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ORIGINAL COMMUNICATION

Traumatic brain injury fast-forwards Alzheimer's pathology: evidence from amyloid positron emission tomorgraphy imaging

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Abstract

Purpose Traumatic brain injury (TBI) has been proposed as a risk factor for Alzheimer's disease (AD), although the mechanisms underlying the putative association are poorly understood. We investigated elderly individuals with a remote history of TBI, aiming to understand how this may have influenced amyloidosis, neurodegeneration, and clinical expression along the AD continuum.

Methods Total of 241 individual datasets including amyloid beta (Aβ) positron emission tomography ([^{18}F]-AV45), structural MRI, and neuropsychological measures, were obtained from the Alzheimer's Disease Neuroimaging Initiative. The data were stratified into groups with (TBI +) or without (TBI −) history of head injury, and by clinical dementia rating (CDR) scores, into subgroups with normal cognition (CDR = 0) and those with symptomatic cognitive decline (CDR ≥ 0.5). We contrasted the TBI + and TBI − subgroups with respect to the onset age and extent of cognitive decline, cortical thickness changes, and Aβ standard uptake value (SUVr).

Results Compared to the TBI −/CDR ≥ 0.5 subgroup, the TBI + /CDR ≥ 0.5 subgroup showed a 3–4 year earlier age of cognitive impairment onset (ACIO, $p = 0.005$). Among those participants on the AD continuum (Aβ +, as defined by a cortical SUVr ≥ 1.23), irrespective of current CDR, a TBI + history was associated with greater Aβ deposition and more pronounced cortical thinning. When matched for severity of cognitive status, the TBI + /CDR ≥ 0.5 group showed greater Aβ burden, but earlier ACIO as compared to the TBI −/CDR ≥ 0.5, suggesting a more indolent clinical AD progression in those with TBI history.

Conclusion Remote TBI history may alter the AD onset trajectory, with approximately 4 years earlier ACIO, greater amyloid deposition, and cortical thinning.

Keywords Traumatic brain injury · Alzheimer's disease · Alzheimer's Disease Neuroimaging Initiative (ADNI) · [^{18}F]-AV45 PET · Amyloid · Voxel-based morphometry

Introduction

Traumatic brain injury (TBI) is associated with an increased likelihood of developing dementia later in life [1, 2]. Current thinking holds that a TBI event initiates or favours pathological pathways leading to neurodegenerative disorders, including chronic traumatic encephalopathy and Alzheimer's disease (AD) [3, 4]. The term TBI encompasses several forms of injury, including concussion, contusion, diffuse axonal injury (DAI), or open and closed head injury, as may occur during motor vehicle accidents, falls, violent assaults, and military combat [5]. Several reviews have suggested that the severity or number of TBI injuries might correlate with the risk for subsequent development of dementia

For the Alzheimer's Disease Neuroimaging Initiative: Data used in the 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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[3, 4, 6]. Furthermore, epidemiology studies have indicated an increased prevalence of dementia, or shorter latency to its onset, among those who have seemingly recovered from a TBI earlier in life. For instance, a study comparing 178,779 military veterans with history of TBI to an equally large cohort of uninjured control veterans revealed that even a mild TBI imparted a more than two-fold higher risk of dementia diagnosis later in life [7]. Another analysis of over 1200 TBI survivors and a similar-sized cohort of age- and gender-matched elderly people showed a 5 year earlier mean age of clinical AD onset in those with a TBI history [8]. In previously healthy elderly individuals, a TBI event was associated with a 1.5-fold higher risk of developing dementia within the first 5 years following the injury [9], and older adults with self-reported TBI history had a 3–4 year earlier onset of cognitive impairment compared to a control group without any such injury [10]. Furthermore, a study of 2133 cases with autopsy-confirmed AD showed a mean 2.3 year earlier onset of AD among those who had reported a history of TBI [11]. On the other hand, some researchers have questioned the evidence for an association with AD, proposing that TBI may be more strongly linked to elevated risk for later development of Lewy body disease or parkinsonism rather than AD [12–15]. While it is abundantly clear that TBI sets the stage for greater vulnerability for neurodegenerative diseases later in life, there is a need to understand better the pathways supporting this association, if timely interventions are to be developed.

According to the National Institute on Aging and Alzheimer's Associations' updated framework (NIA-AA) published in 2018, AD is defined as a continuum characterized by biomarkers of aggregated Aβ and tau, neurodegeneration, and ultimately by cognitive decline. Among these markers, evidence of aggregated Aβ—which can be measured in vivo by amyloid positron emission tomography (PET) or in cerebrospinal fluid—defines an individual as being on the AD continuum, irrespective of their tau burden, neurodegeneration, or present clinical status [16].

Post-mortem findings have indicated increased rates of Aβ positivity in those dying in the early months/years after a severe head injury [17] and a greater prevalence of tau pathology (and relatively more severe tau and Aβ pathology) in long-term survivors of a single TBI event [18, 19]. These findings were most striking in subjects aged less than 60 years, because AD pathology was essentially absent in the control population for that age group. Similarly, an [^{11}C]-PiB PET study of Aβ in TBI survivors in early and middle adulthood (all ≤ 55 years old) indicated significantly elevated standardized uptake value ratio (SUVr) in the cortical grey matter and the striatum [20], while another study reported increased [^{11}C]PiB uptake in the precuneus and cerebellum [21]; this latter study found that tracer uptake in the posterior cingulate cortex negatively correlated with fractional anisotropy in the cingulum bundle, suggesting an association between Aβ deposition and neurodegeneration.

While a considerable body of epidemiological evidence indicates that TBI imparts increased risk of dementia in later life, other biological studies suggest an increased prevalence and/or severity of AD-associated pathology in younger, non-demented TBI survivors. This study aimed to interrogate the ADNI database to reveal how a history of TBI modulates neuropathology and clinical dementia expression in individuals on the AD continuum. We further examined the brain volumetric changes and the age of cognitive impairment onset (ACIO) in relation to TBI history, with correction for the differing Aβ-positivity rates between the TBI and control groups. As such, this study is the first case-controlled analysis of the effect of TBI history on the development of cognitive and imaging markers of AD.

Materials and methods

Data used in this research were derived from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. Its primary goal was to combine serial MRI, PET, other biomarkers, and neuropsychological assessments to characterize the progression of AD. Ethics approval of this study to use the de-identified data was obtained through the Human Research Ethics Committee at The University of Queensland, Australia (IRB number #2017000630).

Study participants

Complete imaging datasets comprising [^{18}F]-AV45 PET and structural T1-weighted MRI from 241 elders were downloaded from the ADNI database. Based on self-reported history of TBI in earlier life, the total cohort included 41 participants with TBI and 200 age-matched non-TBI controls. The self-reported history of TBI was identified if the person had "concussion" and/or "head injury". We also downloaded neuropsychological battery test scores collected by ADNI for each participant (http://adni.loni.usc.edu/). Each participant had had their *APOE* genotype ascertained, and positivity was defined as carrying one or two *APOE-ε4* alleles.

Participants were classified into four groups based on their self-reported history of TBI and whether they were symptomatic (clinical dementia rating (CDR) score ≥ 0.5) or asymptomatic (CDR = 0) for present cognitive decline. The four groups were (1) participants with self-reported history of TBI and a CDR ≥ 0.5 (TBI + /CDR ≥ 0.5, $n = 19$); (2) those with a TBI history and CDR = 0 (TBI + /CDR = 0, $n = 22$); (3) participants without history of TBI and a

CDR ≥ 0.5 (TBI −/CDR ≥ 0.5, $n = 100$); and (4) those with no TBI history and CDR = 0 (TBI −/CDR = 0, $n = 100$) (Fig. 1).

To examine the impact of TBI on levels of amyloid binding (PET) and neurodegeneration (MRI atrophy), analyses were undertaken of the subgroup of participants on the AD continuum. Our definition of being on the AD continuum was having a positive amyloid PET, as defined by a mean cortical SUVr > 1.23, this being the threshold recommended by ADNI [22]. Amyloid positive scans were also confirmed with a visual read of all PET scans by a clinician with experience in rating amyloid PET (PJN), who was blinded to the group classifications. The reason for focusing on the AD continuum for these imaging analyses was to isolate the effect of TBI on these biomarkers. For instance, if there were an increased rate of amyloid positivity in the TBI + compared to TBI – group (as was indeed the case, see below), then finding higher average levels of amyloid binding or atrophy in the TBI + group could simply be a reflection of this group containing more individuals on the AD continuum. We were interested, however, not only in whether TBI confers a greater risk of AD, but also in whether it alters the pathological expression of AD. Therefore, to address that question, we contrasted voxel-wise analyses of amyloid binding and cortical atrophy in TBI + and TBI – participants who were all on the AD continuum (as defined above). These Aβ + subgroups were also stratified into symptomatic (CDR > 0.5) and asymptomatic (CDR = 0) as follows: TBI +/CDR ≥ 0.5, $n = 17$; TBI +/CDR = 0, $n = 13$; TBI −/CDR ≥ 0.5, $n = 86$; TBI −/CDR = 0, $n = 39$ (Fig. 1). In addition, we checked the T2-FLAIR images to identify any possible lesion or abnormalities in those with self-reported history of TBI, to be included as a confounding factor in our analysis if present. This screening revealed that none of the TBI + participants had any gross abnormalities in their MRI scans, other than atrophy attributable to normal ageing or Alzheimer's neurodegeneration.

The ACIO for CDR ≥ 0.5 participants was defined as the age when memory complaints were first reported either by the participant or an informant. The time since injury was defined as the time interval between the last reported TBI and the date of the PET scan; some participants in the database reported up to three TBI incidents. Details of the demographics and clinical information of the participants included in this study are summarized in Table 1 and Fig. 1.

Study design

To assess whether TBI influenced the risk of being amyloid positive on PET, we used a Chi-squared test to compare numbers of Aβ + and Aβ – cases in the TBI + and TBI – groups. Subsequent analyses aiming to examine the effect of TBI history on Aβ and neurodegeneration then focused only on those participants identified as being on the AD continuum by the criterion of a positive PET scan (SUVr > 1.23). Finally, to explore the effect of TBI in the symptomatic population, we

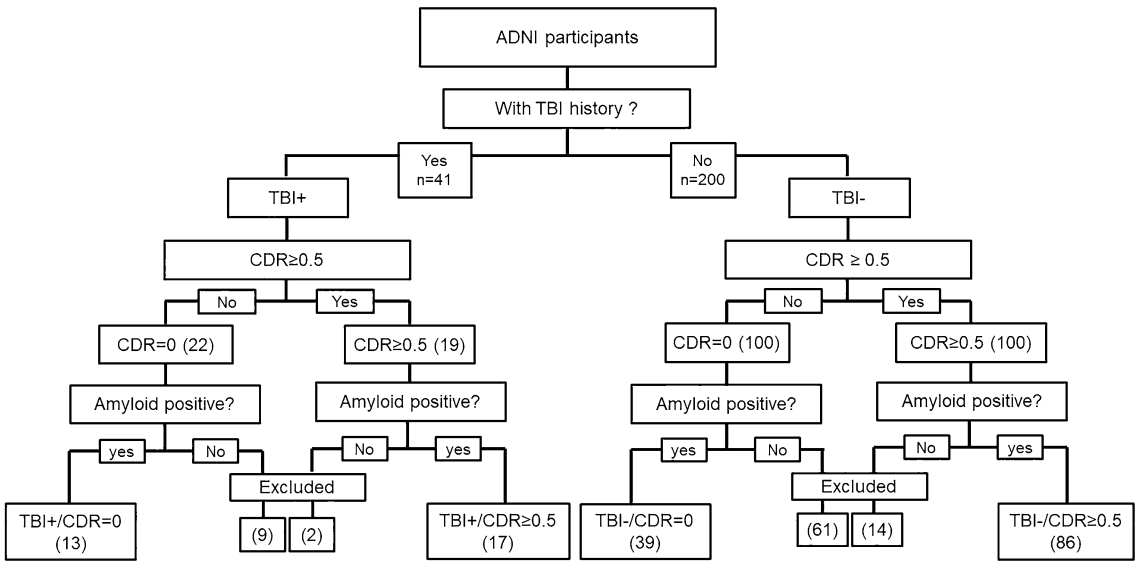

Fig. 1 Group stratification. Participants with a history of traumatic brain injury (TBI) were classified based on clinical dementia rating (CDR) and Aβ-positive PET scans (Aβ+) (where the mean cortical uptake scaled to the reference region (SUVr) > 1.23). CDR, clinical dementia rating; TBI+, participants with self-reported history of TBI; TBI −, participants without history of TBI; TBI + /CDR = 0, TBI + participants with CDR = 0; TBI −/CDR = 0, TBI − participants with CDR = 0; TBI + /CDR ≥ 0.5, TBI + participants with CDR ≥ 0.5; TBI −/CDR ≥ 0.5, TBI − participants with CDR ≥ 0.5

Table 1 Demographics of the participants in the four different groups

	TBI −/CDR ≥ 0.5	TBI −/CDR = 0	TBI +/CDR ≥ 0.5	TBI +/CDR = 0	*p* overall
Number of participants	*n* = 100	*n* = 100	*n* = 19	*n* = 22	
Age (SD) in years	73.6 (7.8)	70.9 (5.8)	73.5 (8.9)	74.1 (8.1)	0.035
Gender: female/male	48/52	50/50	5/14	9/13	0.265
Handedness: right/left	91/9	89/11	18/1	21/1	0.846
Education (SD) in years	15.8 (2.7)	16.7 (2.4)	15.9 (2.5)	17.6 (2.4)	0.004
APOE-ε4 status (−/+)	64/36	31/69	11/8	9/13	< 0.001
Aβ positivity					< 0.001
Aβ negative	14 (14%)	61 (61%)	2 (11%)	9 (41%)	
Aβ positive	86 (86%)	39 (39%)	17 (90%)	13 (59%)	
Loss of consciousness (yes/no)			7/12	10/12	0.81
TBI description:					0.848
Concussion			11 (58%)	11 (50%)	
Head injury			8 (42%)	11 (50%)	
Number of TBI events (SD)			1.26 (0.56)	1.27 (0.55)	0.956
Once			15	17	
Twice			3	3	
Three times			1	2	
Years Since TBI (SD)			31.1 (22.5)	38.6 (26.5)	0.956
Cerebral cortex SUVr	1.49 (0.14)	1.22 (0.14)	1.59 (0.31)	1.36 (0.23)	< 0.001
Age of cognitive impairment onset (years)	70 (2.8)		66.3 (3.6)		0.005
MOCA	19.0 (4.2)	23.3 (2.5)	20.2 (4.2)	23.5 (2.9)	< 0.001
MMSE	23.0 (2.4)	29.0 (1.2)	25.2 (2.7)	28.6 (1.3)	< 0.001
ADAS Total	21.2 (7.5)	5.2 (3.1)	18.5 (9.7)	5.6 (3.1)	< 0.001
ADAS-Cog	31.5 (9.1)	8.2 (4.5)	27.3 (12.4)	8.7 (5.2)	< 0.001

TBI + participants with self-reported traumatic brain injury, *TBI −* participants without self-reported traumatic brain injury, *CDR* Clinical Dementia Rating scale, *TBI + /CDR = 0* TBI + participants with CDR = 0, *TBI −/CDR = 0* TBI − participants with CDR = 0, *TBI + /CDR ≥ 0.5* TBI + participants with CDR ≥ 0.5, *TBI −/CDR ≥ 0.5* TBI − participants with CDR ≥ 0.5, *MMSE* Mini-Mental State Exam, *MOCA* Montreal Cognitive Assessment, *ADAS* Alzheimer's Disease Assessment Scale

compared the TBI + and TBI – subsets who were Aβ + and had CDR ≥ 0.5.

Cognitive measures

All participants had completed the following tests and scales for assessment of cognition: Everyday Cognition (Ecog); Clinical Dementia Rating (CDR); Mini-Mental State Exam (MMSE); Montreal Cognitive Assessment (MOCA); Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog); Geriatric Depression Scale; and Functional Assessment Questionnaire (FAQ); the Clock Drawing test; Clock Copy test; Rey Auditory Verbal Learning test; Category Fluency test; Trial Making test; Boston Naming test; and the American National Adult Reading Test.

MRI/PET image acquisition

At each imaging site, participants underwent the standardized ADNI MRI protocol. Quality control of the MRI data was performed at a designated MRI Centres, and detailed descriptions of both protocols are found at http://adni.loni.usc.edu/methods/documents/mri-protocols/. Amyloid PET images were acquired using the radiotracer Florbetapir ([^{18}F]-AV45). Data acquisition procedures were standardized across all ADNI sites [23]. In brief, 370 MBq (10 mCi; ± 10%) [^{18}F]-AV45 was administered as an intravenous bolus infusion. After a 50 min uptake phase, a series of four PET frames of 5 min each was acquired. After decay and attenuation correction, each frame was

iteratively reconstructed in 3D with a matrix = 128 × 128, FOV = 256 × 256 mm, and slice thickness = 3.27 mm, and converted to standard uptake values (SUV) before averaging to a single frame.

Data pre-processing

Study-specific template generation

A study-specific template was generated from all individual T1 images using Statistical Parametric Mapping (SPM12, www.fil.ion.ucl.ac.uk/spm) and used to normalise the PET images to a common standard space as described in [24]. The individual T1-weighted MRI images were segmented into grey matter, white matter, and cerebrospinal fluid based on a priori anatomical templates. The segmented T1-weighted MRI images were then resampled to 1.5 mm isotropic resolution. The SPM-DARTEL pipeline [25] was run for six iterations to produce the study-specific template, the normalisation of individual T1 images into the study-specific common space, and the warp field deformation maps of the T1 images, to be used later for normalization of the PET data into the common space. The cerebellum grey-matter mask was then defined based on the study-specific template and the inverse T1-to-study-specific-template transformations, which were used to resample the standard cerebellum mask to the individuals' native space.

Pre-processing of the [^{18}F]-AV45 PET data

The [^{18}F]-AV45 PET images in DICOM format were pre-processed by the ADNI team as described in http://adni.loni.usc.edu/methods/pet-analysis-method/pet-analysis/. We used the SUV maps smoothed at 8 mm isotropic resolution downloaded from ADNI. We linearly co-registered the SUV maps to the corresponding native-space T1-weighted MRI image of each participant to generate the co-registered SUV maps. To generate the SUVr maps, each individual's SUV map was scaled to the mean activity in the cerebellar grey matter, which served as the reference region. The individual brain grey-matter SUVr map was generated using a mask created from the grey-matter segment of the T1-weighted image. These grey-matter SUVr maps were normalised to the structural study-specific template using the warp field deformation maps generated for the T1-to-study-specific-template normalization (non-linear registration) using DARTEL.

Cortical thickness pre-processing

The T1-weighted MR images were skull-stripped prior to pial surface and grey-white matter interface reconstruction using Freesurfer (FS v6.0.0, http://surfer.nmr.mgh.harvard.edu). Errors in pial surface delineation were corrected manually [26]. The main structures affected by this procedure were the lateral occipital cortex, inferior temporal gyrus, pre- and post-central gyri, and occipito-temporal gyrus. Following this manual correction of the segmentation, the reconstruction was repeated for improved accuracy. The cortical thickness was calculated from the intensity and continuity information of the generated surfaces. The reconstructed maps were smoothed using a 20-mm FWHM Gaussian kernel [26].

Statistical analysis

Analysis of neuropsychological measures

To assess for differences between the subgroups in the different neuropsychological measures, we used one-way analysis of variance (ANOVA) followed by post hoc Wilcoxon signed-rank tests to compare continuous data, and by Chi-Squared tests to compare categorical data. Analyses were performed with R (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria), with Bonferroni correction ($p \leq 0.05$) for multiple comparisons. Descriptive data are presented as mean and standard deviation throughout the article, unless indicated otherwise.

The effect of TBI on amyloid burden and neurodegeneration

Comparison between the TBI + and TBI − groups in the number of Aβ + scans A chi-squared test was performed to compare the numbers of Aβ + and Aβ − cases in the TBI + and TBI − groups, using the positivity threshold SUVr > 1.23 [22].

Voxel-based analysis of amyloid PET data To examine the effect of TBI on amyloid burden in those participants on the AD continuum (i.e. with Aβ + scans), we performed a voxel-based analysis of mean SUVr maps in the TBI + and TBI − groups, irrespective of their CDR scores. The voxel-based analysis was conducted using the general linear model (GLM) with a permutation test of 5000 iterations using the program FSL-randomise, and corrected for multiple comparisons using family wise error correction ($p \leq 0.05$). We also performed an ANOVA analysis of the mean cortical SUVr values to identify group differences in the Aβ burden, with Bonferroni correction ($p \leq 0.05$). The gender, education level, age, and APOE-ε4 status were considered as nuisance factors in this analysis.

Analysis of cortical thickness To assess the impact of TBI on neurodegeneration for those on the AD continuum, group differences in cortical thickness were assessed by contrasting Aβ + /TBI + to Aβ + /TBI − groups, irrespec-

tive of individual CDR scores. This was achieved by entering the smoothed deformation grey-matter cortical maps into the GLM, with TBI + versus TBI − as the contrast, and running the "mri_glmfit" function in Freesurfer. The cortical thickness analysis was corrected for age, gender, education level, and APOE-ε4 status as nuisance covariates, and the resultant statistical maps were corrected for multiple comparisons using false discovery rate ($p \leq 0.05$).

The effect of TBI in the cognitively symptomatic AD population

To test the effect of TBI on Aβ deposition, the 17 participants with Aβ + scans in the TBI −/CDR ≥ 0.5 group were randomly matched to other subjects with Aβ + scans in the TBI + /CDR ≥ 0.5 group. The groups were matched for MMSE score, gender, education level, age, and APOE-ε4 status. We then ran an ANOVA to identify group differences in the total cortical SUVr values (considered as a single ROI) and the ACIO. To ensure that MMSE was a valid index of dementia severity, a similar second analysis in which the groups were matched for ADAS-Cog scores was also performed. Lastly, we undertook an analysis of the effect of TBI history on cognitive status in groups matched for the cortical [^{18}F]-AV45 SUVr (considered as a single ROI), gender, education level, age, and APOE-ε4 status. For this, 17 participants with Aβ + scans in the TBI −/CDR ≥ 0.5 group were randomly matched to the 17 Aβ + scans in the TBI + /CDR ≥ 0.5 group, and differences in MMSE scores and ACIO were tested for significance, with Bonferroni corrected ($p \leq 0.05$).

Results

Demographics and clinical characteristics of the complete cohort

The group demographics and clinical characteristics are shown in Table 1. A higher percentage of Aβ + cases was observed in the TBI + /CDR = 0 group (59%; 13/22) than in the TBI −/CDR = 0 group (39%; 39/100) (chi-squared: $p \leq 0.001$) (Table 1). The mean SUVr values of the entire cortex as a single ROI showed significantly higher amyloid deposition in the TBI + /CDR = 0 group compared to the TBI −/CDR = 0 group ($p = 0.015$) (Fig. 2). We also found that the mean ACIO was about 4 years earlier in the TBI + /CDR ≥ 0.5 group than in the TBI −/CDR ≥ 0.5 group ($p = 0.005$, Table 1).

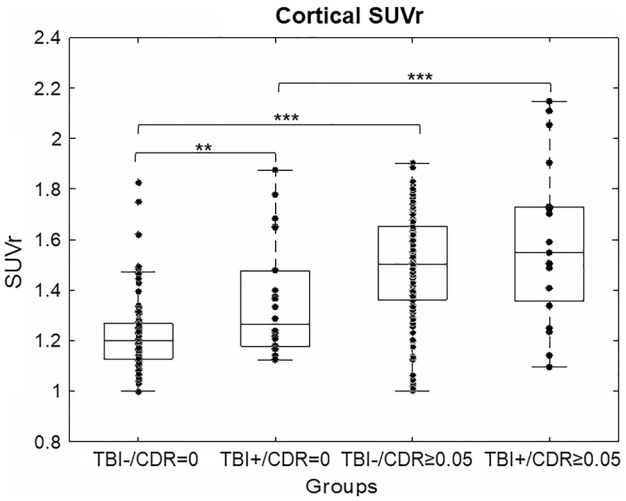

Fig. 2 Differences in cortical Aβ deposition between TBI + and TBI − participants. The mean cerebral cortical [^{18}F]-AV45 SUVr, compared between all four groups showed that the CDR ≥ 0.5 groups exhibited significantly higher Aβ deposition compared to the CDR = 0 groups, irrespective of TBI history, and that the TBI + /CDR = 0 group showed significantly higher mean [^{18}F]-AV45 SUVr when compared to the TBI −/CDR = 0 group. $^{**}p \leq 0.01$; $^{***}p \leq 0.001$

The effect of TBI on amyloid burden and neurodegeneration in participants on the AD continuum

Focusing on Aβ + cases participants with and without history of TBI, there was no significant difference in the proportion of symptomatic subjects between groups ($p > 0.05$). TBI + participants did not show greater cognitive impairment compared to the TBI − group (Table 2). In the symptomatic cases (i.e. CDR ≥ 0.5), those with TBI + showed earlier ACIOas compared to TBI − groups (64.8 ± 2.34 years vs. 68.5 ± 2.36 years, $p \leq 0.001$; Fig. 3A).

Figure 3B, C depicts the effect of TBI history on Aβ deposition and cortical thickness among the Aβ + cases. The results showed that TBI was associated with significantly higher Aβ deposition—reflected by higher [^{18}F]-AV45 SUVr—in the bilateral medial frontal cortex (dorsal and ventral), precuneus, anterior and posterior cingulate cortex, cuneus, lingual gyrus, fusiform gyrus, supramarginal gyrus, posterior part of the superior temporal gyrus, temporal pole, orbitofrontal gyrus, inferior frontal gyrus, cerebellum, and right superior frontal gyrus, as compared to those Aβ + cases without a history of TBI (i.e., TBI − groups) ($p \leq 0.01$; Fig. 3B).

In addition, compared to the TBI − group, cortical thickness was reduced in the TBI + group in several cerebral cortical regions, including the bilateral middle frontal gyrus, orbitofrontal gyrus, supramarginal gyrus, superior parietal lobule, precuneus, posterior cingulate

Table 2 Cognitive performance in Aβ + groups

	TBI −	TBI +	*p* value
Age at cognitive impairment onset	68.5 (2.36)	64.8 (2.34)	**< 0.001**
Number of subjects (CDR ≥ 0.05/CDR = 0)	86/39	17/13	
Gender (Female/Male)	66/59	9/21	0.025
Age	72.74 (7.37)	74.55 (7.18)	0.21
Loss of consciousness (Yes/NO)		15/15	
Number of TBI injuries			
Once		24	
Twice		5	
Three times		1	
Education (years)	15.80 (2.62)	16.40 (2.67)	0.26
ADAS	16.8 (9.91)	13.06 (9.59)	0.06
ADAS-Cog	24.88 (13.58)	19.27 (13.05)	**0.04**
CDR	0.61 (0.45)	0.5 (0.44)	0.20
MOCA	20.02 (4.37)	21.15 (3.74)	0.18
MMSE	24.78 (3.42)	26.67 (2.7)	**0.004**
FAQ	9.53 (8.32)	7.22 (8.71)	0.17
GD Total	1.35 (1.42)	1.45 (1.43)	0.74
Every day cognitive test			
Memory	2.99 (0.89)	2.56 (0.92)	**0.02**
Language	2.34 (0.83)	2.29 (0.87)	0.77
Plan	2.25 (0.96)	2.07 (0.94)	0.33
Organization	2.47 (0.95)	2.1 (0.94)	0.05
Divided attention	2.68 (1.01)	2.42 (0.98)	0.21
Visuospatial	2.12 (0.93)	1.85 (0.8)	0.14
Total score	2.48 (0.82)	2.22 (0.83)	0.12
Neuropsychological battery tests			
Clock copy test	4.53 (0.83)	4.67 (0.94)	0.43
Clock drawing test	3.7 (1.38)	4 (1.21)	0.26
Logic memory			
Delayed recall	5.22 (6.1)	8.45 (6.01)	**0.01**
Story units	7.2 (5.53)	10 (5.55)	**0.01**
Rey auditory verbal learning test			
Recognition scale	8.48 (4.64)	10.42 (4.21)	**0.03**
Number of errors	2.07 (2.14)	1.82 (2.11)	0.55
Category fluency test	14.86 (6.19)	16.91 (6.42)	0.10
Boston naming test	24.11 (5.72)	26.39 (3.81)	**0.03**

TBI + participants with self-reported traumatic brain injury, *TBI* − participants without self-reported traumatic brain injury, *CDR* Clinical Dementia Rating, *TBI* + */CDR* = *0* TBI + participants with CDR = 0, *TBI* −*/CDR* = *0* TBI − participants with CDR = 0, *TBI* + */CDR* ≥ *0.5* TBI + participants with CDR ≥ 0.5, *TBI* −*/CDR* ≥ *0.5* TBI − participants with CDR ≥ 0.5, *MMSE* Mini-Mental State Exam, *GDtotal* Geriatric Depression Scale, *FAQ* Functional Assessment Questionnaire, *MOCA* Montreal Cognitive Assessment

cortex, angular gyrus, middle temporal gyrus, inferior temporal gyrus, hippocampus, and visual cortex (cuneus, lingual gyrus, fusiform gyrus, superior, middle, and inferior occipital cortex), and left medial frontal gyrus (dorsal and ventral), anterior cingulate cortex, and superior frontal gyrus ($p \leq 0.05$; Fig. 3C).

The effect of TBI in the Aβ + , symptomatic population

In the symptomatic (CDR ≥ 0.5) Aβ + groups, when TBI − and TBI + subgroups were matched for MMSE scores, we found significantly higher Aβ deposition

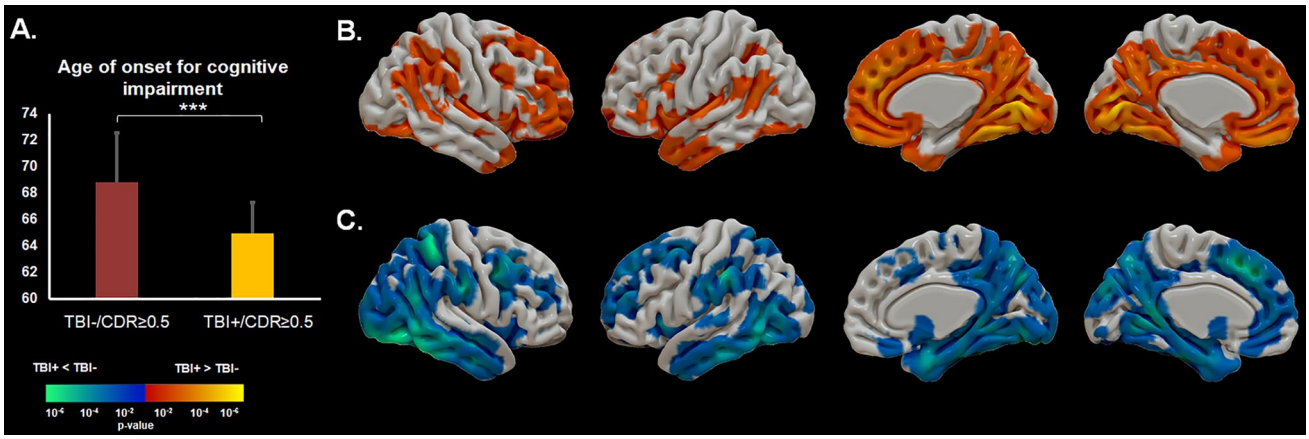

Fig. 3 Differences in age of onset, Aβ deposition and cortical thickness between participants on the AD continuum (Aβ+) with and without self-reported TBI history, irrespective of present CDR status. Part **A** shows a 3–4-year earlier age of cognitive impairment onset in the TBI+/CDR ≥ 0.5 group compared to the TBI −/CDR ≥ 0.5 group. Considering all Aβ+participants irrespective of CDR status, the TBI+group showed greater deposition of Aβ (**B**) and reduced cortical thickness (**C**) compared to the TBI − group (analyses corrected for nuisance covariates: age, gender, education, and APOE-ε4 status). ***$p \leq 0.001$

Table 3 Investigation of the TBI effect on Aβ deposition and age at the onset of cognitive impairment after matching for MMSE, ADAS-Cog, or Aβ levels (in Aβ+cases)

	TBI −/CDR ≥ 0.5	TBI+/CDR ≥ 0.5	*p* overall
MMSE matched			
Number of participants	17	17	
MMSE	23.8 (1.47)	23.8 (1.47)	1
Age	73.6 (3.89)	73.9 (7.15)	0.45
Cortical SUVr	1.51 (0.24)	1.65 (0.27)	**0.05**
Age at cognitive impairment onset	68.8 (3.89)	64.8 (2.34)	**< 0.001**
ADAS-Cog matched			
Number of participants	17	17	
ADAS-Cog	28.9 (11.75)	28.9 (12.12)	0.28
MMSE	23.4 (2.62)	23.8 (1.47)	0.28
Age	73.3 (2.06)	73.9 (7.15)	0.4
Cortical SUVr	1.51 (0.14)	1.65 (0.27)	**0.05**
Age at cognitive impairment onset	67.0 (4.58)	64.8 (2.34)	**0.04**
Cortical SUVr matched			
Number of participants	17	17	
MMSE	23.2 (2.77)	23.8 (1.47)	0.8
Age	73.3 (2.06)	73.9 (7.15)	0.4
Cortical SUVr	1.6 (0.21)	1.65 (0.27)	0.49
Age at cognitive impairment onset	68.4 (2.06)	64.8 (2.34)	**< 0.001**

TBI+ participants with self-reported traumatic brain injury, *TBI −* participants without self-reported traumatic brain injury, *CDR* Clinical Dementia Rating, *TBI+/CDR ≥ 0.5* participants with CDR ≥ 0.5 with a history of TBI, *TBI −/CDR ≥ 0.5* participants with CDR ≥ 0.5 without a history of TBI, *MMSE* Mini-Mental State Exam, *ADAS-Cog* Alzheimer's disease Assessment Scale-Cognitive

($p = 0.05$), and again a 3–4 year earlier ACIO ($p \leq 0.001$) in the TBI+subgroup (Table 3, top). When the analyses were repeated matching for ADAS-Cog scores, the TBI+group likewise showed increased in amyloid deposition ($p = 0.05$) and earlier AOCI ($p = 0.04$) (Table 3, middle). Finally, when the TBI − and TBI+groups were matched for total cortical SUVr, the TBI+subgroup showed earlier ACIO as compared to the TBI − subgroup ($p \leq 0.001$), but no significant difference in MMSE scores ($p > 0.05$; Table 3, bottom).

Discussion

This is the first study to investigate the association between self-reported history of TBI earlier in life and the age at first reported onset of cognitive deficits, present amyloid burden, and cortical thickness (a neurodegeneration marker) in a population on the AD continuum, as identified by their Aβ + PET scans. These cross-sectional results constitute preliminary but compelling evidence that TBI favours the cerebral accumulation of Aβ in later life within the continuum of AD progression as reflected by the Aβ positivity, in conjunction with earlier ACIO and more significant cortical thickness loss. The results, furthermore, revealed that the group with a past history of TBI had a higher proportion of Aβ + scans, when using the recommended cut-off for positivity to [^{18}F]-AV45 SUVr [22].

TBI has been associated with short-term cognitive impairment, including transient amnestic memory impairment, confusion, and disorientation [27], while long-term cognitive impairment is reported in up to 65% of survivors of moderate-to-severe TBI [28, 29]. Having a history of TBI has been linked to the risk for several forms of dementia, including AD [3, 4, 6–10], chronic traumatic encephalopathy [30–32], and Lewy body disease or parkinsonism [12–15]. These associations between TBI and later development of dementia may possibly reflect a reduced capacity of the brain to resist or compensate for an ongoing pathology following TBI, thus leading to a lack of cognitive reserve. Alternately, the association could be further modulated through intervening factors such as post-traumatic stress disorder [33]. In the current study, self-reported history of TBI predicted fast-forwarding of the onset of cognitive impairment by about 4 years in TBI + / CD ≥ 0.5 subgroup as compared to the TBI −/CD ≥ 0.5 subgroup. This finding is consistent with past studies that reported a 2–4 year earlier onset of cognitive impairment in survivors of TBI [8, 10, 11]. Prospective investigations with large cohorts shall be required to substantiate the causality of TBI history on the risk of developing AD, as distinct from other neurodegenerative diseases. Let us suppose that the increased dementia risk after TBI is mediated through a reduction in cognitive reserve. This might then bring forward the age of symptom onset for those who were destined in any case to develop the disease, which would potentially resolve the conflicting results in certain past studies [12–15]. For instance, because AD is usually a disease of the aged, its prevalence is partially censored by deaths from other causes. Therefore, reducing even slightly the age of onset could create the appearance that TBI is a cause of excess AD cases. Careful accounting for age of onset in future studies may potentially reconcile past conflicting results. Furthermore, the hypothesis of loss of cognitive reserve hypothesis might help to explain the increased risk of TBI survivors for other degenerative diseases [12–15].

A key aim of the present study was specifically to examine the impact of TBI history on amyloid deposition, as opposed to dementia in general. In addition to revealing an earlier ACIO, present results also showed that those with a self-reported TBI history had relatively greater Aβ deposition, as depicted by the higher percentage of Aβ + cases in the non-demented TBI + /CDR = 0 subgroup as compared to the TBI −/CDR = 0 subgroup. Moreover, within those apparently following the AD continuum (i.e. Aβ + cases), our voxel-based PET analysis showed that self-reported history of TBI was associated with greater Aβ burden in widespread cortical regions matching the spatial profile of AD amyloid pathology [21, 34]. This spatial overlap is consistent with a model in which a TBI predisposed individuals to amyloid deposition in the context of their later transition to AD pathology; however, as the data are cross-sectional, we can make no claims regarding causality or time course. There could, for instance, have been an acute, stepwise increase of amyloid that persisted long after the TBI, to which the amyloidosis of AD was later added. Previous studies showed increased density of Aβ plaques in surgically resected tissue surrounding contusions in brain of acute TBI survivors and in post-mortem examinations of recent TBI victims [17–19, 33, 35–39]. Moreover, PET investigations of living TBI survivors have shown increased Aβ deposition in cortical regions overlapping with those typically involved in AD [20, 40, 41], but also including AD-atypical regions such as the cerebellum [21, 39]. This might suggest that TBI is an independent causative factor in Aβ deposition, which, by extension, may potentially influence the trajectory of AD progression through its spatial overlap with AD pathology. However, in a post-mortem examination of brains from TBI survivors obtained more than 3 years following their injury, Aβ plaques were evident in only one-third of the cases [36], suggesting the possibility that plaque accumulation occurs only in select predisposed individuals. This speculation could again be accommodated within a hypothesis that TBI brings forward the age of symptom onset, but only in those predisposed to develop AD.

In addition to the observed exacerbation of Aβ burden, we found that history of TBI was associated with reduction of cortical thickness in several regions, including mesial temporal lobe and posterior cingulate cortex. Earlier investigations likewise revealed that past TBI history was significantly associated with atrophy following a similar distribution to the present findings [42–45]. However, as with the amyloid PET findings, the present cross-sectional design cannot establish the time course of the progression of cortical thinning in the aftermath of TBI. Interestingly, although the MRI data suggested worse neurodegeneration in TBI

survivors, there was no evidence of worse cognitive impairment in this group. Indeed, in the analysis of those on the AD continuum, the TBI + group were slightly less impaired (Table 2). Likewise, in the final analysis that focused on those with symptomatic AD, although the TBI + subgroup had an earlier age of symptom onset, they were matched both for age and dementia severity (as defined by MMSE and also verified using ADAS-Cog). In other words, despite a 4-year longer symptom duration, they did not show worse cognitive impairment, suggesting that TBI survivors with symptomatic AD have had a more indolent disease course. Again, invoking the cognitive reserve hypothesis, we suppose that acquired loss of reserve might be the driver for the earlier onset of ADS seen in the TBI group. Furthermore, gender differences in the composition of the two groups might contribute to this observation. Future studies of longitudinal design shall be required to identify the possible causes of the seemingly lesser cognitive impairment in TBI + group.

Chief among the limitations of this study is the small number of participants with TBI history (see Table 1). The retrospective nature of TBI reporting is also a major limitation—a prospective study design would better enable assessment of the critically important issues of nature and severity of the TBI and possible effects of comorbidities. A future prospective study recruiting from populations providing detailed information on the nature and severity of their TBI would help to elucidate the complex relationship between TBI, cerebral amyloid burden, and brain atrophy later in life.

Conclusion

In this retrospective, cross-sectional study, a self-reported history of TBI was associated with increased rate of amyloid positivity, increased Aβ deposition and greater cortical thinning among those on the AD continuum, along with earlier ACIO, suggesting that TBI may alter the trajectory of AD development.

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Author contributions AZM, PN, and FN decided on the study concept and design. ADNI project members collected the data used in the preparation of the manuscript. AZM performed the data analysis and wrote the manuscript. FN, PC, and PN read the manuscript and provided a critical feedback on the results and the written manuscript.

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Data availability The original data used in this project and that support the findings of this study are openly available through (https://ida.loni.usc.edu), upon approval from the ADNI project administration.

Code availability The different software packages used in the preparation of this manuscript are publicly available. In addition, the codes used for the analysis of the data are available upon request from the corresponding author.

Declarations

Conflict of interest The authors report no competing interests.

Ethical approval This research involves de-identified human data collected by ADNI project. This study obtained ethics approval to use de-identified data from the Human Research Ethics Committee of the University of Queensland, Australia (IRB number #2017000630).

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication No individuals' information was used in the preparation of any of the figures. All data used in the preparation of the manuscript were of group levels, without any individual images or personal information used in the preparation of the manuscript.

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