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Clinical Features of Patients with Alzheimer's Disease and a History of Traumatic Brain Injury

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Alzheimer's disease · Traumatic brain injury · Age of onset · Cognition · Neuropsychiatry

Abstract
Introduction: Traumatic brain injury (TBI) has been associated with a greater risk of developing Alzheimer's disease (AD). Less is known about the clinical features of AD patients with TBI history. The objective of this study was to examine whether a history of TBI and specific injury characteristics are associated with differences in age of disease onset, cognitive features, and neuropsychiatric symptoms (NPSs) in AD patients. ***Methods:*** Biomarker-proven AD patients (CSF or amyloid PET) were selected from the Amsterdam Dementia Cohort. TBI events were classified by age at injury (TBI <25 or ≥25 years) and TBI severity (loss of consciousness, multiple events). Cognitive composite scores were calculated from results of a neuropsychological test battery. NPSs were assessed with the Neuropsychiatric Inventory Questionnaire (NPI-Q). Linear regression analyses were utilized to examine associations between TBI, TBI characteristics, and clinical outcome measures. ***Results:*** Among the 1,755 selected AD patients (mean age = 65.2 years), 166 (9.5%) had documented ≥1 TBI in their medical history. Overall, TBI history was not related to differences in age of disease onset, but age at injury <25 years old was associated with 2.3 years earlier age at symptom onset ($B = -2.34$, $p = 0.031$). No significant associations were found between TBI history or TBI characteristics and differences in cognition or NPSs. ***Conclusion:*** Our results underscore previous findings on the vulnerability of the brain during critical maturation phases and suggest that an early TBI may contribute to lower resilience to neurodegenerative changes.

Introduction

The long-term consequences of traumatic brain injury (TBI) have received growing attention in recent decades. Single and repetitive TBI have been linked to progressive neurodegeneration and identified as a risk factor for numerous neurodegenerative diseases, such as Alzheimer's disease (AD) [1–4], frontotemporal dementia [5–7], Parkinson's disease [3, 4, 8], and amyotrophic lateral sclerosis [3, 4, 9, 10]. In addition, progressive cognitive decline and behavioral changes have been described in former

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contact sports athletes and related to chronic traumatic encephalopathy (CTE): a neurodegenerative disease highly associated with repetitive concussive and/or subconcussive impacts to the head [11, 12].

AD is the most prevalent neurodegenerative disease, accounting for 60–80% of all dementia cases [13]. The link between AD and TBI has been established in multiple nationwide observational cohorts and case-control studies, which showed that TBI is a risk factor for the clinical diagnosis of AD, increasing with the frequency and severity of TBI [2, 14, 15]. This relationship however was not detected in a pathology-confirmed AD cohort [16]. TBI has also been suggested as a risk factor for an earlier onset of AD, but a lack of robust evidence means it remains contentious [17–22]. The exact underlying mechanism of how TBI contributes to the neuropathological features of AD, deposits of extracellular amyloid beta (Aβ) plaques and intracellular tau tangles [23], remains poorly understood. Some studies found that both Aβ and tau pathology were widespread in postmortem tissue of patients with a history of TBI but without clear clinical AD, thus indicating overlapping pathways between TBI and AD [24, 25].

Despite the interest in the relationship between AD and TBI, no previous research has investigated the cognitive features of AD patients with a TBI history. Both AD and TBI involve complex changes in cognitive abilities, though it may be hypothesized that the executive domain is more affected in AD patients with TBI history compared to AD patients without a TBI history because TBI is likely to inflict frontal structures and tends to impair executive functioning [26]. There also remains sparse literature on the noncognitive features of this population, such as neuropsychiatric symptoms (NPSs). Some studies have found a higher rate of NPSs in all-type dementia patients with a TBI history (disinhibition, apathy, and motor disturbances) [27, 28]; however, these studies were not specified to AD.

It has not yet been established whether clinical AD features are influenced by specific TBI characteristics, for instance, age at injury, severity, and frequency of TBI. Some studies have suggested that TBI at an older age is more likely to impact long-term cognitive functioning, increases the risk for AD, and affects the clinical course of AD [1, 29, 30]. While, in contrast, CTE research evidenced that earlier age of head injury exposure is linked to more severe and earlier onset of disease characteristics [31–34]. Despite the fact that the severity and frequency of TBI further elevates the risk for AD, there also remains scarce evidence on whether these injury characteristics impact age of disease onset and other clinical features of AD. Therefore, this study aimed to examine whether a history of TBI and specific injury characteristics are associated with differences in age of disease onset, cognitive features, and NPSs in a well-defined, biomarker-proven AD population.

Materials and Methods

Study Population

We selected our population from the Amsterdam Dementia Cohort (ADC): patients who visited the tertiary memory clinic between September 1997 and January 2021 [35]. During this visit, diagnostic cognitive screening was conducted, including neurological examination, neuropsychological assessment, magnetic resonance imaging, APOE genotyping, and lumbar puncture for cerebrospinal fluid (CSF) analysis. A consensus diagnosis was made by a multidisciplinary panel, including a neurologist, a neuropsychologist, a radiologist, and a psychiatrist. Patients provided written consent to use their clinical data for future research purposes.

We selected patients with (1) baseline diagnosis of "probable AD" or "mild cognitive impairment (MCI) due to AD," including (2) an AD biomarker profile in CSF and/or (3) a positive amyloid positron emission tomography (PET) scan. For AD biomarkers in CSF, we used standardized diagnostic laboratory cutoffs, which includes an abnormal phosphorylated-tau (p-tau)/$A\beta_{42}$ ratio measured with Elecsys (ratio >0.020) or a combination of abnormal $A\beta_{42}$ and p-tau measured with INNOTEST ($A\beta_{42}$ <813, p-tau >52). Amyloid PET scan was conducted using ^{11}C-PiB, ^{18}F-florbetaben, ^{18}F-flutemetamol, or ^{18}F-florbetapir tracers and visually rated by a nuclear medicine physician according to our local protocol. Visually read results were dichotomized into "positive" or "negative." Patients with normal or unavailable CSF/PET biomarkers were excluded from analysis (N = 1,051). APOE e4 genotype was available for 93.8% and divided into APOE e4 carriers (carrying one or two e4 alleles) and noncarriers.

Traumatic Brain Injury

Information about TBI was reported in the medical history as brain injury, head injury, concussion, or brain contusion, including three different TBI characteristics: age of TBI, whether there was loss of consciousness (LOC), and whether there were multiple TBI events. We grouped TBI history into a single dichotomous variable for our main analysis (history of TBI: present or absent) and created multiple TBI subgroups for sub-analyses. For the first sub-analysis, age of TBI was subdivided into age of TBI <25 years and ≥25 years old. In case of multiple injuries, we applied the age of the first experienced TBI. This cutoff point was based on previous reports about brain maturation to indicate a period of different vulnerability for environmental stress. Although brain volume seems to reach its peak around the age of 12 years, it is widely established that the brain, especially the prefrontal cortex, further matures and rewires until the mid-20s [36]. Besides, previous reports showed that development and maturation of a majority of white matter microstructures continues until the age of 25 years before it reaches a plateau phase [37, 38].

Table 1. Overview of all neuropsychological tests

Neuropsychological tests
Attention
Digit Span Forward
Stroop Color Word Test (sum of task 1 and 2)
Trail Making Test part A
Executive functioning
Digit Span Backward (ratio)[a]
Verbal Fluency Test
Stroop Color Word Test task 3 (ratio)[b]
Trail Making Test part B (ratio)[c]
Language
Visual Association Test (naming)
Animal Fluency Test
Memory
Rey Auditory Verbal Learning Test
Visual Association Test (part A)
Visuospatial
The Visual Object and Space Perception Battery: number location and fragmented letters
Rey Complex Figure Test

[a] Divided by Digit Span Forward to adjust for attention. [b] Divided by Stroop Color Word Test task 2 to adjust for processing speed. [c] Divided by Trail Making Test part A to adjust for processing speed.

For the second sub-analysis, we combined TBI with LOC and multiple TBI events to create two subgroups. TBI groups were subdivided into "minor TBI" (single TBI without LOC) or "major TBI" (TBI with LOC and/or multiple TBI) in order to represent the effect of severity and cumulative impacts. We decided to merge these two TBI characteristics as the number of cases with multiple TBI events was only limited ($N = 25$), and the majority of cases with multiple TBI have also experienced LOC. Age of TBI was available for 92.2% of all TBI cases, and information about LOC and TBI frequency was available for 83.0%.

Outcome Measures

Age of Disease Onset

To determine the age of disease onset, we used data about symptom duration and age at diagnosis, both assessed during diagnostic cognitive screening. Symptom duration is determined by the clinician and indicates the patient's or informant's perception on the number of years of disease-related cognitive or behavioral complaints. This measure has been used to determine age at symptom onset. As the objective clinician's diagnosis is likely to be more sensitive than patient's subjective view, we determined age at diagnosis as a second marker for age of AD onset.

Cognition

Global cognition was assessed with the Mini-Mental State Examination (MMSE), and dementia severity was staged with the Clinical Dementia Rating (CDR) Scale. A comprehensive standardized test battery has been used to examine five cognitive domains, as displayed in Table 1. Attention and processing speed was assessed using the Digit Span Test (forward), the Stroop Color Word Test (SCWT) (sum of scores of table I and II), and Trail Making Test (TMT) part A [39–41]. Executive functioning was assessed by the Letter Fluency Test (sum of three trials), the Digit Span Test (backward), the SCWT (table III), and the TMT part B [39–42]. Test scores were corrected for attention/processing speed. Language was tested with the naming task of the Visual Association Test (VAT) and the Animal Fluency Test [43, 44]. Memory was assessed with Dutch version of the Rey Auditory Verbal Learning Test (immediate recall, sum of five attempts) and the VAT part A [43, 45]. Visuospatial abilities were tested with The Visual Object and Space Perception Battery (number location and fragmented letters) and the Rey Complex Figure Test (recognition) [46, 47]. Higher scores indicate better performance, except from the pace-dependent tests (TMT, SCWT). Scores were inverted for these tests and subtests. Test scores which were not normally distributed were log-transformed. We transformed the neuropsychological data into *Z*-scores, using the raw means and standard deviation of our own study population. Subsequently, we calculated mean composite scores of all five domains by averaging all completed test scores per domain (missing data: attention, 8.5%; executive, 10.7%; language, 8.6%; memory, 7.8%; visuospatial, 19.2%).

Neuropsychiatric Symptoms

The Neuropsychiatric Inventory Questionnaire (NPI-Q) was completed by the caregiver or another close informant, in order to measure 12 NPS items (delusions, hallucinations, agitation/aggression, dysphoria/depression, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor, night-time behavior, and appetite/eating). The NPI-Q is a well-validated and common tool in clinical and research practice to measure NPSs in AD patients [48]. Each item was scored for frequency (range 0–4) and severity (range 0–3) and transformed to a total severity score (frequency x severity, range 0–12). We calculated the total NPI-Q score as the sum of all 12 total severity scores (range 0–144). Higher scores indicate more severe NPSs. NPI data were available for 78.5% of all patients, and missing cases were excluded from analyses.

Statistical Analysis

All data analyses were performed using IBM SPSS Statistics (version 26). We used χ^2 tests, independent *t* tests, and Mann-Whitney U tests where appropriate, to compare baseline characteristics between AD patients with TBI history (TBI+) and AD patients without TBI history (TBI−). For our main analysis, linear regression analyses were used to assess associations between TBI history (independent variable) and age of disease onset, cognitive functioning, and NPSs (dependent variables). For our sub-analyses, we utilized linear regression models to test the effect of age at injury and TBI "severity" on age of disease onset, cognitive functioning, and NPSs. We built models with the subgroups: TBI <25, TBI ≥25 years, and TBI− as categorical independent variables, by transforming TBI <25 and TBI ≥25 into dummy variables with TBI− as the reference variable. The same was performed for the subgroups "major TBI," "minor TBI," and TBI−. All models were adjusted for several relevant factors. Models with age of disease onset as dependent variable were corrected for sex, APOE e4 genotype, and educational level; models with cognitive measures as dependent variables were corrected for age, sex, APOE e4 genotype, disease stage (MCI or dementia), and educational level; and the NPS models were corrected for age, sex, and disease stage.

Significance was thresholded at a p value of <0.05, and significant outcomes were corrected for multiple testing by the false discovery rate approach. Since we have three different main outcome groups (age of disease onset, cognitive functioning, and NPSs), the false discovery rate method was conducted for each outcome group separately.

Results

Demographics

Our cohort consisted of 1,755 participants with MCI (12.5%) or dementia (87.5%) due to AD. The mean age was 65.2 years (SD = 8.0), and 927 participants (53.1%) were female. Among these participants, 166 (9.5%) had reported one or more TBI in their medical history. In the TBI group, we found that 58 participants (35.5%) have experienced a TBI at an early age (<25 years), 79 participants (47.6%) experienced TBI with LOC, and 25 participants (15.1%) experienced two or more TBI events. Overall, there were 90 participants (54.2%) that experienced LOC and/or multiple TBI events, thus classified as major TBI. We compared baseline characteristics between AD patients with and without TBI history (TBI+ vs. TBI−). Baseline results revealed a significant lower percentage of APOE e4 carriers in the TBI+ group (48.1% vs. 69.6%, χ^2 (1) = 29.840, $p < 0.001$). In addition, the TBI+ group consisted of relatively less dementia patients (77.7% vs. 88.5%, χ^2 (1) = 16.157, $p < 0.001$). No differences were found in sex, symptom duration, and educational level between the two groups. All baseline characteristics of our cohort are displayed in Table 2.

Age of Disease Onset

No significant differences were found for age at symptom onset (mean difference = 0.500, $p = 0.431$) and age at diagnosis (mean difference = 0.547, $p = 0.366$) between AD patients with and without TBI history. Linear regression models also showed that medically reported TBI history was not associated with differences in age of disease onset, when controlling for sex, APOE e4 genotype, and educational level (age at symptom onset: unstandardized beta [B] = 0.608, $p = 0.363$, age at diagnosis: $B = 1.200$, $p = 0.118$). Regarding the age of TBI, linear regression analysis showed that TBI <25 was negatively associated with age at symptom onset ($B = -2.340$, $p = 0.031$) and age at diagnosis (B −2.310, $p = 0.041$) in AD patients, after adjustment for sex, APOE4 genotype, and educational level. This indicates that a TBI under the age of 25 years was associated with approximately 2.3 years earlier symptom onset and AD diagnosis. TBI ≥25 was associated with a significant higher age at symptom onset ($B = 2.885$, $p = 0.001$) and a higher age at diagnosis ($B = 2.828$, $p = 0.001$). Major TBI tends to have a positive association with age at diagnosis ($B = 1.672$, $p = 0.061$); however, not on a significant level (shown in Table 3).

Cognition

We found no associations between TBI and cognitive outcome scores with linear regression analyses, after con-

Table 2. Baseline characteristics of the study population

	TBI+	TBI−
N (%)	166 (9.5)	1,589 (90.5)
TBI <25, *n* (%)	58 (35.5)	
Major TBI, *n* (%)	90 (54.2)	
Sex, female (%)	83 (50.0)	844 (53.4)
Age, mean (SD)	65.7 (7.2)	65.2 (8.0)
Symptom duration, years, mean (SD)	3.1 (2.1)	3.1 (2.4)
Dementia, *n* (%)	129 (77.7)	1,407 (88.5)[a]
APOE e4 carrier, *n* (%)	75 (48.1)	1,037 (69.6)[a]
Education (Verhage), mean (SD)	5.0 (1.3)	5.1 (1.2)
MMSE, median [IQR]	22 [8]	22 [7]
CDR, median [IQR]	1.0 [0.5]	1.0 [0.5]

TBI+ indicates Alzheimer's disease patients with reported TBI. TBI− indicates Alzheimer's disease patients without TBI history. TBI <25 indicates TBI under the age of 25 years. Major TBI indicates TBI with loss of consciousness and/or multiple TBI events. TBI, traumatic brain injury; SD, standard deviation; MMSE, Mini-Mental State Examination; CDR, clinical dementia rating. [a] Significant difference ($p < 0.001$).

Table 3. Linear regression analysis between TBI and age of onset

	Age at diagnosis		Age at symptom onset	
	B	*p* value	*B*	*p* value
TBI+	0.608	0.363	0.642	0.357
TBI <25	−2.310	0.041[a]	−2.340	0.031[a]
TBI ≥25	2.828	0.001[a]	2.885	0.001[a]
Major TBI	1.672	0.061	1.516	0.104
Minor TBI	−1.387	0.233	−0.891	0.483

TBI <25 indicates age of TBI under 25 years old; TBI ≥25 indicates age of TBI older than 25 years old. Major TBI indicates TBI with loss of consciousness and/or multiple TBI events. Minor TBI indicates single TBI without loss of consciousness. Values are displayed as unstandardized coefficients (*B*) and corresponding *p* values. Models are adjusted for the variables sex, APOE e4 genotype, and educational level. TBI, traumatic brain injury. [a] Significance remains after adjustment for multiple testing.

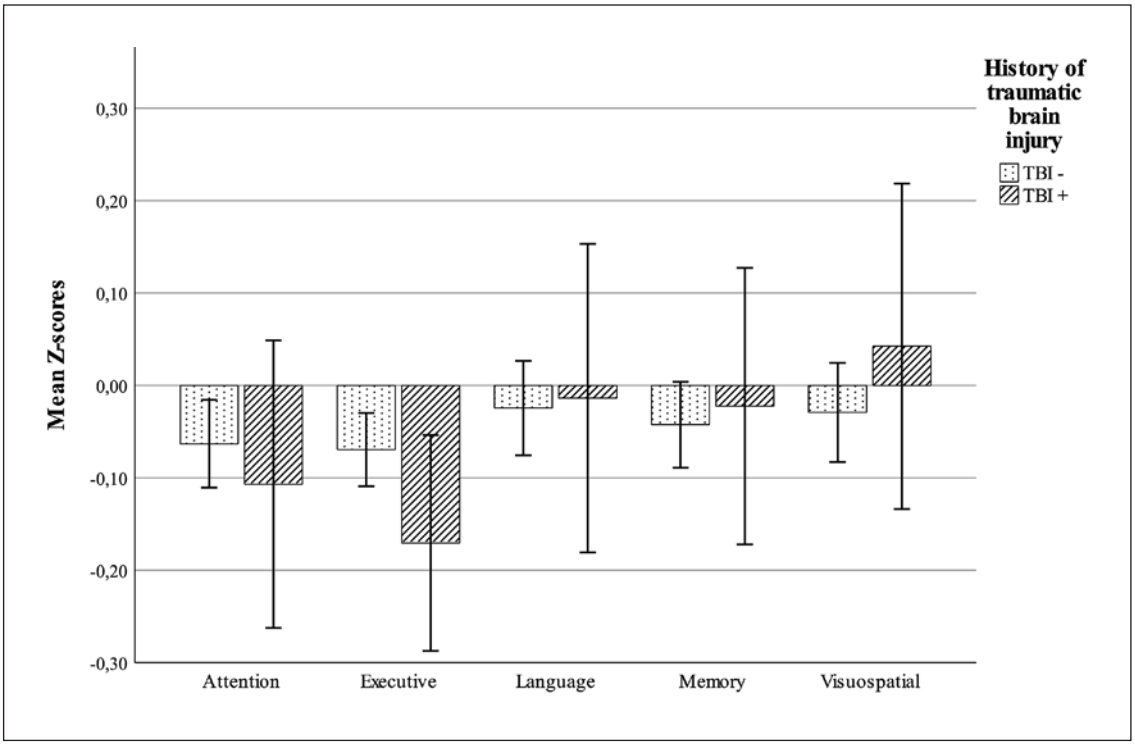

Fig. 1. Mean Z-scores of composite scores of each cognitive domain in dementia patients. Error bars display the 95% confidence interval. MCI cases were excluded in this figure because the significant higher amount of MCI cases in the TBI+ group will influence the visualization of group differences.

trolling for age, sex, educational level, disease stage, and APOE e4 genotype (Attention $B = -0.019$, $p = 0.786$; Executive $B = -0.015$, $p = 0.807$; Language $B = 0.056$, $p = 0.389$; Memory $B = 0.001$, $p = 0.991$; Visuospatial $B = 0.135$, $p = 0.099$). Figure 1 displays the distribution of mean *Z*-scores for each cognitive domain in the two subgroups (TBI+, TBI–). We also did not find an effect of TBI <25, TBI ≥25, major TBI, and minor TBI on cognitive performance (shown in the online suppl. Table; see www.karger.com/doi/10.1159/000526243 for all online suppl. material).

Neuropsychiatric Symptoms

Overall, we found no significant differences in NPSs between the two subgroups (shown in Fig. 2). There was a slight nonsignificant association between TBI and degree of anxiety ($B = 0.268$, $p = 0.199$) and degree of aberrant motor behavior ($B = 0.226$, $p = 0.188$), after adjustment for age, sex, and disease stage. No effect was found of TBI <25 on NPSs scores, but a late TBI (TBI ≥25) was associated with a higher degree of aberrant motor behavior ($B = 0.437$, $p = 0.048$). Significance did not survive correction for multiple testing. Major TBI was associated with a higher degree of irritability ($B = 0.678$, $p = 0.022$), and there was a tendency for a higher total NPI score in this subgroup ($B = 1.846$, $p = 0.180$). The significant value for irritability however did not survive multiple testing (shown in the online suppl. Table).

Discussion

The most remarkable result from this study is that a medically reported TBI, which happened under the age of 25 years, was associated with 2.3 years earlier disease onset in AD patients. There were no statistically significant associations between TBI history, including different TBI characteristics, and cognition or NPSs. We also found a lower percentage of the APOE e4 genotype in AD patients with a TBI history, compared to patients without TBI history.

To the best of our knowledge, this is the first study to show that an early age at injury possibly affects the age of disease onset in AD patients. The long-term consequenc-

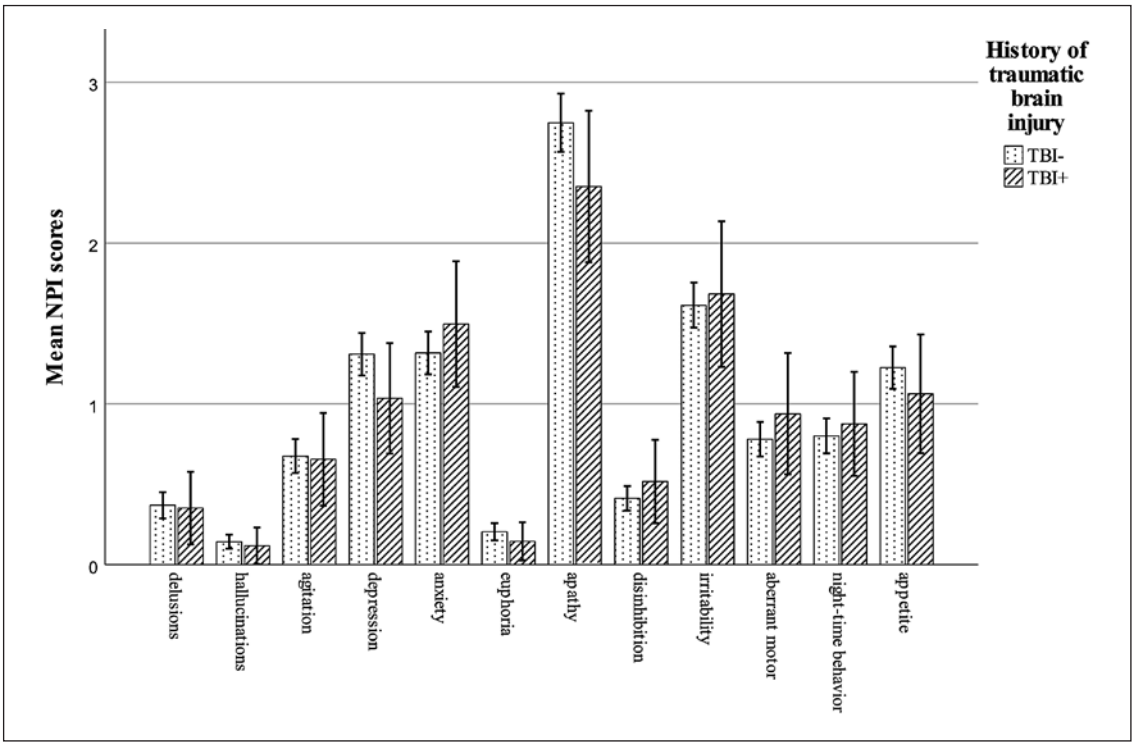

Fig. 2. Mean NPI severity score for each subdomain. Error bars display the 95% confidence interval.

es of TBI during childhood or adolescence have been previously studied, and early TBI has been associated with an increased risk of multiple medical and social problems during adulthood [49, 50]. Alosco et al. [31] demonstrated that exposure to tackle football at a younger age was associated with an earlier age of symptom onset among pathological confirmed CTE cases. It is widely acknowledged that brain development continues until an age of approximately 25 years, and it may be assumed that brain structures are more vulnerable to disruptions in this period [36, 37]. These early disruptions may cause less resilience or higher vulnerability to neurodegenerative changes in the brain later at life, and the threshold to compensate for pathological burden may be lowered. This vulnerability theory competes against the theory of neuroplasticity. Some argue that juvenile brains actually have greater capacity to adapt to insults, such as TBI, compared to the older brain [51]. There remain many uncertainties regarding both vulnerability and neuroplasticity theories, and future studies are needed to further establish the effect of juvenile TBI on long-term cognitive performance and the onset of neurodegenerative diseases.

Interestingly, no significant association was found between overall TBI history and age of disease onset in AD patients in our study. This finding is in line with a small number of older reports [20–22] but in contrast to some recent publications. One study reported a 2.5-year earlier symptom onset in clinically diagnosed AD patients with TBI history [17], and another study reported similar results in a cohort of autopsy-confirmed AD cases [19]. However, the mean age of the population in these studies was notably higher than our cohort, and the age at injury was not taken into consideration. It could be hypothesized that an early age at injury may have driven the association in these studies, but further evidence is required to confirm this.

We observed that cognitive profiles and NPSs in AD patients with TBI history may not differ from non-TBI AD patients, and this may not be affected by age at injury. This potentially contributes to sparse literature on this topic. In regards to cognition, one study has indicated a faster decrease in functional impairment among AD patients with TBI history, although this was limited to patients with a recent TBI event [30]. Another study revealed worse functioning on the TMT-A test and Boston

naming test in a cognitively impaired population with TBI history compared to non-TBI controls, but this was across a spectrum of multiple neurodegenerative and non-neurodegenerative disorders [52]. In addition, TBI history in combination with a diagnosis of post-traumatic stress disorder was associated with worse cognitive performance in former veterans with MCI [53]. Other studies have found no association between TBI history and faster cognitive decline or progression from MCI to dementia in AD patients [54, 55]. Regarding NPSs, only two studies demonstrated that TBI history was associated with an elevated risk for disinhibition, apathy, and aberrant motor symptoms, yet this was found in an all-type dementia population [27, 28]. Our findings may suggest that TBI is a risk factor for AD but may not alter clinical features once the disease has been developed. This finding needs to be interpreted cautiously, given the fact that our study was limited to cross-sectional analysis with only baseline assessments; hence, differences in cognitive functioning and NPSs could not be detected along the complete disease trajectory.

We considered positive AD biomarkers as an inclusion criterion for our population in order to reach the greatest diagnostic accuracy and highest degree of homogeneity, which is one of the major strengths of our study. However, we are aware that our research has limitations. Our cohort consisted of considerably young AD patients from a tertiary referral clinic, and results may therefore not be generalizable to the older AD population, which often has more comorbidities and different pattern of cognitive deficits compared to younger AD patients. Another limitation is that information about TBI history has been collected from medical history documentation instead of a standardized TBI assessment tool and may have led to unrecognized or not properly classified TBI events. In fact, previous work has demonstrated the inaccuracy of using medical files to identify single and repetitive TBI events in history [56]. Subconcussive impacts to the head may have also been unrecognized, due to lack of information about participation in contact sports or professional military service, which are often accompanied with such repetitive head impacts. It could be hypothesized that our TBI collection method predominantly identifies TBI events with clinical significance, and our study may primarily represent the effects of these type of trauma. Nevertheless, the shortcomings of our method need to be considered when interpreting our results. Another limitation is the potential bias of recalling medical history from the patient's childhood or adolescence. It may be argued that these early TBI events have only been recalled when they have been relatively severe, whereas TBI events at an older age have also been remembered when they have been relatively mild. It could be hypothesized that our results did not solely reflect a juvenile effect but also a severity effect of these early TBI events, even though the distribution of major TBI and minor TBI events was equal between the two subgroups. The question is however whether TBI severity actually has effect on early AD onset as our results demonstrated that TBI with LOC and multiple TBI was even tended to be associated with a higher age of disease onset.

In summary, the findings of our study give some indications that TBI during childhood, adolescence, or early adulthood may influence age of disease onset in AD patients, given its association with a 2.3-year earlier age at symptom onset, but TBI may not affect cognitive characteristics and NPS profiles in this population. Given that our results are based on cross-sectional analysis and limited by the TBI collection tool, the findings should consequently be treated with considerable caution. We recommend future studies to focus on the effect of TBI on the clinical and cognitive features along the complete trajectory of AD, with the use of a validated TBI assessment battery.

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Statement of Ethics

This research is in accordance with the World Medical Association Declaration of Helsinki. This study is part of the Amsterdam Dementia Cohort and was approved by the Medical Ethics Committee of the VU medical center (protocol number: P2016.061). Written informed consent was obtained from all participants who participated in this study.

Conflict of Interest Statement

Dewi K. Caton is a part-time employee of the Brain Research Center. Philip Scheltens has received consultancy fees (paid to the institution) from ACImmune, Alkermes, Alnylam, Alzheon, Anavex, Biogen, Brainstorm Cell, Cortexyme, Denali, EIP, ImmunoBrain Checkpoint, GemVax, Genentech, Green Valley, Novar-

tis, Novo Nordisk, PeopleBio, Renew LLC, and Roche. He is a PI of studies, CogRx, FUJI-film/Toyama, IONIS, UCB, and Vivoryon. He is a part-time employee of Life Sciences Partners Amsterdam. Everard G.B. Vijverberg has received consultancy fees (paid to the institution) from Biogen, Brainstorm Cell, ImmunoBrain Checkpoint, New Amsterdam Pharma, and Treeway. He is a PI of studies with ACImmune, CogRx, Green Valley, IONIS, Janssen, Roche, Rodin Therapeutics, Sanofi, UCB, and Vivoryon.

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Author Contributions

Suzan van Amerongen contributed to the design of the study protocol, performed data collection, and drafted the manuscript. Dewi K. Caton, Yolande A.L. Pijnenburg and Philips Scheltens contributed intellectually on the study protocol and critically appraised the manuscript. Everard G.B. Vijverberg oversees the data collection and supervised the manuscript draft. All the authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

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