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Traumatic brain injury alters neuropsychiatric symptomatology in all-cause dementia

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Abstract

INTRODUCTION: Traumatic brain injury (TBI) may alter the course of neuropsychiatric symptom (NPS) onset during dementia development. The connection between TBI, NPS, and dementia progression is of increasing interest to researchers and clinicians.

METHODS: Incidence of NPS was examined in participants with normal cognition who progressed to all-cause dementia based on whether TBI history was present (n=130) or absent (n=849). Survival analyses were used to examine NPS incidence across 7.6±3.0 years of follow-up.

RESULTS: Participants with TBI history had increased prevalence and incidence of apathy (44.7% vs. 29.9%, p=0.0062; $HR_{adj.}$=1.708, p=0.0018) and motor disturbances (17.2% vs. 9.5%, p=0.0458; $HR_{adj.}$=2.023, p=0.0168), controlling for demographics and type of dementia diagnosis. Earlier anxiety onset was associated with TBI (692 days prior to dementia diagnosis vs. 161 days, p=0.0265).

DISCUSSION: History of TBI is associated with increased risk for and earlier onset of NPS in the trajectory of dementia development.

Keywords

Traumatic brain injury; dementia; Alzheimer's disease; neurodegeneration; neuropsychiatric symptoms; neuropsychiatry; geriatric psychiatry; all-cause dementia; acquired brain injury; anxiety; apathy; motor disturbances; mild behavioral impairment

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1 | Introduction

The complex interplay between history of traumatic brain injury (TBI) and neurodegenerative conditions represents an active area of research with considerable progress in recent years. A prominent theory is that TBI may prompt or moderate the trajectory of cognitive decline in aging, resulting in earlier onset of dementia syndromes in some individuals [1–4]. Interestingly, the cognitive and other neuropsychiatric symptoms (NPS; e.g., poor attention, executive dysfunction, apathy) that may persist chronically post-TBI mimic the symptomatology of other dementia syndromes [5,6]. In fact, previous work in the database utilized here, the National Alzheimer's Coordinating Center Uniform Data Set (NACC-UDS), showed that TBI history was associated with clinician misdiagnosis of Alzheimer's disease (increased false-positives evaluated using gold-standard autopsy neuropathology) [7].

Despite extensive investigation into connections between (1) TBI and dementia or (2) NPS with cognitive decline in dementia, there is little research into the influence of TBI on NPS in the course of dementia development. NPS following TBI are often transient; however, in a portion of the population, symptoms persist permanently and cause a significant decrease in quality of life, independent of associated dementia onset [8,9]. Given that NPS accompany cognitive decline at some point during the disease course for 97% of patients with dementia, NPS represent an important component of pattern recognition and treatment of dementia syndromes [10,11]. While few studies exist, limited data suggest that TBI history can influence NPS presentation in dementia. For example, in all-cause dementia, one study found those with TBI history displayed elevated disinhibition prevalence compared to those without [12]. In Parkinson's disease, another study found patients with TBI history reported increased rates of depression during the disease course [13].

In this short report, we utilize NACC-UDS data to examine connections between TBI, NPS, and cognitive decline in all-cause dementia. Our objective was to evaluate differences in NPS incidence and time of NPS onset relative to dementia diagnosis between participants with and without TBI history, who progress from normal cognition to all-cause dementia. We hypothesized that TBI history would be associated with greater incidence and earlier time at onset (relative to time at dementia diagnosis) of each NPS.

2 | Methods

2.1 | Participants

Longitudinal data on demographics, medical history, NPS, cognitive status, and clinical ratings of dementia severity were prospectively collected from n=40,858 participants from September 2005-June 2019 by Alzheimer's Disease Research Centers (ADRC), funded by the National Institute on Aging (United States). All participants (or designated healthcare agents) provided informed consent. These data comprise the NACC-UDS (data collection protocols described previously) [14]. This dataset includes participants with normal cognition, mild cognitive impairment (MCI), and clinically-diagnosed dementia who are followed approximately annually.

To be included in the present study, participants must have had normal cognition at one time-point prior to dementia diagnosis, completed ≥3 visits, and progressed to a diagnosis of all-cause dementia. Exclusion criteria comprised missing data regarding TBI history and incident TBI following study enrollment.

2.2 | Primary Outcomes

TBI history was assessed using the NACC-UDS variable, NACCTBI. This term is collected mainly using subject self-report (or caregiver/co-participant report in patients unable to provide self-report data) and is inclusive of varying TBI severities, with and without loss-of-consciousness, including blast and sport-related TBI. Dementia status was assessed using the clinician-rated NACCUDSD variable, with a score of 1 indicating normal cognition and a score of 4 indicating dementia. MCI was assessed as Mini-Mental State Examination score ≤27. NPS were assessed using the Neuropsychiatric Inventory Questionnaire (NPI-Q), which comprises 12 emotional/behavioral symptoms rated as present/absent within the past month by an informant, and if present, rated as mild, moderate, or severe. Because of the potential for symptoms to occur unrelated to the trajectory of dementia (e.g., psychosocial stressor, illness, etc.), only stable MCI and NPS were considered incident, which required MCI or NPS to be present at ≥2 consecutive evaluations. Other NACC-UDS data used in the present investigation include: age, years of education, sex, race, type of dementia diagnosis, and ApoE status.

2.3 | Statistical Analysis

Statistical analyses were completed in R (v3.6.1). Mean differences between participants with and without TBI were assessed using Welch's T-tests and differences in proportions were assessed using Chi-square tests with Yates' continuity correction. NPS incidence over time (relative to time at dementia diagnosis) was assessed using survival analyses with TBI history as a predictor variable (Kaplan-Meier and Cox proportional hazard models corrected for age at initial visit, sex, race, years of education, and dementia diagnosis). Differences in time at NPS onset were assessed within the subsets of participants reporting each NPS (with and without TBI history) using Welch's T-tests. Effects of TBI regarding changes in symptom severity over time were assessed using linear mixed-effects modeling including above control variables.

3 | Results

Following application of inclusion and exclusion criteria, n=979 participants with an average of 7.59±3.00 years of follow-up were included for analysis (Table S1). Participants with (n=130) and without (n=849) TBI history did not differ in age at initial visit, age at dementia diagnosis, sex, race or ApoE status. Those with TBI differed from those without regarding type of dementia diagnosis, with a lower proportion of Alzheimer's disease and a greater proportion of hydrocephalus and unclassified dementia in those with TBI history.

Compared to those without, participants with TBI history had greater prevalence of apathy (44.7% vs. 29.9%, $X^2(1,N=712)=7.5038$, $p=0.0062$) and motor disturbances (17.2% vs. 9.5%, $X^2(1,N=684)=3.9904$, $p=0.0458$), defined using the NPI-Q, by final follow-up (Table

S2). On Cox proportional hazard modeling and survival analyses, TBI history was associated with greater risk of incident apathy ($HR_{adj.}$=1.546, $CI_{95\%}$=1.092,2.188, p=0.0141) and motor disturbances ($HR_{adj.}$=1.997, $CI_{95\%}$=1.092,3.651, p=0.0246) over time, controlling for age, sex, race, years of education and dementia diagnosis (Figure 1E, Figure 1L, Table S3).

Examining mean time at onset of MCI and NPS, relative to time of dementia diagnosis, participants with TBI history had earlier onset of anxiety (692 days before dementia diagnosis vs. 161 days, t(38.095)=2.3083, p=0.0265) (Table S2, Figure 2D) but did not differ with respect to MCI or other NPS. Notably, neither total prevalence of anxiety nor incidence of anxiety over time differed between groups.

In linear mixed-effects modeling, TBI was not associated with differences in NPS severity over time in either unadjusted models including only time and TBI history, or multivariable models adjusted for age, sex, race, years of education and dementia diagnosis (Table S4). There were no significant interaction effects of time and TBI history in either models.

4 | Discussion

This investigation found evidence that TBI history alters the course of NPS development in patients progressing from normal cognition to diagnosis of all-cause dementia. Specifically, TBI history was associated with greater incidence of apathy and motor disturbances, as well as earlier mean time of onset regarding anxiety. Of note, this study did not replicate previous findings of increased disinhibition prevalence in participants with TBI in the context of all-cause dementia [12]. It should be considered that incidence of many NPS (agitation, anxiety, apathy, delusions, disinhibition, elation, and motor disturbances) appeared elevated in the TBI group before dementia diagnosis, though most differences were not significant. While this may indicate no true difference between groups, it is possible the current sample is underpowered regarding participants with TBI history. Further research is required to draw firm conclusions.

This investigation found that anxiety symptoms presented, on average, 1.90 years before dementia diagnosis in participants with TBI history compared to 0.44 years before diagnosis in those without. This difference of 1.46 years represents a substantial window, possibly presenting a valuable opportunity for early intervention and caregiver planning in this population. Moreover, evidence from moderate-to-severe TBI suggests that anxiety might even play an active role in exacerbating risk of degenerative change in the months and years following injury [15]. While neurobiological mechanisms underlying this risk warrant further study, previous work suggests post-TBI neurodegeneration may be driven by neuroinflammatory processes [16]. Relatedly, neuroinflammatory markers are chronically elevated in anxiety, with some authors suggesting that anxiety and stress may contribute to post-TBI neurodegeneration through this pathway [17]. Given literature demonstrating the importance of inflammatory processes in dementia progression, earlier anxiety onset in this context is compelling [18]. Recently, anxiety has also been demonstrated to be associated with decline in frontal cognitive function (digit symbol modality, an executive functioning test) [19]. Notably, apathy (another significant domain in the present study) is also

associated with frontal decrements. Further study is required to investigate the interplay of NPS with dementia development and progression. Notably, data regarding type and severity of TBI is not available in the NACC-UDS, representing an important limitation of this study and a priority for future research. Self-reporting of TBI history also represents a key limitation. Separate directional hypotheses were made *a priori* for each of the 11 NPS included in this investigation and as such no corrections for multiple comparisons were performed. However, it warrants consideration that the probability of type I error may be increased by this approach, warranting future study to further validate these findings.

5 | Conclusion

Comparable to MCI, these findings suggest that NPS may precede dementia diagnosis in a substantial proportion of patients. The present findings suggest that earlier onset and greater incidence of NPS may be precipitated by TBI. This raises the hypothesis that TBI exerts this effect on NPS by introducing vulnerability to neurodegeneration within certain underlying networks. If true, this may have important implications for other related NPS associated with the same underlying network disruption. Of note, the construct of mild behavioral impairment is a useful framework by which related NPS may be grouped by underlying network disruption.[20] Considering the present findings, this represents a priority for future investigation in the context of neurodegenerative disease and TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ADRC	Alzheimer's Disease Research Center
MCI	Mild cognitive impairment
NACC-UDS	National Alzheimer's Coordinating Center Uniform Data Set

NPI-Q	Neuropsychiatric Inventory Questionnaire
NPS	Neuropsychiatric symptoms
TBI	Traumatic brain injury

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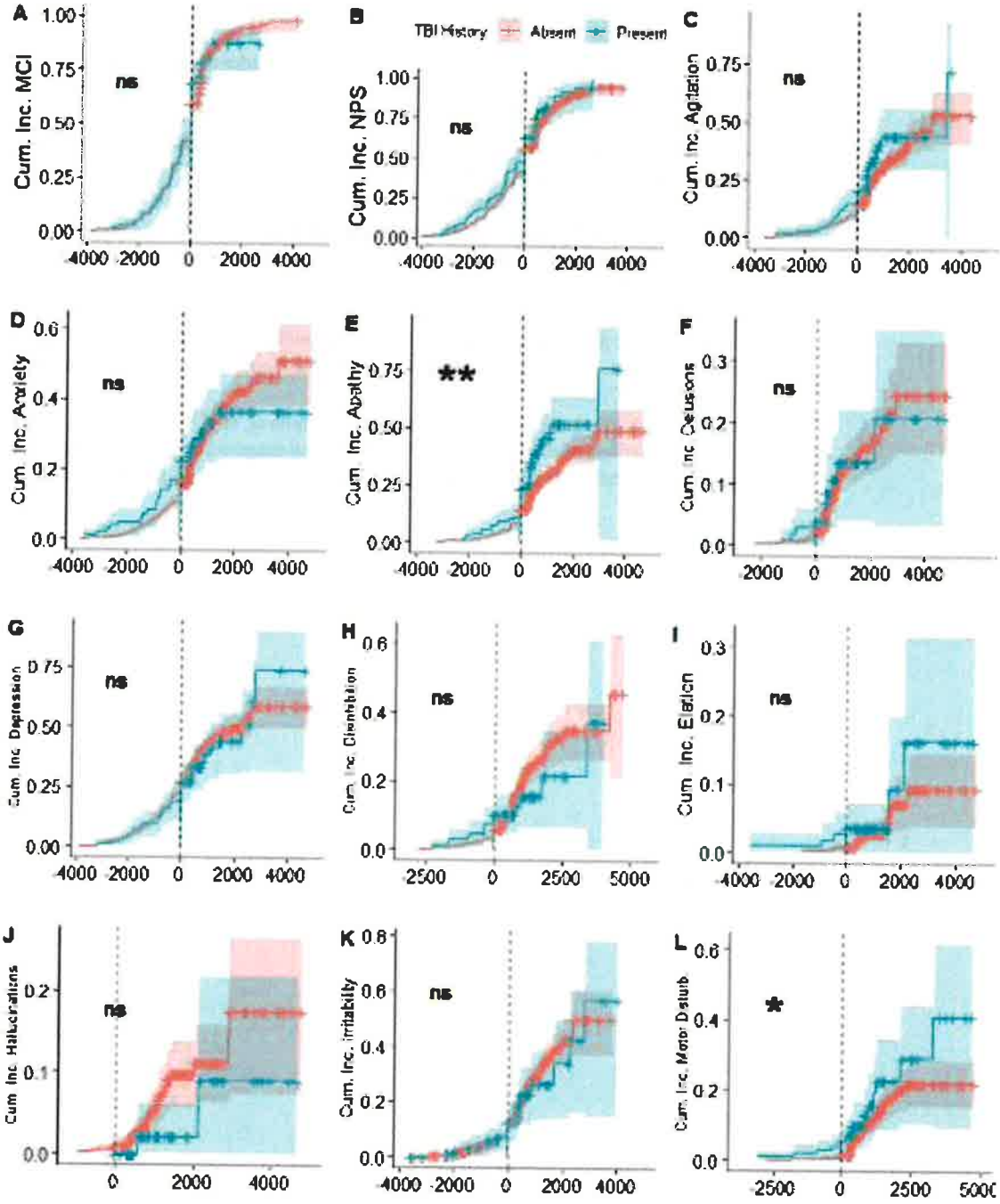

Figure 1:

Cumulative incidence plots (Kaplan-Meier method) illustrating symptom development for participants with (teal) and without (orange) history of traumatic brain injury (TBI), relative to time at dementia diagnosis (time = 0, dashed line). X-axis represents days relative to dementia diagnosis with negative values indicating incidence prior to diagnosis. Cumulative incidence is reported for MCI (A), any NPS (B), agitation (C), anxiety (D), apathy (E), delusions (F), depression (G), disinhibiton (H), elation (I), hallucinations (J), irritability (K),

and motor disturbances (L). **: $P < .01$; *: $P < .05$. ns, not significant; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms (any)

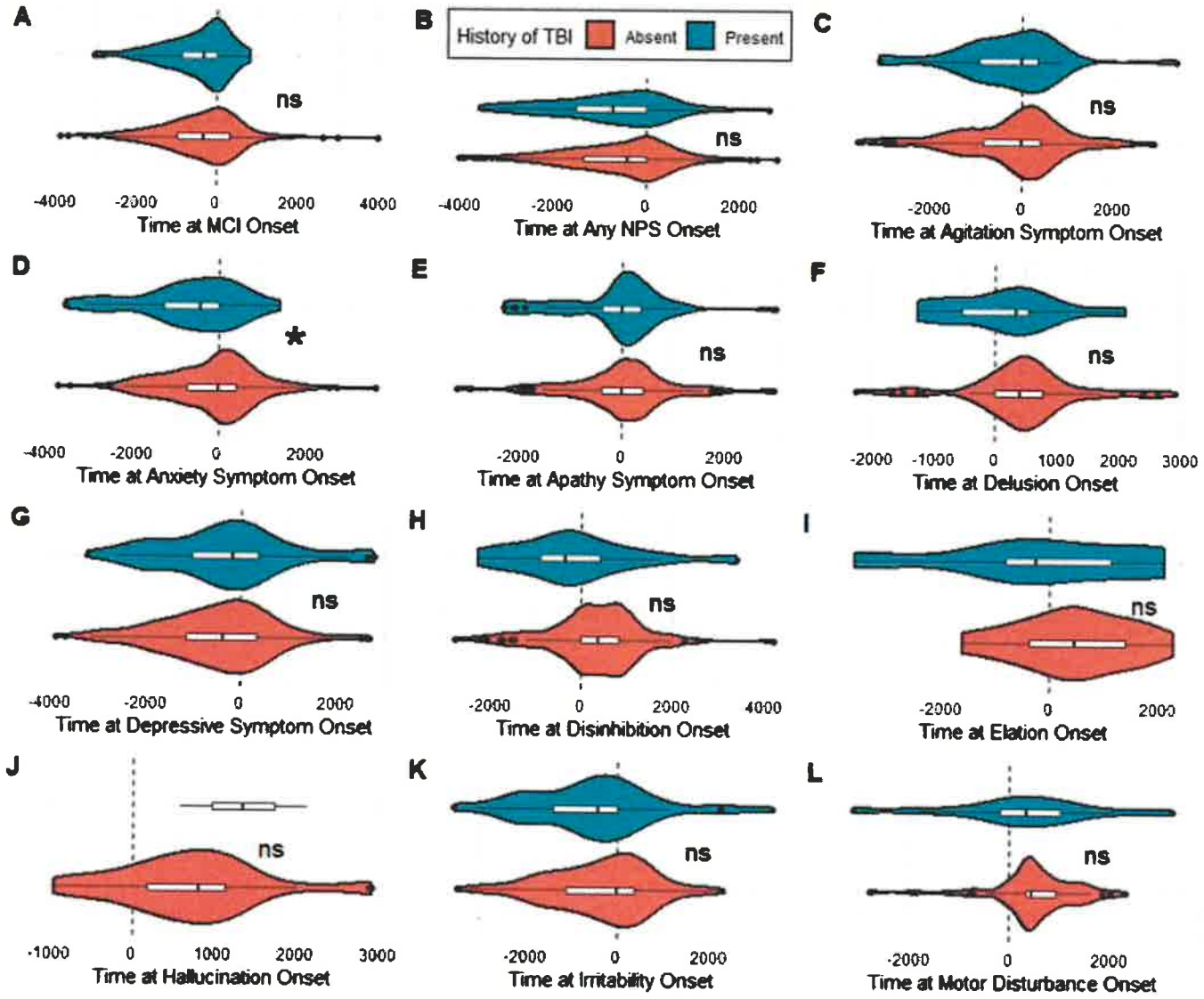

Figure 2:

Violin plots illustrating time at symptom onset for participants with (teal) and without (orange) history of traumatic brain injury (TBI), relative to time at dementia diagnosis (time = 0, dashed line). Time at onset of symptoms is reported for MCI (A), any NPS (B), agitation (C), anxiety (D), apathy (E), delusions (F), depression (G), disinhibiton (H), elation (I), hallucinations (J), irritability (K), and motor disturbances (L). *: $P < .05$. ns, Not significant; MCI, mild cognitive impairment; NPS, neuropsychiatric symptoms (any)