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Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury

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ABSTRACT

Introduction: Traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) are risk factors for early onset of Alzheimer's disease (AD) and may accelerate the progression rate of AD pathology. As amyloid-beta (Aβ) plaques are a hallmark of AD pathology, we hypothesized that TBI and PTSD might increase Aβ accumulation in the brain.

Methods: We examined PET and neuropsychological data from Vietnam War veterans compiled by the US Department of Defense Alzheimer's Disease Neuroimaging Initiative, to examine the spatial distribution of Aβ in male veterans' who had experienced a TBI and/or developed PTSD. Subjects were classified into controls, TBI only, PTSD only, and TBI with PTSD (TBI_PTSD) groups and data were analyzed using both voxel-based and ROI-based approaches.

Results: Compared to controls, all three clinical groups showed a pattern of mainly increased referenced standard uptake values (SUVR) for the amyloid tracer [^{18}F]-AV45 PET, with rank order PTSD > TBI_PTSD > TBI > Control, and same rank order was seen in the deficits of cognitive functions. SUVR increase was observed in widespread cortical regions of the PTSD group; in white matter of the TBI_PTSD group; and cerebellum and precuneus area of the TBI group, in contrast with controls. The [^{18}F]-AV45 SUVR correlated negatively with cerebrospinal fluid (CSF) amyloid levels and positively with the CSF tau concentrations.

Conclusion: These results suggest that both TBI and PTSD are substantial risk factors for cognition decline and increased Aβ deposition resembling that in AD. In addition, both PTSD and TBI_PTSD have a different pathways of Aβ accumulation.

1. Introduction

Post-traumatic stress disorder (PTSD) is an anxiety disorder occurring in response to traumatic stress such as may occur in combat. A retrospective study of t veterans with PTSD showed a two-fold higher risk of developing dementia compared to veterans without PTSD even after adjusting for other comorbidities (Yaffe et al., 2010), and PTSD increases the risk for dementia and Alzheimer's disease (AD) (Cohen et al., 2013; Finfer and Cohen, 2000; Wang et al., 2010; Yaffe et al., 2010b). Traumatic brain injury (TBI) is one of the leading causes of death and disability in the young population (Finfer and Cohen, 2000). Survivors of TBI often suffer from permanent neurological and cognitive deficits, with increased risk for developing AD. There is considerable comorbidity of PTSD with TBI, especially among war veterans (Alway et al., 2016; Amen et al., 2015), which raises the question of whether the two conditions interact regarding the risk of neurodegenerative changes and dementia.

The most common form of dementia is AD, which is characterized by brain pathology consisting of extracellular Aβ plaques, intraneuronal tangles of phosphorylated tau protein, synapse loss, and neuronal loss

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[1] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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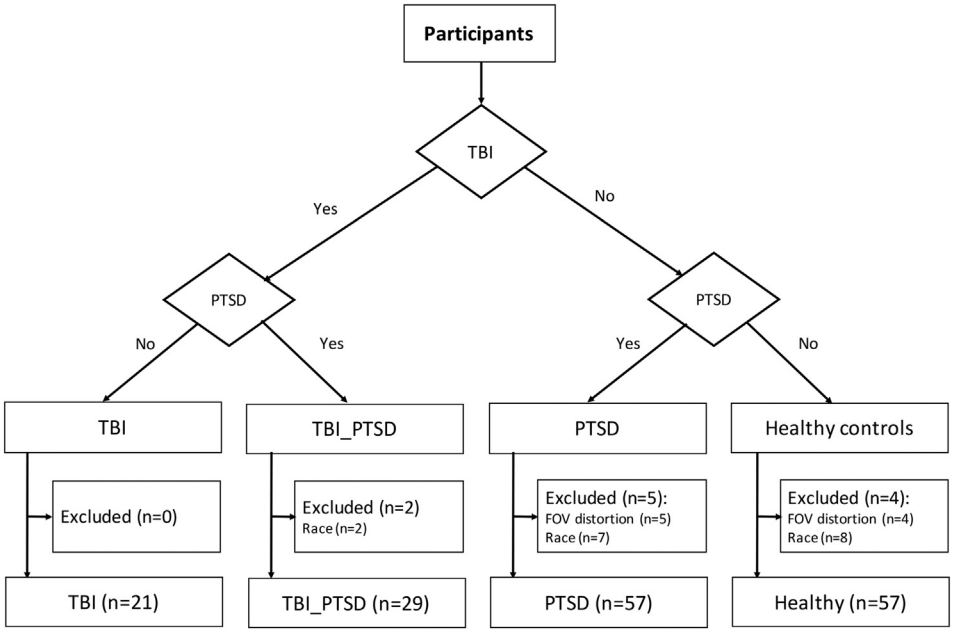

Fig. 1. Final groups and clinically classified subjects. Subjects were classified into four different groups including healthy controls, traumatic brain injury (TBI), post-traumatic stress disorder (PTSD), and TBI subjects with PTSD (TBI_PTSD).

(Hardy, 2002; Kerbler et al., 2015).The transition from mild cognitive impairment (MCI) to AD can be monitored in PET studies with amyloid-beta (Aβ) ligands such as [^{11}C]-PiB and [^{18}F]-AV45 (Florbetapir) (Nemmi et al., 2014; Saint-Aubert et al., 2013). Increased Aβ plaque deposition has been reported in post mortem examination of brain from TBI victims (Johnson et al., 2012), and is now being documented in PET studies of TBI patients. For example, in a [^{11}C]-PiB PET study of TBI patients, researchers found increased Aβ deposition in the posterior cingulate cortex, cerebellum and striatum (Scott et al., 2016), regions that extensively overlapped with the pattern of Aβ deposition found in AD brain. Indeed, Aβ plaques have been observed in about one third of TBI subjects (Johnson et al., 2012, 2010), irrespective of patient's age, suggesting that TBI is a causative factor in Aβ deposition (Uryu et al., 2007). Interestingly, Aβ plaques were seen shortly after an injury event (Ikonomovic et al., 2004) but not in long term survivors of TBI (Chen et al., 2009), suggesting that enhanced amyloid clearance mechanisms may compensate for an acute injury-related accumulation.

There is scant documentation of the relationship between PTSD with amyloid deposition. Studies in rodent models of PTSD due to chronic stress indicated accelerated amyloid plaque formation and Aβ release (Rothman et al., 2012). To investigate this phenomenon, the Department of Defense (DOD) funded a component of the Alzheimer's Disease Neuroimaging Initiative (ADNI) specifically to investigate amyloid burden, cognitive changes, and brain structural/functional changes in Vietnam War veterans. A preliminary analysis of data from the DOD-ADNI consortium showed worse global cognitive function in Vietnam War veterans with PTSD, but did not reveal the expected and hypothesized increase in Aβ burden when considering the entire cerebral cortex as a single volume of interest (Weiner et al., 2017). We hypothesized that the earlier analysis of this data may have missed focal alterations in Aβ deposition in the subgroup of long-term PTSD survivors, and furthermore that spatial mapping of Aβ might distinguish the PTSD group from groups with TBI and cases of mixed TBI and PTSD (TBI_PTSD). To test these linked hypothesis, we undertook a voxel-based re-analysis of the DOD-ADNI data sets, and made a statistical comparison of the PTSD, TBI and TBI_PTSD group findings contrasted with demographically matched control material.

2. Materials and method

2.1. Study subjects

Data used in the preparation of this article were obtained from the DOD-ADNI as part of ADNI database (adni.loni.usc.edu) which was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the mild cognitive impairment progression and early onset of AD. DOD-ADNI aimed at investigating the effect of TBI and PTSD on brain function and structure, and identifies the risk for progression to AD. For up-to-date information, see www.adni-info.org.

Ethical approval to use the de-identified data was also obtained from the Human Research Ethics Committee of the University of Queensland, Australia (IRB number #2017000630). Data were collected as part of a multicenter trial run by the DOD-ADNI initiative. In addition, as part of DOD-ADNI, all subjects signed an informed consent form including all the experimental procedures.

A total of 190 male Vietnam War veterans (age = 74.8 ± 6.2 years) were recruited by the DOD-ADNI study. After a rigorous quality control of the PET imaging data for motion, attenuation and other image artifacts, there remained 166 subjects (age 73.7 ± 6.2 years). These individuals belonged to one of four clinical groups: healthy controls without psychiatric or neurological illness (n = 57 subjects), PTSD without TBI (PTSD; n = 57 subjects), PTSD with TBI (TBI_PTSD; n = 29 subjects), and moderate/severe TBI without PTSD (TBI; n = 21 subjects), as shown in Fig. 1. We excluded from our study a total of 17 male veterans of non-Caucasian ethnicity, as shown in Fig. 1. Here, our intention was to eliminate confounds due to possible ethnicity-related differences in brain volume (Isamah et al., 2010) and grey matter integrity (Liu et al., 2015), as shown in Fig. 1. All subjects had served during the Vietnam War with or without documented history of moderate-severe non-penetrating TBI related to military service, and with/without evidence of PTSD identified using the Structured Diagnostic Interview for DSM-V & Clinician Administered PTSD Scale (CAPS) with a cut-off score of 30 (refer to Fig. 1. for further details on the study population).

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