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Research article

Self-reported traumatic brain injury and in vivo measure of AD-vulnerable cortical thickness and AD-related biomarkers in the ADNI cohort

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HIGHLIGHTS

- Preclinical AD with mTBI had smaller cortical thickness in mean and three AD-vulnerable cortical regions.
- The mean AD-vulnerable cortical thickness was correlated with CSF tau in preclinical AD subjects with mTBI.
- There was no such statistical difference in normal, MCI due to AD, and AD groups.

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ABSTRACT

In this study, we aimed to investigate whether self-reported mild traumatic brain injury (mTBI) was associated with decreased AD-vulnerable cortical thickness, and to assess the relationship between AD-vulnerable cortical thickness and AD-related biomarker in the Alzheimer's Disease Neuroimaging Initiative subjects. We identified 45 self-reported mTBI subjects, who had structural MRI, 18F-AV45 PET, and cerebrospinal fluid (CSF) data. Of them, eight subjects were normal; ten were preclinical AD; seventeen were MCI due to AD; ten were AD. Additional demographics-controlled 45 subjects were included. Cortical thickness of eight AD-vulnerable regions, mean AD-vulnerable cortical thickness, 18F-AV45 PET mean amyloid SUVR, CSF Aβ42, CSF total tau (T-tau), and CSF phosphorylated tau (P-tau) were compared between mTBI and non-TBI groups. Correlational analysis was done to investigate the relationship between mean AD-vulnerable cortical thickness and mean amyloid SUVR, CSF Aβ42, CSF T-Tau, CSF P-Tau. Our study revealed that preclinical AD subjects with self-reported mTBI had smaller cortical thickness in mean and three AD-vulnerable cortical regions than non-TBI subjects ($P < 0.05$). The mean AD-vulnerable cortical thickness was correlated with CSF T-tau ($r = -0.81$, $P = 0.001$). There was no statistical difference in the comparison of normal, MCI due to AD, and AD groups. Our study indicated that among individuals with preclinical AD, but not normal, MCI due to AD and AD subjects, self-reported mTBI was associated with more decreased AD-vulnerable cortical thickness which was related to CSF tau pathology, suggesting the possible early involvement of tau pathology in the decreased AD-vulnerable cortical thickness of self-reported TBI subjects.

1. Introduction

Multiple epidemiological studies have proved a history of traumatic brain injury (TBI), even the mild type (mTBI) was associated with accelerated cognitive impairment and Alzheimer's disease (AD) [1–9]. As for the underlying neuropathological changes, there is no complete consensus as TBI is a heterogeneous process and chronic neurodegeneration after TBI might include multiple pathological changes [10]. Several studies have found the presence of Aβ deposition in moderate to severe TBI brain from acute period to

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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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chronic period [11–13]. Furthermore, tau pathology was also found in patients with a history of repetitive concussion or even a single TBI [14,15]. The overlap pathology between chronic TBI and AD leads to the conclusion that a history of TBI would initiate or accelerate the process of AD-related neuropathology.

Cortical thickness is a comprehensive biomarker, reflecting multiple upstream pathological changes caused by various cellular events [16,17]. Decreased cortical thickness has been found in mTBI patients or military veterans [18–21]. To be noted, a recent study revealed that combination of a history of mTBI and polygenetic risk for AD was associated with reduced cortical thickness in AD-vulnerable regions [22]. However, the underlying pathology of TBI-related cortical thickness reduction in AD-vulnerable regions is unknown.

In this study, we hypothesized that (1) compared with non-TBI subjects, mTBI subjects who were classified as normal, preclinical AD, MCI due to AD, or AD will show more cortical thickness reductions in the AD-vulnerable cortical regions; (2) the decreased cortical thickness will depend at least partially on Aβ pathology revealed by 18F-AV45 PET mean amyloid SUVR and CSF Aβ42, and tau pathology revealed by CSF total tau (T-tau) and CSF phosphorylated tau (P-tau). We aimed to investigate whether a history of mTBI was associated with in vivo neuroimaging measurement of AD-related neuropathology using the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort data.

2. Material and methods

2.1. Subjects

Data used in the preparation of this article were obtained from the ADNI database (adni.loni.usc.edu). The ADNI 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 magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org.

The ADNI study was approved by the local Institutional Review Board at each institution. Written informed consent was obtained from each subject in accordance with the Declaration of Helsinki. Self-reported TBI subjects were identified from the "recent medical history details log" excel in the ADNI database, which contained TBI related information such as TBI causes, time of loss of consciousness and post-traumatic anterograde amnesia. The included subjects should have complete structural MRI, 18F-AV45 PET and CSF data. For structural MRI data, cortical and hippocampal segmentations should be of acceptable quality and processed by the same FreeSurfer version software. Thus, we only included the ADNI G0 and ADNI 2 subjects whose MRI data were processed by FreeSurfer 5.1. Finally, we identified 45 mild closed head injury subjects from the ADNI cohort according to the Mayo Clinic TBI standards [23].

Based on the NIA-AA research criteria [24], these subjects were classified as normal (n = 8), preclinical AD (n = 10), MCI due to AD (n = 17), and AD dementia (n = 10). The normal group was defined as the subjects with normal cognitive function and without biomarkers of AD-related pathology. Preclinical AD was defined as the subjects with normal cognitive function and biomarkers of AD-related pathology. MCI due to AD and AD dementia was defined as the subjects with biomarkers of AD-related pathology, apart from meeting the corresponding clinical core criteria. The cutoffs of AD-related pathology examinations were as follows: 192 pg/mL for CSF Aβ42, 93 pg/mL for CSF T-tau, [25] or 1.11 for 18F-AV45 PET mean amyloid SUVR [26]. Additional age, gender, education and APOE genotype controlled 45 subjects without TBI history were also selected into this study from the ADNI G0 and G2 cohort. All the control subjects should also have complete structural MRI, 18F-AV45 PET and CSF data.

2.2. Neuroimaging and CSF data processing

All subjects included in this study were scanned using the ADNI 3T MRI scanning protocol (GE, Philips or Siemens). Cortical reconstruction and volumetric segmentation are performed with the same FreeSurfer 5.1 image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Cortical thickness data was downloaded from "UCSF – Cross-Sectional FreeSurfer (5.1), Version: 2016-08-01" excel in the ADNI database. The AD-vulnerable cortical regions including entorhinal cortex, temporal pole, inferior temporal gyrus, middle temporal gyrus, inferior parietal cortex, superior parietal cortex, precuneus, and posterior cingulate cortex were analyzed in this study (Fig. 1). These regions have been proved to be sensitive to the progression from normal cognition to the onset of clinical symptoms of MCI [27].

18F-AV45 PET data was downloaded from "UC Berkeley – AV45 Analysis, Version: 2016-10-17" excel analyzed by UC Berkeley and Lawrence Berkeley National Laboratory. We chose to use the summary florbetapir cortical SUVR normalized by the whole cerebellum. This technique has been proved to be effective in quantitatively measuring amyloid deposits in the brains [28] and currently used in clinical practice. CSF data were downloaded from "UPENN CSF Biomarker Master, Version: 2016-07-05". We chose to use the first baseline CSF Aβ42, T-tau, and P-tau data for each subject. The measurement methods were described elsewhere [25].

2.3. Statistical analysis

All statistical tests were performed by IBM SPSS Statistics for Windows version 20.0. Continuous variables were expressed as mean (standard deviation) for normal distribution data or median (interquartile range) for non-normal distribution data. Percentages were used to express the categorical variables. Group differences for demographic data and neuropsychological data were analyzed using two-sample *t*-test for continuous variables or chi-square tests for classification variables between TBI group and non-TBI group. As there were several non-normal distribution data, group difference of the imaging parameters was compared using Mann–Whitney *U* test between TBI group and non-TBI group. Pearson or Spearman analysis as appropriate were used to investigate the relationship between mean AD-vulnerable cortical thickness and mean amyloid SUVR, CSF biomarkers in the normal, preclinical AD, MCI due to AD and AD group. P values less than 0.05 indicated statistical significance. The significance was not corrected for multiple comparisons.

3. Results

3.1. Subject demographics

The characteristics of self-reported mTBI and non-TBI subjects are shown in Table 1. There were no significant differences in age, gender, education, APOE genotype and psychometric tests score between mTBI groups and non-TBI groups (P > 0.05).

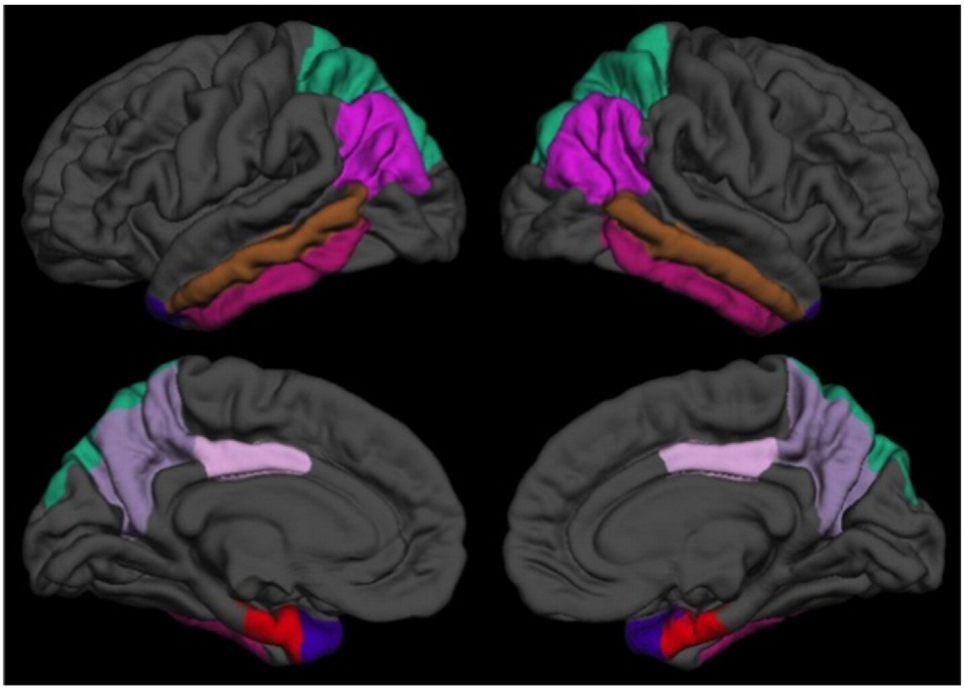

Fig. 1. Map of the eight of AD-vulnerable regions based on FreeSurfer cortical labels, shown on the pial surface of the left (left) and right (right) hemispheres for lateral (top) and medial (bottom) views. Green: superior parietal cortex, Pink: inferior parietal cortex, Brown: middle temporal gyrus, Purple: inferior temporal gyrus, Grey: precuneus, White: posterior cingulate cortex, Red: entorhinal cortex, Blue: temporal pole. The figure was cited from https://doi.org/10.1016/j.nicl.2016.06.010.

Table 1
Demographics between mTBI group and non-TBI group.

Characteristic	Normal		Preclinical AD		MCI due to AD		AD dementia	
	Non-TBI (n = 8)	mTBI (n = 8)	Non-TBI (n = 10)	mTBI (n = 10)	Non-TBI (n = 17)	mTBI (n = 17)	Non-TBI (n = 10)	mTBI (n = 10)
Age, y	68.63 (5.26)	67.63 (6.65)	72.70 (4.81)	73.50 (6.20)	72.18 (6.12)	73.65(6.86)	72.30 (10.32)	72.80 (8.31)
Male, %	50	50	60	60	88.24	88.24	60	60
Education, y	17.13 (3.04)	17.50 (1.69)	17.00 (2.11)	17.20 (2.35)	16.94 (2.84)	17.00 (3.04)	16.10 (1.97)	15.60 (2.27)
Apo ε4, %	50	50	50	50	64.71	66.67	50	50
MMSE	29.25 (0.71)	29.63 (0.74)	29.10 (0.99)	28.50 (0.85)	27.47 (2.00)	28.12 (1.73)	21.10 (2.13)	21.40 (3.60)
CDR-SB	0	0	0	0	0.5	0.5	0.85 (0.47)	0.95 (0.44)
Age at TBI		29.88 (23.20)		30.00 (23.66)		37.71 (27.35)		36.40 (21.37)
TBI causes								
Fall		2		2		2		1
Motor vehicle accident		0		2		5		1
Sports-related injury		0		3		1		5
Physical assault		0		0		1		0
Undocumented		6		3		8		3

Data are presented as mean (standard devastation).

3.2. Cortical thickness, CSF biomarkers, and mean amyloid SUVR

The cortical thickness of eight AD-vulnerable regions, CSF biomarkers, and 18F-AV45 PET mean amyloid SUVR in different groups are shown in Table 2. Compared with preclinical AD non-TBI subjects, self-reported mTBI subjects had more decreased cortical thickness in the mean AD-vulnerable cortical thickness ($P = 0.038$), as well as three individual ROIs: inferior parietal cortex ($P = 0.005$), superior parietal cortex ($P = 0.009$), and precuneus ($P = 0.015$). The CSF P-tau was also higher in the preclinical AD with self-reported mTBI group ($P = 0.028$). There were no significant differences in cortical thickness, CSF biomarkers, and mean amyloid SUVR in the comparison of other groups ($P > 0.05$).

3.3. Relationship between mean AD-vulnerable cortical thickness and CSF biomarkers, and mean amyloid SUVR

The correlational study results are shown in Table 3. Among all the preclinical AD subjects, the mean AD-vulnerable cortical thickness was correlated with CSF T-Tau ($r = -0.55$, $P = 0.018$) and CSF P-Tau ($r = -0.60$, $P = 0.007$). In the group of preclinical AD with mTBI, mean AD-vulnerable cortical thickness was correlated with CSF T-Tau ($r = -0.81$, $P = 0.016$). In the group of preclinical AD without mTBI subjects, normal subjects, MCI due to AD subjects and AD subjects, no correlation was found in the correlation analysis.

Table 2
Cortical thickness, CSF biomarkers and mean amyloid SUVRs in self-reported mTBI group and non-TBI group.

Cerebral cortex, mm	Normal		Preclinical AD		MCI due to AD		AD dementia	
	Non-TBI (n = 8)	mTBI (n = 8)	Non-TBI (n = 10)	mTBI (n = 10)	Non-TBI (n = 17)	mTBI (n = 17)	Non-TBI (n = 10)	mTBI (n = 10)
Entorhinal cortex	3.56 (0.33)	3.51 (0.20)	3.49 (3.33, 3.83)	3.62 (3.24, 3.69)	3.68 (2.82, 3.85)	3.37 (3.00, 3.58)	2.80 (0.56)	2.71 (0.50)
Temporal pole	3.62 (0.20)	3.59 (0.14)	3.72 (0.20)	3.70 (0.31)	3.44 (0.43)	3.51 (0.37)	3.03 (0.58)	3.14 (0.24)
Inferior temporal gyrus	2.86(0.13)	2.74 (0.15)	2.81 (0.14)	2.78 (0.19)	2.72 (0.19)	2.68 (0.20)	2.45 (0.14)	2.50 (0.17)
Middle temporal gyrus	2.88(0.11)	2.77 (0.13)	2.82 (0.12)	2.73 (0.17)	2.82 (2.67, 2.90)	2.68 (2.55, 2.87)	2.55 (2.29, 2.67)	2.60 (2.43, 2.70)
Inferior parietal cortex	2.44 (0.12)	2.35 (0.16)	2.47 (0.08)	2.28 (0.20)*	2.33 (0.21)	2.31 (0.13)	2.15 (2.01, 2.22)	2.17 (2.03, 2.28)
Superior parietal cortex	2.15 (0.12)	2.10 (0.15)	2.24 (0.18)	2.00 (0.22)*	2.09 (0.25)	2.13 (0.11)	1.91 (0.20)	1.97 (0.13)
Precuneus	2.33 (0.11)	2.23 (0.12)	2.38 (0.12)	2.19 (0.20)*	2.24 (0.19)	2.27 (0.13)	2.02 (0.21)	2.11 (0.14)
Posterior cingulate cortex	2.51 (0.13)	2.41 (0.20)	2.58 (2.38, 2.67)	2.48 (2.46, 2.57)	2.44 (0.20)	2.51 (0.18)	2.38 (0.16)	2.37 (0.16)
Mean thickness	2.80 (0.07)	2.71 (0.11)	2.82 (0.10)	2.70 (0.19)*	2.68 (0.21)	2.68 (0.15)	2.39 (0.21)	2.43 (0.14)
CSF, pg/mL								
CSF Aβ42	239.75 (33.00)	230.38 (28.98)	158.39 (43.88)	146.61 (30.32)	136.91 (24.33)	146.95 (30.85)	131.88 (17.49)	122.32 (29.95)
CSF T-Tau	55.00 (45.68, 64.53)	44.25 (37.30, 51.55)	50.05 (20.42)	67.13 (29.66)	62.60 (45.70, 93.20)	78.25 (54.60, 97.88)	148.14 (72.95)	143.71 (62.34)
CSF P-Tau	28.70 (10.84)	26.25 (6.36)	20.20 (17.40, 35.30)	40.10 (21.95, 49.55)*	33.59 (16.82)	35.58 (17.41)	57.34 (27.86)	90.38 (48.95)
18F-AV45 PET								
Amyloid SUVR	1.04 (0.04)	1.04 (0.05)	1.14 (0.22)	1.21 (0.19)	1.25 (0.21)	1.31 (0.19)	1.45 (0.21)	1.46 (0.15)

Data are presented as mean (standard devastation) for normal distribution data and median (interquartile range) for non-normal distribution data.
* $P < 0.05$ with mann-whitney *U* test.

Table 3
Correlations between mean AD-vulnerable cortical thickness and CSF biomarkers and mean amyloid SUVRs.

Cortical thickness	Mean amyloid SUVRs	CSF Aβ	CSF T-tau	CSF P-tau
All normal subjects	−0.50	0.42	0.47	0.47
Normal subjects with mTBI	−0.58	0.26	0.17	0.05
Normal subjects without mTBI	−0.62	0.59	0.55	0.39
All preclinical AD	−0.14	0.27	−0.55*	−0.60*
Preclinical AD subjects with mTBI	−0.09	0.49	−0.81*	−0.31
Preclinical AD subjects without mTBI	−0.31	0.43	−0.55	−0.48
All MCI due AD subjects	−0.15	0.05	−0.05	−0.03
MCI due AD subjects with mTBI	−0.03	−0.23	−0.06	−0.03
MCI due AD subjects without mTBI	−0.23	0.30	−0.11	−0.30
All AD subjects	−0.38	−0.09	−0.18	−0.07
AD subjects with mTBI	−0.24	0.10	−0.17	−0.28
AD subjects without mTBI	−0.45	−0.26	−0.19	0.01

* $p < 0.05$ with Pearson or Spearman analysis as appropriate.

4. Discussion

Multiple epidemiological studies have proved a history of TBI, even mTBI was associated with accelerated cognitive impairment and AD [1–9] To be noted, the study of Li et al. [29] using the same ADNI database reported TBI history to be a significant risk factor for cognitive decline in older adults. In our study, we further investigate whether a history of mTBI was associated with decreased AD-vulnerable cortical thickness using the same ADNI database. Our study revealed that among individuals with preclinical AD, but not normal, MCI due to AD and AD subjects, self-reported mTBI was associated with more decreased AD-vulnerable cortical thickness which was related to CSF tau pathology.

Consistent with our hypothesis, our study revealed that mTBI history was significantly associated with decreased cortical thickness in three and mean AD-vulnerable regions in the preclinical AD group. The study of Palacios EM et al. [30] also revealed that chronic severe TBI had cortical thinning in multiple cortical regions including five AD-vulnerable regions. As the subjects were all mild closed TBI in our study, the effect of TBI on the brain would be diffuse and extensive. The fact that only three AD-vulnerable regions exhibiting significance in our study could be explained in terms of the TBI severity between studies.

Intriguingly, there was no such obvious trend in the normal, MCI due to AD and AD groups. We speculated that the effect of mTBI history on AD-vulnerable cortical thickness might be most obvious in the early stage of cognitive impairment. In the later stage of cognitive impairment, the impact of mTBI history on cortical thickness might be diluted by other well-established risk factors like APOE genotype, and thus the difference of AD-vulnerable cortical thickness disappeared. As this was a cross-sectional study, further longitudinal large studies would be needed to test our hypothesis.

Furthermore, we found no significant difference in 18F-AV45 PET mean amyloid SUVR between mTBI group and non-TBI group, as was also indicated in previous studies [31,32]. However, the study of Mielke MM et al. [33] showed that self-reported TBI was associated with greater amyloid deposition in the brain in individuals with MCI but not cognitively normal. The discrepancy could be due to different inclusion criteria. Our study only included mild TBI subjects, while the study of Mielke MM et al. [33] included all TBI subjects with at least momentary loss of consciousness or memory, and thus might contain moderate to severe TBI subjects.

At present, CSF tau has been proved to be a useful biomarker to reflect brain damage in severe TBI or repetitive TBI patients [34]. As the CSF P-tau was higher in the self-reported mTBI preclinical AD group, our study indicated that mTBI history could promote the phosphorylation of tau protein in the preclinical AD, possibly by accelerating the rate at which Aβ triggers downstream tau pathology, or directly exacerbate downstream tau pathology [35]. Therefore, early examination of tau pathology in the subjects with mTBI history is recommended in order to early detect the involvement of possible AD process.

Our study also revealed that the mean AD-vulnerable cortical thickness was correlated with CSF T-tau and CSF P-Tau in all preclinical AD subjects, and CSF T-Tau in mTBI preclinical AD subjects. Elevated CSF tau had been revealed to be associated with AD-vulnerable cortical thinning in preclinical AD subjects [36]. As there were also significant differences in both mean AD-vulnerable cortical thickness and CSF P-tau between mTBI preclinical AD subjects and non-TBI preclinical subjects, our study indicated that the effect of mTBI history on decreased AD-vulnerable cortical thickness could have a relationship with elevated tau pathology.

Our study had several limitations. Firstly, although the whole study sample size reached a relatively considerable number, the number of subjects divided into each group was small. But this is the first preliminary study to investigate the impact of mTBI history on AD-vulnerable cortical thickness in a wide range of subjects from normal subjects to AD patients. Future large sample size study is needed to replicate our result. Secondly, the information about the diagnosis of mTBI was self-reported, which could bring recall bias. Thirdly, our study was a cross-sectional study. Although we found more decreased AD-vulnerable cortical thickness related to CSF tau in preclinical AD mTBI subjects, we could not confirm the order of causal effect. Future large-scale prospective studies are needed to further confirm our conclusion.

5. Conclusion

Among individuals with preclinical AD, but not normal, MCI due to AD and AD subjects, self-reported mTBI was associated with more decreased cortical thickness in three and mean AD-vulnerable cortical regions which was related to CSF tau pathology. Our results suggested that the effect of mTBI history on AD-vulnerable cortical thickness might be most obvious in the early stage of cognitive impairment. And the effect of mTBI history on decreased AD-vulnerable cortical thickness could have a relationship with elevated CSF tau pathology. Our study indicated the importance of documenting TBI history even the mild type, as a history of mTBI may bring long-term negative neurodegenerative consequences.

Conflict of interest

The authors declare no conflict of interest.

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