useful in identifying individuals at risk for AD. Performance on this instrument will allow direct comparison with subjects at all stages of ADNI.

7.2.5.2.11. Trailmaking A and B are measures of attention, cognitive flexibility and executive function [216]. It has been used for decades and is included in ADNI. It was originally developed for military purposes and has an excellent track record while being efficient to administer.

7.2.5.2.12. Clinical Dementia Rating (CDR) [217]**:** The CDR describes five degrees of impairment in performance on each of 6 categories of cognitive functioning including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.

7.2.5.2.13. Activities of Daily Living | Functional Assessment Questionnaire (FAQ) [218]**:** Based on an interview with a study companion or qualified partner, a subject is rated on their ability to carry out ten complex activities of daily living.

7.2.5.2.14. Neuropsychiatric Inventory (NPI) [219]**:** The Neuropsychiatric Inventory (NPI) is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on an interview with a study companion or qualified partner.

7.2.5.2.15. Geriatric Depression Scale [220]**:** The Geriatric Depression Scale (Short Form) is a self-report scale designed to identify symptoms of depression in the elderly. The scale consists of 15 questions that the subject is asked to answer yes or no on the basis of how they felt over the past week.

7.2.5.2.16. Armed Forces Qualification Test/Armed Services Vocational Aptitude Battery: Preinjury intelligence is a strong predictor of long term decline in many cohorts including those with Traumatic Brain Injury among these variables [86]. Preinjury intelligence [221,222] can be estimated by the Armed Forces Qualification Test/Armed Services Vocational Aptitude Battery which were administered prior to the completion of basic training. As part of the ADNI cognitive battery we will re-administer the exact same tests

given to the subject and use change of these tests as a major dependent variable in data analysis. We will use the AFQT and ASVAB as 1) measures of cognitive reserve; 2) the change in the score from its original use in Basic Training to the time of the study will be used as an important outcome measure to test hypotheses.

7.3. Lumbar puncture for CSF (To be done at ADNI sites): All samples will be collected in the morning before breakfast and after an overnight fast. The ADNI–preferred method for obtaining CSF is lumbar puncture with a small caliber atraumatic needle (22 gauge Sprotte needle) and collection by gravity into a polypropylene container. To clear any blood from minor trauma associated with needle insertion, the first 1-2 mL of CSF are discarded (or more if needed) to eliminate blood, and then 20 mL of CSF are collected from each patient for use and treatment in the following manner:

1. The first 2 mL will be used for standard tests such as cell counts, glucose, and total protein with determinations done at local laboratories.
2. The remaining CSF will be collected into polypropylene collection tubes and transferred to polypropylene shipping tubes as outlined in the Procedures manual. CSF is frozen upright on dry ice for at least 20 minutes before being packaged along with the frozen plasma and serum. CSF samples are shipped frozen on dry ice, day of collection, via Federal Express overnight delivery to the Penn AD Biomarker Fluid Bank Laboratory. The day after the Lumbar Puncture each study participant or a person designated to speak for them will be contacted by phone 24 hours after the Lumbar Puncture to confirm the participant's well-being and query about any new adverse events.

7.3.1. Analysis of CSF for amyloid and tau proteins and proteomics (To be done at the U Penn. ADNI Biomarker Core, J. Trojanowski and L. Shaw): CSF samples will be assayed to measure levels of Aβ42, total tau (t-tau) and tau phosphorylated at threonine 181 ($p\text{-}tau_{18p}$) with ADNI SOPs using the validated Luminex xMAP multiplex immunoassay and Innogenetics monoclonal antibody AlzBio3 reagents [5,177,223]. These tests are relative quantitative assays for CSF Ab1–42, t-tau and p-tau181 since no international reference standards for the analytes prepared in CSF are available. The kit reagents include a mixture of three xMAP color-coded carboxylated microspheres, each containing a bead set coupled with well-characterized capture mAbs specific for $Ab_{1–42}$ (4D7A3; bead region 56), t-tau (AT120; bead region 2) or $p\text{-}tau_{181}$ (AT270; bead region 69), and a vial with analyte-specific biotinylated detector mAbs (3D6 for $Ab_{1–42}$ and HT7 for t-tau or $p\text{-}tau_{181}$). Calibration curves are produced for each biomarker using aqueous buffered solutions that contain the combination of three biomarkers at concentrations ranging from 56 to 1,948 pg/mL for recombinant t-tau, 27–1,574 pg/mL for synthetic $Ab_{1–42}$ and 8–230 pg/mL for a synthetic tau peptide phosphorylated at the threonine 181 position (the $p\text{-}tau_{181}$standard). Quality control of the assay system is continuously monitored by including in each analytical run two never-before thawed aliquots of CSF pool samples and 2 to 3 retest samples of never-before thawed aliquots of subjects from the immediately previous run [5,177,223]. This immunoassay system has been in operation for the past 5 years, and biomarker core staff have accumulated extensive experience in performance including participation in a 7 center interlaboratory study [177], and ongoing participation in the World-wide ADNI-sponsored International CSF QC program as one of the reference laboratories [5]. From this experience the robustness of this immunoassay is demonstrated by consistency of performance: (a) %CV values for CSF pool aliquots ranging from 7.6-9.3% for $Ab_{1\text{-}42}$, 5-11.2% for t-tau and 9.5-16.6% for $p\text{-}tau_{181}$ over 51 runs and 3 different lots of the manufacturer's reagents; (b) average %CV for test/re-test analyses of 118 ADNI subject CSF samples of 5.7%, 5.6% and 11.5% for $Ab_{1\text{-}42}$, t-tau and $p\text{-}tau_{181}$, respectively. Detection of an AD CSF profile for t-tau, $p\text{-}tau_{181}$ and Aβ42 in subjects here will be achieved using receiver operating characteristic (ROC) cutpoints and logistic regression models derived from our ADNI studies. Our data showed that CSF Aβ42 was the most sensitive biomarker for AD detection in CSF from non-ADNI autopsy-confirmed subjects with an ROC area under the curve of 0.913 and sensitivity for AD detection of 96.4% [223]. A unique bimodal characteristic of the distribution of CSF Aβ42 was detected in each ADNI subgroup, and a logistic regression model for Aβ42, t-tau and *APOε4* allele count provided the best delineation of mild AD. Application of cutpoints for the 4 most sensitive parameters for AD CSF pathology, i.e. Ab42, t-tau/Ab42, $p\text{-}tau_{181}$/Ab42 and the LRTAA (Logistic Regression of Tau, Aβ and APOEε4 alleles) model, showed the presence of an AD-like CSF profile in 89.1%, 91.8%, 94.6% and 89.1%, respectively in the 37 MCI subjects who converted to probable AD at 12 months. Support for our hypothesis that these AD biomarker indices are reliable harbingers of probable AD comes from our finding that a comparable incidence of CSF AD profiles was observed for MCI→AD converters at 24 months (89.7%, 88.2%, 92.6% and 88.2%, respectively; for more details, see

http://www.adni-info.org/index). Thus, the pathological CSF biomarker signature of AD we defined effectively detects mild AD in a large multisite prospective clinical investigation, and this signature appears to predict conversion from MCI to AD. The cutoff values established by Shaw et al. [223] were validated in a follow-up study that accurately classified AD patients independent of clinical diagnosis [224]. Further substantiation of these diagnostic cutpoints is illustrated by the data integration studies done in collaboration with other ADNI investigators [9,178,179,225-230]. All analysis data will be uploaded to the clinical database at ADCS and will be available on the UCLA/LONI/ADNI website without embargo.

7.4. Amyloid PET scans (Overseen by the ADNI PET Core at UC Berkeley, W. Jagust and U Mich R. Koeppe):

7.4.1. Acquisition: Current ADNI activities involve the acquisition of amyloid PET images using the radiotracer [^{18}F]AV-45, now known generically as Florbetapir [24-27]. This tracer was selected for ADNI2 for several reasons, including its long half-life relative to the short 20-min half-life of [^{11}C] that permits delivery to all current ADNI sites. Furthermore, Florbetapir distribution in the living brain has been shown to correlate well with the presence of amyloid plaques, and the pathological criteria for AD after the same brains were studied pathologically [24-27]. In addition, the manufacturer has partnered with local radiopharmacies and established a national distribution network for tracer, permitting us to scan subjects throughout North America and all currently enrolling ADNI sites. As of today, we have acquired [^{18}F]Florbetapir scans on approximately 275 ADNI participants and have a detailed and functional protocol for image acquisition and analysis that will be applied to this study. Key elements are identified below.

7.4.1.1. Site qualification and data acquisition (To be done by R Koeppe at U Mich): All ADNI sites participating in the Florbetapir protocol are already qualified for PET imaging using this procedure. If new sites are identified for this study, they will be qualified using standard methods that have been applied to current sites. New sites will be provided with a Hoffman phantom (we have purchased 4 at the start of ADNI) and a technical manual (developed as part of ADNI) and advice from the PET team. The phantom will be imaged using standardized procedures as defined in the technical manual (basically an acquisition identical to the clinical acquisition described below). All phantom images will be forwarded to the University of Michigan where they will be reviewed and, if not approved, repeated. Site will be qualified based upon interest and results of the phantom imaging in addition to clinical criteria.

Subjects will be scheduled by the clinical sites, working in conjunction with the PET centers. Logistical arrangements for ordering and transportation of Florbetapir to all sites have already been established. The Florbetapir protocol will entail the injection of 10 mCi of tracer followed by an uptake phase of 50 min during which time the state of the subject is not important. At 50 minutes subjects will be positioned in the scanner and 4 x 5 min frames of emission data collected. PET/CT scans will precede this acquisition with a CT scan for attenuation correction; PET-only scanners will perform a transmission scan following the emission scan. As we have done to-date in ADNI, sites will be required to use a single iterative reconstruction for all scans that is optimized for the instrument and which cannot change during the protocol. The vast majority of sites are experienced with this; new sites will be instructed as part of the qualification procedure. At the time of imaging, all sites will fill out a PET imaging form as we have instituted for ADNI. This provides data on important parameters not captured routinely in all image headers such as amount of tracer injected, exact times of injection, subject state, etc. These data are reviewed at the time of the QC checks. These forms are filled out online by the PET technologist or study coordinator – compliance has been high because they are required for reimbursement.

7.4.1.2. Data flow and QC: All data will be uploaded to the UCLA Laboratory of Neuroimaging (LONI) as we have done to-date with ADNI. Instruction in this protocol is provided as part of site qualification and all PET sites are currently familiar with this. Data are de-identified as part of the upload and placed into quarantine until they pass QC. Dr. Koeppe's laboratory at the University of Michigan is notified when new scans are uploaded, and QC is performed within 24 hours followed by pre-processing of the images.

Procedures for assuring scan quality involve the following and will be performed on all human PET scans.

1. Download all PET data sets from LONI.
2. Convert raw Image data of any format to CTI format as needed and store on local computer.
3. Raw Image QC Process

a. Visual inspection of all images: including both frames (temporal) and planes (spatial).

b. Extract and inspect all header information, and check versus required scan protocol.
c. Co-register (six degrees of freedom, rigid-body) all frames to first frame of the raw dynamic image set. Assess subject motion by magnitude of translation and rotation parameters.
d. Recombine co-registered frames to create both registered dynamic and registered average (averaged over all frames) image sets in native image geometry and orientation.
e. Determine image quality metrics (global correlation, global mean square error, global absolute error) both between frames on raw dynamic image data sets both pre- and post-coregistration. This includes comparisons between all frames pairs (e.g. 15 comparisons for a 6-frame study).
f. Inspect PET scan information form completed by site for each scan. Note errors and correct.
g. Complete PET QC form (e.g. pass, fail with reprocessing, fail with rescan, fail without rescan).
4. Pre-analysis processing steps:
a. Reorient and resample baseline FDG-PET images into a standard image matrix and image orientation (160x160x96 voxels; 1.5mm voxel size in all three dimensions).
b. As above, create dynamic and averaged image sets in standard image matrix.
c. Perform image intensity normalization on all data sets, to set global average of the normalized and thresholded image set to 1.0 (iterative process that makes average of all voxels above 0.5 equal to 1.0). Scans will be normalized to cerebellar gray matter, such that its value will be 1.0.
d. Smooth images from all PET scanner models/vendors by an amount determined from Hoffman phantom scans, in order to achieve a uniform effective resolution of 8 mm FWHM.
e. Upload all "pre-analysis" processed images to LONI (four image sets total).
As noted, these procedures have all been successfully employed as part of ADNI to-date for both FDG and PIB tracers, and many of the procedures for standardization of images have been published.

7.4.2. Analysis: Data will be analyzed by 2 laboratories that have participated in the analysis and reporting of PET data in ADNI: Dr Jagust's at UC Berkeley and Dr Reiman's at Banner Inst Phoenix Arizona. All results will be tabulated and uploaded so that summary numerical measures will be available immediately on the web. Each site will also upload any templates, regions, and final image results for free access by the scientific community.

7.4.2.1. Anatomically oriented region of interest analyses: Dr. Jagust, UC Berkeley: We will define ROIs using a standard template in standard space – the AAL atlas [231]. The AAL atlas will be "reverse normalized" to the spatial dimensions of the Florbetapir images, and counts will be extracted from these ROIs in order to widely sample cortex, using regions that include prefrontal cortex, lateral parietal, medial parietal (precuneus/posterior cingulate), and lateral temporal cortex. A cerebellar ROI will be defined as a reference tissue. We have used these methods in our laboratory in Berkeley with [^{11}C]PIB and note that they work well and have been validated [232-234]. The fundamental datum of these analyses will be tracer uptake in an ROI or group of ROIs normalized to cerebellum, or basically a standardized uptake value ratio (SUVR). In addition to using an averaged cortical uptake value as we have done in ADNI, we recognize that post-TBI or PTSD subjects may pose different issues. One question is whether the topography of tracer uptake is the same for these individuals as in AD. This question will be answered using data-driven voxelwise approaches (See 7.4.2.2 below). In addition, there may be no specific "pattern" in these disorders. In such cases, we can use multiple ROIs to define the regions in the brain for each subject in which tracer uptake is maximal or crosses a threshold of "positive" that we have defined using our control data. These approaches will provide an index of brain amyloidosis that is independent of any pre-specified cortical ROIs.

7.4.2.2. Voxelwise analyses: Dr Eric Reiman Banner Inst.: This group has extensive experience with such analyses of Florbetapir data using SPM5. Statistical brain mapping strategies will be used to analyze continuous PET measurements on a voxel-by-voxel basis in the different subject groups, thus providing regional information about between-group differences in baseline Florbetapir measurements. We will begin by performing straightforward SPM between-group comparisons to define the pattern of Florbetapir uptake in each group in comparison to each other and to the AD and MCI patients recruited into ADNI. Assuming patterns are similar, a Florbetapir statistical ROI (sROI) will be empirically characterized and an sROI-to-cerebellar SUVR threshold determined using an ROC-derived sensitivity and specificity analysis using ADNI data; this threshold will be applied to the acquired data to define the proportion of amyloid-positive subjects in each group. We will also apply automated anatomical labeling (AAL), an SPM sub-routine for the characterization of regions-of-

interest (ROIs) to characterize and compare regional and mean cortical SUVr's. Finally, we will use our recently developed amyloid convergence index (ACI) to characterize and compare measurements of fibrillar Aβ burden in brain regions that are preferentially affected by AD—a technique that had better power to discriminate Aβ burden in AD patients from controls than more conventional image analysis techniques.

7.5. MRI scans (Overseen by ADNI MRI Core, Dr. C. Jack, Mayo Clinic): The MRI Core will coordinate all MRI acquisition, processing, and analysis. Key personnel at the central lab at Mayo include Drs. Jack, Bernstein, and Gunter and Bret Borowski, RTR and Kaely Steinert, RTR. Functions of the central core MRI lab include the following: 1) MRI protocol creation, distribution, and site certification; 2) Quality control; 3) Accommodating MRI upgrades; 4) MR data pre-processing - unwarping and bias field correction of the IR SPGR scans; 5) Scanner monitoring with the ADNI phantom. We designate the MRI protocol as provisional at this time, because detailed technical surveys of MR equipment have not been conducted at all enrollment sites. The feasibility of performing some imaging sequences in a consistent manner is dependent on scanner technology. Without knowing precisely the MRI platforms that must be supported, it is premature to rigidly finalize the MRI protocol. Our provisional plan, however, is to perform all imaging on GE 3T systems. Imaging will be performed on currently qualified ADNI GE systems. Approximately 1/3 of the ADNI sites have GE systems, and we estimate that an additional 5 GE systems will need to be qualified to meet recruitment needs of the study. Our rationale for selecting GE systems is that diffusion tensor imaging (DTI) is done only on GE systems in ADNI 2. It is not possible to standardize DTI across MR vendors using product sequences. DTI will be part of the DOD TBI protocol, and we wish to have a protocol that is consistent across all recruitment sites. The MRI protocol was designed with several considerations in mind. Among the most important were restricting the study to manufacturer-available pulse sequences (also called a "product" pulse sequence). A "work-in-progress" (WIPS) or "research pulse" sequence is not routinely available from the vendor. WIPS sequences require that a formal research agreement exists between the vendor and MRI site. WIPS pulse sequences also require special attention (e.g., conversion, recompilation, and redistribution) each time the software revision of the MRI system is upgraded. One of the most important lessons learned in ADNI 1 was the difficulties with using WIPS sequences in a large multi-center study. Consequently, this DOD ADNI TBI project will be limited exclusively to manufacturer-available pulse sequences. A second key consideration was the duration of exam. A complex (long) MR exam in which many sequences are acquired would maximize the amount of data collected per exam. However, a shorter less complex exam would be met with greater patient acceptance and lower attrition. We therefore settled on an upper time limit of approximately 35 minutes of scan time for the MRI protocol beyond which we would be concerned about excessive patient burden. The value of the 3D T1-weighted volumetric and FLAIR scans in the context of acquiring brain data relevant to TBI and dementia is clear. We included DTI in the protocol because of the suspected relationship between traumatic shearing injury and later risk of dementia. DTI may provide the best objective evidence of shearing-type TBI available. A T2* gradient echo (T2*GRE) is included to capture evidence of hemosiderin deposition which could be due to remote cortical contusion, shearing injury, or prior subarachniod hemorrhage (superficial siderosis). We included resting state task free fMRI in the protocol because of the increasing interest in functional network analysis as a possible precursor of future dementia.

7.5.1. Acquisition (To be done at the ADNI Sites): The MRI protocol will provisionally consist of the following image sequences:

7.5.1.1. 3D T1-weighted volume: This will be an IR-SPGR sequence which is the GE product analogue to MPRAGE. This sequence will not be accelerated because the reliability of acceleration for multi site studies has not yet been established. Specific protocol parameters for various 3T GE systems can be found at http://www.adni-info.org/Scientists/MRIProtocols.aspx. Spatial resolution will be approximately 1mm cubed. Structural/morphometric analyses will be performed with this sequence. This sequence will undergo unwarping and bias field corrections at Mayo Clinic as is done in ADNI and as described in [11].

7.5.1.2. FLAIR: FLAIR images will be used for quantitative measures of white matter hyper intensity (WMH) burden and for qualitative grading of lacunar infarctions and evidence of closed head injury – e.g. cortical contusions.

7.5.1.3. T2*GRE: This sequence will be used to capture evidence of traumatic hemosiderin deposition. We will use a T2*GRE rather than susceptibility weighted imaging sequence (SWI) because the latter requires an SWI software license. It is unlikely that every site will have purchased the SWI license. Therefore, in order to

acquire data on remote hemorrhagic TBI in a uniform manner across all sites, a standard sequence (T2*GRE) that is available on any scanner will be used.

7.5.1.4. DTI: We will use the same DTI sequence as in ADNI. Protocol parameters again can be found at http://www.adni-info.org/Scientists/MRIProtocols.aspx. But, the relevant resolution parameters are 2.7mm cubed spatial resolution; 41 diffusion encoding directions and 5 B0 volumes. Imaging time is 7-11 minutes depending on the specific gradient system.

7.5.1.5. Resting state EPI-BOLD: The task-free fMRI sequence will consist of 103 volumes at 3.3mm cubed resolution. The duration is 7 minutes.

7.5.2. MRI Image Analysis

Principle Investigators of the 4 funded image analysis groups and their responsibilities for image analyses are described below:

7.5.2.1. Morphometry - 3D T1 images. Norbert Schuff, UCSF: 3D T1 images will be analyzed using the probabilistic-based FreeSurfer (FS) software. The FreeSurfer pipeline consists of five stages: an affine registration with Talairach space, an initial volumetric labeling, bias field correction, non-linear alignment to the Talairach space, and a final labeling of the volume. The fully automated labeling of volumes is achieved by warping a population-based brain atlas to the target brain and by maximizing an a-posteriori probability of the labels given specific constraints [235]. The procedures have been extensively validated. Volume measurements of about 96 anatomical brain regions will be computed [236]. In addition to volumes, thickness, curvature and other geometric measures will be computed for cortical regions. For longitudinal measurements of change, a Markov chain-based protocol will be applied [236], in which past measurements are used as priors for current measurements.

7.5.2.2. CerebroVascular Disease, infarcts and brain injury: Charles DeCarli, UC Davis: This group will calculate measures of white matter disease burden. The validated, fully-automated WMH detection method aligns the imaging data to a template image, where WMHs are identified on a per-voxel basis based on image intensities and prior knowledge of the probability of WMH occurrence at each location in the brain [237]. In addition, a trained and validated expert will determine the gross locations, sizes, and etiologies of MRI-evident infarcts and intensity abnormalities on FLAIR and T2*GRE consistent with closed head injury using the same reliable, repeatable protocol that has been used for ADNI and a variety of other studies, including the Framingham Heart Study.

7.5.2.3. Diffusion Tensor Imaging: Paul Thompson, UCLA. This group will analyze DTI images. The following steps are employed. Correction for motion artifacts, eddy currents, susceptibility artifacts: Motion artifacts and eddy current artifacts cause spatial misalignment and geometric distortion among DTI data volumes scanned with different diffusion gradient directions [238]. We use the FMRIB software library (FSL, http://www.fmrib.ox.ac.uk/fsl/) to correct for geometric distortions due to motion, eddy current, and susceptibility artifacts. DTI data are then registered by 9-parameter transformation to the ICBM space. All DTI scans are denoised using Riemannian methods [239] and mutually-registered to a geometrically-centered mean tensor image, using our validated fluid registration method based on information theory, driven by the full 6D diffusion tensor [240]. Group Statistical Analyses: We will perform a voxel-by-voxel analysis of the following DTI-derived measures: fractional anisotropy (FA), geodesic anisotropy (GA), mean diffusivity (MD), and parallel and transverse diffusivity (diffusion tensor eigenvalues). To improve power, we will correct all these indices for fiber crossing/mixing using our tensor deconvolution methods [226,241-243]. We will also perform statistical analysis of the full 6D diffusion tensor, which can boost power in group DTI analyses [226,244-246]. ROI-based Analyses: To provide regional summaries, we will also fluidly align the parcellated Mori DTI81 atlas to our mean DTI template and compute average values of all DTI indices in regions of interest [247]. To boost power, we will also use the training-testing method [248,249] to create statistically-defined ROIs for minimal sample size analyses.

7.5.2.4. Resting State Functional Connectivity C. Jack, Mayo Clinic: Pre-processing: Removal of time dependent drifts of the fMRI signal, elimination of the first three slices to allow for acquisition signal to reach steady state and inter-frame motion correction within the time series of each subject using a six-degrees-of-freedom co-registration. Each patient's pre-processed fMRI scan will be co-registered (based on their first frame) to their 3D T1 scan and then be co-registered to the Talairach atlas. Additional steps that will be applied to remove spurious signals that might affect the neuronal activity are: low pass filtering images from 0.01 Hz to

0.1 Hz, global mean signal removal, removing signal from CSF and white matter and spatially smoothing the images at 8 mm FWHM. Resting State Functional Connectivity (RSFC) Analysis: A sphere of 12 mm will be placed in each of 85 nodes of the main networks which will be standardized through ADNI. To re-check the ADNI-standardized nodes, we will run a group ICA analysis (using the FSL MELODIC group ICA toolbox: http://www.fmrib.ox.ac.uk/fsl/melodic/index.html) and look at each of several main networks in the independent components and re-center the nodes if necessary for this data. Correlation coefficients will be computed between each of the nodes in each network for all subjects and will be z-transformed.

7.6. Genetics. ADNI Genetics Core. A. Saykin, Indiana U: Participants will be genetically characterized by the ADNI Genetics Core led by Dr. Andrew Saykin (Indiana University) using an updated version of the published methods employed in ADNI-1 [14]. In brief, blood samples are collected by the sites under direction of the Clinical Core and shipped to the NIA National Cell Repository for Alzheimer's Disease (NCRAD; http://ncrad.iu.edu/) at Indiana University directed by core co-leader Tatiana Foroud. NCRAD will prepare immortalized cell lines and extract, aliquot and store DNA as previously described. APOE epsilon 2/3/4 alleles and genotypes will be determined from the two relevant single nucleotide polymorphisms (SNPs) in periodic batches. After completion of the TBI, PTSD and control samples, the current high density genome wide array ("gene chip") used in ADNI-2 and by the NIA AD Genetics Consortium (ADGC) will be employed to determine the genotypes needed for genome wide association study (GWAS), pathway and candidate gene studies that investigators may wish to pursue. At present, we plan to use the cost-effective Illumina OmniExpress Beadchip with over 700K SNP and copy number variation (CNV) markers (http://www.illumina.com). *We wish to emphasize to reviewers that the intent of the genotyping in this application is to further expand the sample size of the entire ADNI dataset to examine associations among genetic variation and imaging markers of AD. We recognize that the new genetic data obtained in this study would not have standalone statistical power to examine genetic interactions with TBI and PTSD effects.* DNA from cell lines will be available for approved future projects to test specific hypotheses related to AD, TBI and PTSD risk genes or other questions. Future possibilities made feasible by collection of the proposed samples include exome or targeted loci sequencing and epigenetic studies, although additional support will be required for these assays and associated informatics. The Genetics Core/NCRAD will store, process, track and disseminate genetic samples. Genetic data will receive initial quality control by the Core. Drs. Li Shen (co-leader) and Sungeun Kim will be responsible for the bioinformatics. Data will be shared after QC via the ADNI website at LONI managed by the ADNI Informatics Core directed by Dr. Toga. In addition to standard Illumina GenomeStudio and final report outputs, a set of user friendly files will also be made available. This includes formats for PLINK, a widely available toolkit for SNP, CNV, GWAS and gene- and pathway-based set analyses (http://pngu.mgh.harvard.edu/~purcell/plink/). All of these methods, processes and collaborative arrangements and interactions have been in place and fully operational for several years in ADNI. The Core will also perform basic association analyses of the new TBI, PTSD and control samples separately and in combination with other ADNI samples as appropriate. As in ADNI, the Core will facilitate collaborative projects analyzing these data in relation to key phenotypes such as neuroimaging and fluid biomarkers. In the past 2 years, over 25 publications have resulted from the ADNI GWAS data including GWAS of imaging phenotypes [14,15,250-257] and CSF biomarkers [258], mitochondrial genome patterns [259] as well as CNVs [260]. Several large scale case/control GWAS studies included the ADNI data [261-263]. In addition to AD related phenotypes and gene pathways, specific biological pathways associated with TBI and PTSD can be interrogated for their contribution to the ADNI cognitive, fluid biomarker, MRI and PET phenotypes. Examples include variation in catecholamine genes [264,265] and other pathways identified by prior TBI proteomic studies [266-273]. Similarly, multiple biological pathways identified in research on PTSD [274-280] can be examined for contributions in addition to AD and TBI associated genes to build a more complete model. Twin studies in Veterans have already demonstrated that genetic underpinnings of pre-exposure cognitive functioning are heavily genetically determined [281]. The genetic characterization of the proposed samples will support a wide range of follow-up research.

7.7. Autopsy. ADNI Neuropathology Core. N Cairnes and J. Morris, Wash U: Neuropathology will be performed free for this DOD grant by the ADNI Neuropath Core Directed by Nigel Cairnes and John Morris at Wash U in St. Louis and pick up any costs on the ADNI grant as few autopsies are expected during the period of the DOD grant.

7.8. Informatics: Database at ACDS and Imaging Database at LONI ADNI Informatics Core. A. Toga, UCLA: Data capture at the San Francisco Telephone Interviewing site and ADNI sites will utilize the ADCS data management system. This system, which includes secure data-transmission, redundant multi-sited backups, real-time quality checks, multi-level access control and electronic signature capability, flexible reporting and analysis routines, and full Title 21 CFR Part 11 compliance, is currently used in ADNI as well as all ADCS therapeutic trials. The Laboratory of Neuro Imaging (LONI) will serve as the repository for all MRI and PET images and will also be the public portal for data release of images and the clinical data base (from ADCS). LONI has been serving as a central repository for single and multisite neuroimaging research studies for over two decades. We have developed a secure data archive system and associated data de-identification, search, retrieval, conversion and dissemination tools that provide maximal flexibility in data storage and sharing while minimizing complexity of use. The laboratory's Image & Data Archive (IDA) is utilized by thousands of investigators around the globe to safely de-identify, store and share biomedical research data. Our robust computing infrastructure and software combined with our many years of neuroinformatics experience places LONI at the nexus of many multisite imaging and neuroscience studies. LONI has served as a community-centric repository for neuroimaging research studies for the International Consortium for Brain Mapping (2001 to present), the Alzheimer's Disease Neuroimaging Initiative (ADNI) (2004 to present), the Huntington's Disease Neuroimaging Initiative (2007 to present), and the Parkinson's Progression Markers Initiative (2010 to present). LONI currently houses data from more than 10,000 subjects and provides millions of downloads to thousands of investigators across the globe. LONI has available a hardware infrastructure for high performance, security and reliability including fault-tolerant network infrastructure, multiple redundant database and web servers and load balancing of requests across the multiple machines. The LONI IDA has experienced 99.9% uptime over the last six years, ensuring that users around the globe have continual access to data. To augment the network-based security practices and to ensure compliance with privacy requirements, the servers utilize SSL encryption for all data transfers. Sophisticated backup mechanisms protect the integrity of data including two onsite and two offsite backups. The LONI IDA will provide easy to use, platform independent software. It will include: 1) simple and advanced query interfaces for searching the contents of the archive using demographic, image, and clinical metadata; 2) a collections interface for forming logical collections of data and downloading them (or passing them into the LONI Pipeline workflow environment); 3) an archiving interface for de-identifying and transmitting data to the archive; 4) project management interfaces to monitor study progress; 5) a study download interface for perusing or downloading clinical data and documents; 6) a visual analytics interface for obtaining insights from the data.

The LONI IDA will 1) perform image data archiving systems and support; 2) integrate quality assessment data including the process of quarantining and releasing data; 3) establish quality assessment workflows between external evaluators and LONI; 4) integrate demographic and/or clinical data imported from external sources; 5) provide the user access subsystem; 6) make data available via interactive, on-line tabular and graphical tools.

7.9. Statistical analysis ADNI Biostatistics Core. D. Harvey, UC Davis: Primary analyses involve comparing groups on baseline levels of CSF, neuroimaging (MRI and amyloid PET), and cognitive measures associated with AD pathology and annual change in MRI and cognitive measures to assess whether PTSD or TBI is associated with increased evidence for AD compared to Veteran controls. Further analyses will focus on within-group correlations to assess a dose-response association between outcomes and severity of PTSD or TBI and whether TBI or PTSD reduces cognitive reserve. Additional exploratory analyses will also be conducted. We describe the specific analytic methods for hypothesis testing below followed by an assessment of power.

7.9.1. Hypotheses (restated): The primary hypotheses to be tested (all data analyses will be covaried for age, gender, and APOe4 genotype) are that Veterans without MCI (by criteria) or dementia, with a history of moderate to severe TBI during military service, as well as Veterans with ongoing PTSD, have increased evidence for AD, when compared with Veteran controls (without TBI or PTSD) manifested as: 1) greater uptake on Florbetapir amyloid PET scans; 2) lower CSF amyloid beta levels; 3) increased CSF tau/P tau levels; 4) brain atrophy in hippocampus, entorhinal cortex, and parietal/temporal cortices; and 5) greater rates of brain atrophy in hippocampus, entorhinal cortex and parietal/temporal cortices; 6) reduced cognitive function, especially delayed recall.

The second major hypotheses to be tested is that TBI and/or PTSD reduce brain reserve causing greater cognitive impairment after accounting for age, brain amyloid load or hippocampal volume. Greater cognitive

impairments at a given level of brain Aβ or brain volume in the TBI or PTSD group compared with controls would support the hypothesis of reduced cognitive reserve.
The third hypothesis will be that TBI, when compared to controls, is associated with changes detected with DTI in brain regions previously reported to be associated with TBI [180-182].
Finally, we will test the hypothesis that there will be significant correlations between severity of TBI (determined from medical records) and severity of PTSD (CAPS score) on the above-listed outcomes in the TBI and PTSD groups respectively.
Exploratory analyses will be performed to examine other questions; although, after correction for multiple comparisons, the statistical significance of these will be low, requiring future replication. Nevertheless, we will compare the patterns of amyloid deposition (from Florbetapir uptake) and brain atrophy between TBI, PTSD, and control subjects, and with similar patterns from non-Veteran subjects in ADNI. These results of these studies may provide insight into the question of whether or not TBI and PTSD alter the pattern of amyloid distribution or brain atrophy. Such analyses may also give insight into the question of whether TBI or PTSD is associated with reduced cognitive reserve. The relationship between cortical areas with amyloid plaque (from amyloid PET) and underlying white matter integrity as assessed with DTI (if DTI is used) will also be studied to determine if axonal injury resulting from TBI was associated with greater amyloid accumulation, or whether regions of brain with axonal damage have less amyloid accumulation due to disconnection and reduced brain activity.

7.9.2. Primary Analyses: Comparing Groups on Baseline Level (Hypothesis sets one and three): Primary outcomes for these analyses include uptake on Florbetapir scans, CSF amyloid beta, CSF tau and Ptau, volumes of the hippocampus, entorhinal cortex, and parietal/temporal cortices, DTI summary measures (in the third set of hypotheses) and measures of cognitive function, including delayed episodic memory. We will begin with numerical and graphical summaries of the measures within each group to assess the underlying distribution and detect outliers or questionable values which will be flagged and checked with the sites for accuracy. We will then use analysis of variance (ANOVA) for a simple unadjusted comparison between the groups. If the global F-test for group difference is significant, we will follow-up with post-hoc pairwise tests, specifically between the TBI or PTSD groups and the Veteran control group, adjusted for multiple comparisons using the Bonferroni or Tukey's Honestly Significant Difference (HSD) approach. Next, we will use linear regression models that include group as an independent variable to adjust for potential confounders including age, gender, APOe4 genotype, and alcohol dependence. Model assumptions will be assessed through graphical and numerical approaches and transformations or non-linear models will be used if suggested by the diagnostics. Hypotheses will be supported if the TBI and PTSD groups show significantly higher levels of uptake on amyloid PET scans and CSF tau or Ptau than the Veteran controls and significantly lower levels of CSF amyloid beta, MRI volumes, and cognitive function than the Veteran controls.

7.9.3. Primary Analyses: Comparing Groups on Annual Change (Hypothesis sets one and three): Primary outcomes for these analyses include annual change in volumes of the hippocampus, entorhinal cortex, and parietal/temporal cortices and annual change in cognitive function such as delayed recall. We will have two assessments for each person, approximately one year apart. Therefore, for each participant as a measure of annual change, we will construct difference scores between the measures obtained at the follow-up visit and the baseline visit and divide them by the time between the assessments to account for variability in timing of the follow-up assessments between participants. Analyses will be similar to those described above for comparing groups on the baseline level except that the final linear regression models will also be adjusted for baseline level of the outcome measure. Hypotheses will be supported if the TBI and PTSD groups show significantly faster rates of atrophy and cognitive decline than the Veteran controls.

7.9.4. TBI or PTSD associated with reduction in cognitive reserve (Hypothesis set two): The main outcomes for these analyses will be level and annual change in cognitive function, particularly memory while the predictors of interest are group, baseline hippocampal volume, and uptake from the amyloid PET scans. We will use linear regression methods similar to those described above. Of particular interest for these analyses are the interactions between group and the imaging predictors. Power will be limited for these analyses, so results will mainly serve as support for future studies of PTSD, TBI, and cognitive reserve. However, significant interactions suggesting worse cognitive function in the TBI or PTSD groups relative to Veteran controls at a given level of MRI, or amyloid imaging measures would support the hypotheses.

7.9.5. Within-group correlations to assess dose-response: Outcomes for these analyses will be the same as those used for hypothesis sets one, two, and three. Interest lies in assessing whether the baseline levels or rates of atrophy or cognitive decline are associated with severity of TBI or PTSD. Analyses will be performed within each of those groups separately. Severity of TBI or PTSD will be the predictor of interest. We will begin with simple linear regression models that include severity of TBI or PTSD as the independent variable. We will then use multiple regression models to adjust for potential confounders including age, gender, APOe4 genotype and alcohol dependence. As stated above for the primary analyses, model assumptions will be assessed and transformations or non-linear models will be used if suggested by the diagnostics. Secondary hypotheses will be supported if increased severity of TBI or PTSD is significantly associated with lower levels of CSF amyloid beta, MRI volumes, and cognitive function, higher levels of CSF tau or Ptau, and increased rates of brain atrophy and cognitive decline.

7.9.6. Exploratory Analyses: Exploratory analyses will be performed to examine other questions; although, after correction for multiple comparisons, power will be low requiring future replication. Nevertheless, we will compare the patterns (using voxel based methods) of amyloid deposition (from amyloid PET) and brain atrophy between TBI, PTSD, and control subjects, and with similar patterns from non Veteran subjects in ADNI. The results of these studies may provide insight into the question of whether or not TBI and PTSD alter the pattern of amyloid distribution or brain atrophy. Furthermore, the relationships between amyloid deposition, atrophy, and cognitive function may provide insight into the question of whether TBI or PTSD are associated with reduced cognitive reserve. Further exploratory analyses will assess the relationship between cortical areas with amyloid plaque (from amyloid PET) and underlying white matter integrity as assessed with DTI to determine if axonal injury resulting from TBI was associated with greater amyloid accumulation, or whether regions of the brain with axonal damage have less amyloid accumulation due to disconnection and reduced brain activity. Linear regression methods, described above, will be used to assess the association between regional measures of amyloid accumulation and axonal damage.

7.9.7. Power Analysis: Power analyses are presented for each class of primary hypotheses assuming a two-sided test and were calculated using nQuery. For comparison of the TBI or PTSD group to the Veteran controls, assuming alpha = 0.025 to account for multiple comparisons and 65 individuals per group at baseline and 61 per group for longitudinal measures, we will have 80% power to detect a difference as small as 0.55 standard deviations in level and as small as 0.56 standard deviations in rate of atrophy or cognitive decline. For example, using means and standard deviations from measures in the normal controls within ADNI-1, this difference would translate to at least a 6.7% lower hippocampal volume, and at least a 14.7% lower CSF amyloid beta. Because there is little change in the ADNI normals, differences in change will be much more difficult to detect. However, these data will provide initial estimates of how much change is experienced in the TBI and PTSD groups which will help in planning larger scale longitudinal studies of these groups. We will be able to detect at least a doubling of the rate of hippocampal atrophy and at least a quadrupling of the rate of decline in delayed recall in the TBI or PTSD groups compared to the Veteran controls. For within group correlations, we will have 80% power to detect a correlation as small as 0.33 with cross-sectional outcomes and 0.34 with outcomes of change.

8. ADNI Data and publications committee. R Green, Harvard U: All data from this study will be available on the LONI website without any embargo. Dr Robert Green, who chairs the Data and publications committee, will continue to monitor all requests for permissions to access the data and will treat all publications coming forth from this DOD ADNI grant similar to the ADNI publications. All publications must be submitted to the committee for review, prior to submission to journals. The committee tracks these and insures that the DOD ADNI project is properly given acknowledgement in the author line of the paper. There will be no cost to this for this project.

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