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RESEARCH ARTICLE

Effect of traumatic brain injury on mild behavioral impairment domains prior to all-cause dementia diagnosis and throughout disease progression

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Abstract

Introduction: Traumatic brain injury (TBI) may alter dementia progression, although co-occurring neuropsychiatric symptoms (NPS) have received less attention. Originally designed to evaluate behavioral disruption prior to dementia diagnosis, the mild behavioral impairment (MBI) construct relates NPS to underlying neural circuit disruptions, with probable relevance across the progression of neurodegenerative disease. Therefore, the MBI construct may represent a valuable tool to identify and evaluate related NPS both preceding diagnosis of all-cause dementia throughout the progression of disease, representing an important area of inquiry regarding TBI and dementia. This investigation sought to evaluate the effect of TBI on NPS related by the MBI construct in participants progressing from normal cognitive status to all-cause dementia.

Methods: Using National Alzheimer's Coordinating Center data, individuals progressing from normal cognition to all-cause dementia (clinician diagnosed) over 7.6 ± 3.0 years were studied to estimate prevalence of MBI domains in 124 participants with prior TBI history (57 with loss of consciousness [LOC] <5 minutes, 22 with LOC >5 min, 45 unknown severity) compared to 822 without. MBI domain prevalence was evaluated (1) prior to dementia onset (including only time points preceding time at dementia diagnosis, as per MBI's original definition) and (2) throughout dementia progression (evaluating all available time points, including both before and after dementia diagnosis).

Results: More severe TBI (LOC >5 minutes) was associated with the social inappropriateness MBI domain (adjusted odds ratio = 4.034; $P = 0.024$) prior to dementia onset, and the abnormal perception/thought content domain looking across dementia progression (adjusted hazard ratio [HR_{adj}] = 3.703; $P = 0.005$). TBI (all severities)

was associated with the decreased motivation domain looking throughout dementia progression ($HR_{adj.} = 1.546$; $P = 0.014$).

Discussion: TBI history is associated with particular MBI profiles prior to onset and throughout progression of dementia. Understanding TBI's impact on inter-related NPS may help elucidate underlying neuropathology with implications for surveillance, detection, and treatment of behavioral concerns in aging TBI survivors.

KEYWORDS

acquired brain injury, Alzheimer's disease, apathy, dementia, geriatric psychiatry, impulsivity, mild behavioral impairment, neurodegeneration, neuropsychiatry, social inappropriateness, traumatic brain injury

Highlights

- The mild behavioral impairment (MBI) construct links related neuropsychiatric symptoms (NPS) by probable underlying neural network dysfunction.
- Traumatic brain injury (TBI) with loss of consciousness (LOC) > 5 minutes was associated with pre-dementia social inappropriateness.
- TBI was associated with decreased motivation looking across dementia progression.
- TBI with LOC > 5 minutes was associated with abnormal perception/thought content.
- The MBI construct may be useful for examining related NPS across dementia progression.

1 | INTRODUCTION

A growing body of literature suggests that traumatic brain injury (TBI) may contribute to neuropathological changes, increasing risk of Alzheimer's disease (AD) and related dementias.[1–3] Remote TBI has been associated with an increased dementia risk >30 years post-injury,[4] earlier age at dementia onset,[5] and may exert prolonged impact on neuropsychiatric functioning.[6,7]

In patients with dementia, TBI may influence cognitive and behavioral outcomes,[8] impacting quality of life and clinical diagnoses.[9,10] Perhaps due to underlying network dysfunction and/or the introduction of region-specific vulnerabilities to neurodegeneration, growing evidence suggests that TBI affects phenotypes of neuropsychiatric symptoms (NPS) during progression to all-cause dementia.[8,11] Importantly, NPS precede dementia diagnosis in many patients;[11] however, some research suggests that patients with TBI history (any severity) may have an earlier onset of anxiety symptoms and an elevated risk of apathy, motor disturbances, and disinhibition compared to those without.[8,12] Other investigations have found that patients with dementia after TBI had higher rates of depression, anxiety, irritability, and motor dysfunction than dementia patients without TBI history.[13,14] Investigation into how TBI affects neuropsychiatric symptomatology may provide valuable insights into region-/network-specific vulnerabilities to neurodegenerative change throughout dementia progression.

Certain brain networks are particularly vulnerable to TBI. Furthermore, dysfunction of distinct networks is associated with specific NPS. Though TBI may introduce diffuse neurological damage, certain key circuits warrant particular consideration given their vulnerability to TBI and the neuropsychiatric consequences of their disruption. For example, dorsolateral prefrontal circuits (comprising the dorsolateral prefrontal cortex, dorsolateral caudate nucleus, globus pallidus, ventral anterior, and mediodorsal thalamus) modulate cognitive processes including working memory and executive functions and, when damaged, patients may experience a dysexecutive syndrome, presenting as difficulty shifting attention, organizing/retrieving information, and problem solving.[15,16] Orbitomedial frontal circuits (comprising the orbitofrontal cortex, ventral striatum, ventral pallidum, and mediodorsal thalamus) help guide social behaviors, permitting self-correction of inappropriate social context and, when damaged, result in disinhibition, leading to socially inappropriate behavior, impulsivity, and diminished social tact.[16,17] Anterior cingulate circuits (comprising the anterior cingulate cortex, caudate nucleus, and putamen) are responsible for motivation and reward-related behaviors and, when damaged, lead to apathy with restricted emotional responses and difficulty initiating volitional behaviors.[16,18] Additionally, emerging evidence suggests that hippocampal atrophy secondary to moderate–severe TBI may contribute to dysregulation of downstream mesolimbic dopaminergic circuits, increasing risk of hallucinations and delusions.[19] TBI may

damage and/or introduce vulnerability in one or more of these neural circuits, perhaps contributing to the altered NPS phenotypes observed in post-TBI dementia.

Importantly, the mild behavioral impairment (MBI) construct relates NPS to underlying neural circuit disruption.[20] Originally defined by the International Society to Advance Alzheimer's Research and Treatment (ISTAART) as persistent NPS emerging later in life (which are not better explained by a common psychiatric disorder) in the *absence* of dementia,[21] the MBI construct aims to characterize behavioral changes which commonly predate dementia diagnosis,[11] providing a behavioral analog to supplement the more commonly considered concept of mild cognitive impairment (MCI). NPS were further grouped by ISTAART consensus criteria based on shared underlying neurological dysfunction, producing five distinct MBI domains: decreased motivation, affective dysregulation, impulse dyscontrol, social inappropriateness, and abnormal perception/thought content.[22] Although originally developed for classification of pre-dementia symptomatology, given that MBI domains link individual NPS to underlying neural circuit disruption, we posit these same domains have utility when evaluating NPS across the course of dementia.

In this study, we analyzed a national database to examine the relationship between remote TBI and NPS grouped into MBI domains. Our specific objectives were (1) to examine the influence of prior TBI history (preceding study enrollment) on MBI prevalence over time in all-cause dementia (prior to dementia diagnosis, that is, MBI's original definition) and (2) to use MBI domains as a construct for examining the influence of TBI on related NPS across the course of dementia onset and progression. We hypothesized that prior TBI history would be associated with (1) certain MBI construct domains, namely decreased motivation, impulse dyscontrol, and social inappropriateness based on literature suggesting increased risk of these particular MBI domains in the context of TBI and particular vulnerability of associated neural circuits to TBI[8,16,17] and (2) earlier presentation of these MBI domains along the disease course in all-cause dementia.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed traditional (e.g., PubMed) sources. While previous work studied traumatic brain injury (TBI)'s relationship with dementia and its impact on individual neuropsychiatric symptoms (NPS), we are not aware of prior investigations using mild behavioral impairment (MBI) domains to group related NPS by underlying neural circuit disruption post-TBI. Relevant literature is appropriately cited.
2. **Interpretation**: Our findings show that TBI was associated with an increased risk of dysfunction in the MBI domain of decreased motivation. TBI with extended (> 5 minutes) loss of consciousness was associated with MBI domains of social inappropriateness (preceding dementia onset) and abnormal perception/thought content (looking across dementia progression).
3. **Future Directions**: These behavioral findings may suggest altered progression of neurodegenerative changes in all-cause dementia after TBI, though more study is needed. Moreover, the findings suggest that the MBI construct may have utility throughout dementia progression. Future studies should determine whether MBI domains have prognostic utility and subsequent clinical relevance throughout all-cause dementia progression.

2 | METHODS

2.1 | Participants

Data from the National Alzheimer's Coordinating Center Uniform Data Set (NACC-UDS) were analyzed. The NACC-UDS is a large, prospectively collected, longitudinal dataset collected at Alzheimer's Disease Research Centers (ADRCs), funded by the National Institute on Aging (United States). All participants or designated health-care agents provided informed consent. Data collection protocols have been described previously.[23] This study drew from an initial pool of 40,858 participants assessed at 32 ADRCs between September 2005 to June 2019 before application of inclusion/exclusion criteria. Research using the NACC dataset has been approved by the University of Washington Institutional Review Board (IRB) and this secondary data analysis was exempt from additional IRB oversight by the Johns Hopkins University IRB (IRB00237545). Inclusion criteria comprised: normal cognition recorded during at least one time point prior to dementia diagnosis, available data from ≥3 visits, and progression to all-cause dementia diagnosis during the follow-up period. The clinician-rated variable, NACCUDSD, was used to operationalize dementia status, with a score of 1 indicating normal, unimpaired cognition, and a score of 4 indicating clinician-diagnosed dementia (intermediate scores of 2 and 3 were not used in this investigation). Time at dementia diagnosis was operationalized as the first visit date at which a NACCUDSD score of 4 was recorded. Exclusion criteria comprised: missing data regarding TBI history at initial NACC visit, incident TBI after study enrollment.

2.2 | Primary exposure

History of TBI was assessed using the binary NACC-UDS variable, NACCTBI. This item is collected via self-report and includes TBI of varying severities and mechanisms, both with and without loss of consciousness (LOC). Participants were grouped based on TBI history at baseline (i.e., TBI suffered prior to study enrollment). Data regarding timing of TBI relative to baseline assessment were not available. Severity of TBI was assessed using a positive screen for the NACC-UDS variables TRAUMBRF (indicating history of TBI with LOC lasting < 5 minutes) and TRAUMEXT (indicating history of TBI with LOC > 5 minutes) at initial visit.

2.3 | Outcomes

NPS presence and severity were determined using the Neuropsychiatric Inventory Questionnaire (NPI-Q) ,which has previously been validated for use in patients with AD.[24] NPI-Q encompasses 12 emotional/behavioral symptoms rated as present or absent in the past month by participant self-report (or caregiver/co-participant report where necessary). If present, symptom severity is rated mild, moderate, or severe.

MBI domains were operationalized according to the International Society to Advance Alzheimer's Research and Treatment-Alzheimer's Association (ISTAART-AA) research diagnostic criteria.[21] While, by strict criteria, MBI refers to NPS with onset preceding dementia diagnosis, the influence of TBI on the development of these inter-related symptoms was also assessed across the course of dementia onset and progression (i.e., including post-dementia diagnosis). Consistent with previous work from ISTAART-AA,[22] participant NPS (measured by individual NPI-Q domains) were mapped onto relevant MBI domains using a published algorithm:[25]

- Decreased motivation (NPI–apathy/indifference).
- Affective dysregulation (NPI–depression/dysphoria, anxiety, elation/euphoria).
- Impulse dyscontrol (NPI–agitation/aggression, irritability/lability, aberrant motor behavior).
- Social inappropriateness (NPI–disinhibition).
- Abnormal perception/thought content (NPI–delusions, hallucinations).

Cognitive impairment was included in analyses to permit qualitative comparisons regarding timelines of cognitive versus behavioral change. Time of cognitive impairment was operationalized as the time at which a participant scored ≤ 27 on the Mini-Mental State Examination (MMSE; no lower bound). Despite limitations of this approach (e.g., possibility for misclassification), operationalizing cognitive impairment using the MMSE has the advantage of uniform administration and scoring across ADRCs and is minimally affected by the inter-rater variability that may confound multi-center studies. Additionally, prior work in a sample that overlapped with that of the present investigation demonstrated that classification using this cut-off is acceptably sensitive (0.78) and specific (0.78) in detecting MCI in comparably well-educated samples of aging adults, suggesting this cut-off may be a reasonable proxy for clinically relevant cognitive impairment in this population.[26]

To ensure diagnostic stability across time (and not due to medical illness or other causal factors unrelated to dementia progression), cognitive impairment and MBI were only considered persistent if they were present at two or more consecutive time points.[27,28] For MBI, this was operationalized as one or more NPS (of any severity) within the MBI domain presenting at consecutive time points (including different NPS within the same MBI domain across time points), consistent with the ISTAART-AA MBI criteria.

2.4 | Covariates

Other NACC-UDS data included in this study were age at initial visit, years of formal education, sex, race, and type of dementia diagnosis. These covariates were chosen due to known associations with TBI, effects on neurodegeneration, neuropsychological outcomes of neurodegeneration, outcomes after TBI, or a combination of these factors.[29–33] Importantly, TBI may alter neuropsychiatric symptomatology and therefore contribute to misdiagnosis of dementia type, as has been demonstrated elsewhere.[9] However, neurodegenerative disease type is known to affect patients' behavioral symptom profiles (i.e., differing NPS in Parkinson's disease compared to frontotemporal dementia), independent of TBI status. As the causal contributions of each to the outcome of interest (MBI domain presence) could not be differentiated on the basis of the present data, conservatively, type of dementia diagnosis was included as a covariate despite the increased risk of type II error.

2.5 | Statistical analyses

Statistical analyses were conducted using R version 3.6.1. Baseline group differences were assessed using Welch's *t*-tests (continuous outcomes) and chi-square tests with Yates' continuity correction (categorical outcomes). Odds of MBI prevalence prior to dementia diagnosis were assessed using logistic regression modeling. Looking across dementia progression (entire follow-up period), prevalence of symptoms related by MBI domains were estimated using survival analyses with Kaplan–Meier curves and Cox proportional hazard models. Logistic regression and Cox proportional hazard models were adjusted for age at initial visit, sex, race, years of education, and type of dementia diagnosis. Time was operationalized for analysis as the number of days relative to dementia diagnosis, with time at diagnosis set as 0, negative values representing time prior to dementia diagnosis, and positive values representing time after dementia diagnosis. For analyses including TBI severity, participants with LOC < 5 minutes or LOC > 5 minutes were compared to participants with no history of TBI. Change in MBI symptom severity over time in participants with and without TBI history was evaluated using linear mixed-effects modeling including fixed effects of baseline MBI symptom severity, age at initial visit, sex, race, years of education, and type of dementia diagnosis, as well as fixed and random effects of time, TBI history status, and the interaction of TBI status and time. Threshold for statistical significance for all tests was set a priori as $\alpha = 0.05$.

3 | RESULTS

3.1 | Participant characteristics

After application of inclusion/exclusion criteria, $N = 946$ participants, comprising 124 with history of TBI (57 with LOC < 5 minutes, 22 with

TABLE 1 Characteristics and demographics of participants with history of TBI compared to those without history of TBI

Characteristic	TBI cohort ($n = 124$)	No TBI cohort ($n = 822$)	Statistic	*P*-value
Age at initial visit (SD)	76.45 (8.91)	77.52 (9.15)	$t(162.91) = 1.244$	0.216
Age at dementia diagnosis (SD)	82.43 (9.30)	82.92 (9.72)	$t(166.22) = 0.545$	0.587
Sex (% female)	68 (53.1%)	512 (62.3%)	$X^2(1, N = 946) = 2.216$	0.137
Number of evaluations (SD)	**8.15 (2.96)**	**7.33 (2.75)**	**$t(156.66) = -2.894$**	**0.004**
Follow-up time in years (SD)	**8.40 (3.11)**	**7.47 (2.97)**	**$t(158.53) = -3.128$**	**0.002**
Race (%)			$X^2(5, N = 946) = 5.673$	0.339
White	110 (88.7%)	699 (85.5%)		
Black/African American	11 (8.9%)	105 (12.8%)		
Native American	0 (0.0%)	2 (0.2%)		
Native Hawaiian/Other Pacific Islander	0 (0.0%)	0 (0.0%)		
Asian	3 (2.4%)	7 (0.9%)		
Other	0 (0.0%)	5 (0.6%)		
Years of education (SD)	15.93 (8.05)	15.87 (8.22)	$t(172.82) = -0.076$	0.939
Clinical diagnosis (%)			$X^2(10, N = 946) = 16.761$	0.080
Alzheimer's disease dementia	82 (66.1%)	604 (73.5%)		
Dementia with Lewy bodies	7 (5.6%)	28 (3.4%)		
Parkinson's disease	5 (4.0%)	46 (5.6%)		
Frontal temporal dementia	3 (2.4%)	17 (2.1%)		
Vascular dementia	1 (0.8%)	4 (0.5%)		
Prion disease	0 (0.0%)	1 (0.1%)		
Hydrocephalus	3 (2.4%)	4 (0.5%)		
Unknown cause/other	23 (18.5%)	100 (12.2%)		
APOE status (%)			$X^2(6, N = 946) = 6.383$	0.520
$\varepsilon3, \varepsilon3$	51 (41.1%)	396 (48.2%)		
$\varepsilon3, \varepsilon4$	42 (33.9%)	232 (28.2%)		
$\varepsilon3, \varepsilon2$	11 (8.9%)	86 (10.5%)		
$\varepsilon4, \varepsilon4$	5 (4.0%)	36 (4.4%)		
$\varepsilon4, \varepsilon2$	5 (4.0%)	16 (1.9%)		
$\varepsilon2, \varepsilon2$	0 (0.0%)	2 (0.2%)		
Missing/unknown/not assessed	10 (8.1%)	54 (6.6%)		
NPI-Q score at initial visit (SD)	1.74 (3.23)	1.62 (3.01)	$t(131.34) = -0.377$	0.707
NPI-Q score at dementia diagnosis (SD)	4.37 (4.34)	3.96 (4.30)	$t(142.28) = -0.935$	0.351

Note: Differences significant at the $P<0.05$ level are denoted in bold.
Abbreviations: *APOE*, apolipoprotein E; NPI-Q, Neuropsychiatric Inventory Questionnaire; SD, standard deviation; TBI, traumatic brain injury.

LOC > 5 minutes, 45 unknown severity) at study enrollment and 822 without, were included for final analysis (Table 1). Participants were followed for a mean of 7.6 years (standard deviation = 3.0; range = 1.0, 13.4). Figure 1 describes application of inclusion/exclusion criteria. Those with and without history of TBI did not differ in age at initial evaluation, type of dementia diagnosis, sex, race, years of education, or ADRC at which assessments occurred.

3.2 | Pre-dementia MBI

In unadjusted logistic regression modeling, TBI was associated with greater odds of impulse dyscontrol (odds ratio [OR] = 1.614; 95% confidence interval [CI] = 1.031, 2.528; $P = 0.037$) and social inappropriateness (OR = 2.374; 95% CI = 1.035, 5.444; $P = 0.041$) prior to dementia onset (Table 2); however, this was not statistically significant

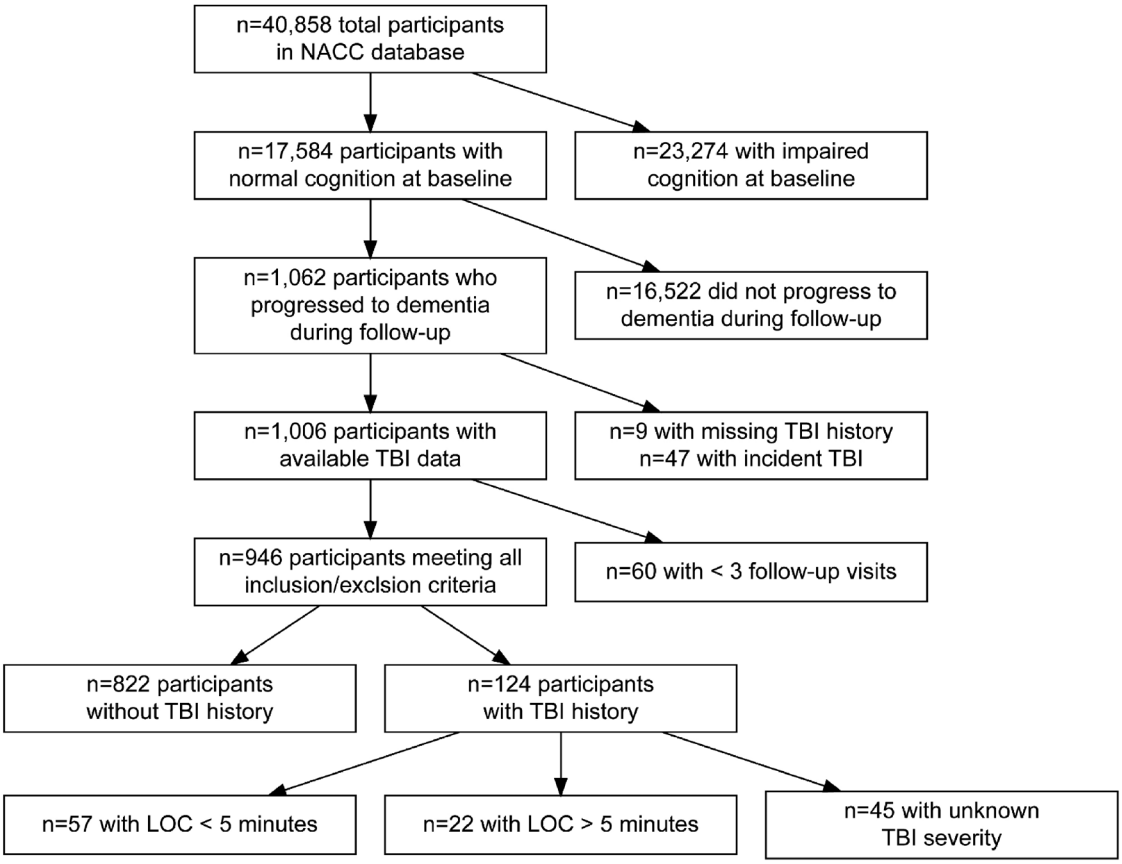

FIGURE 1 Application of inclusion/exclusion criteria and allocation of participants into exposure (TBI history present) and control (TBI history absent) cohorts. LOC, loss of consciousness; NACC, National Alzheimer's Coordinating Center; TBI, traumatic brain injury

in adjusted models. Looking at TBI severity, LOC < 5 minutes and > 5 minutes were both associated with greater odds of decreased motivation (OR = 1.946; 95% CI = 1.005, 3.769; $P = 0.048$ and OR = 2.724; OR = 1.085, 6.841; $P = 0.033$, respectively) prior to dementia onset, though not statistically significant in adjusted models. LOC > 5 minutes was associated with social inappropriateness in both unadjusted (OR = 3.989; 95% CI = 1.286, 12.371; $P = 0.017$) and adjusted ($OR_{adj.} = 4.034$; 95% CI = 1.206, 13.493; $P = 0.024$) models (Table 2).

3.3 | Survival analyses and MBI severity

Examining MBI (any domain) across all time points (including pre- and post-dementia diagnosis) using survival analysis, prevalence was greater in the TBI group in the unadjusted Cox model (hazard ratio [HR] = 1.270; 95% CI = 1.006, 1.603; $P = 0.044$) (Figure 2). Regarding specific MBI domains, decreased motivation and impulse dyscontrol were more prevalent in the TBI group in unadjusted Cox modeling (HR = 1.734; 95% CI = 1.240, 2.425; $P = 0.001$ and HR = 1.372; 95% CI = 1.040, 1.811; $P = 0.025$, respectively; Figure 2; Table 3). In the adjusted models, only decreased motivation was associated with TBI (adjusted HR [$HR_{adj.}$] = 1.546; 95% CI = 1.092, 2.188; $P = 0.014$; Table 3).

Evaluating TBI severity, greater prevalence of decreased motivation was associated with both LOC < 5 minutes and LOC > 5 minutes in unadjusted (HR = 1.689; 95% CI = 1.063, 2.683); $P = 0.026$ and HR = 2.244; 95% CI = 1.220, 4.127; $P = 0.009$, respectively) and adjusted ($HR_{adj.} = 1.643$; 95% CI = 1.032, 2.618; $P = 0.037$ and $HR_{adj.} = 2.048$; 95% CI = 1.100, 3.814; $P = 0.024$, respectively) models. Greater prevalence of abnormal perceptions/thought content was associated with LOC > 5 minutes in both unadjusted (HR = 3.010; 95% CI = 1.215, 7.458; $P = 0.017$) and adjusted ($HR_{adj.} = 3.703$; 95% CI = 1.470, 9.330; $P = 0.005$) models (Figure 3; Table 3). There were no significant differences in time at onset for any MBI domains (Figure S1; Table S2 in supporting information).

On mixed-effects linear regression, no significant effects of TBI or interaction effects of TBI and time were found in unadjusted or adjusted models of MBI severity (Table S1 in supporting information).

4 | DISCUSSION

This study analyzed a large national database to examine associations between TBI and clinical presentation of MBI domains throughout all-cause dementia progression. Examining MBI domains prior to dementia onset only, TBI with LOC > 5 minutes was associated with the social inappropriateness domain. Looking throughout dementia progression (both pre- and post-dementia diagnosis), decreased motivation was more prevalent among participants with TBI (including TBI with LOC

TABLE 2 Odds of MCI/MBI onset *prior* to dementia onset

Cognitive/MBI domain	TBI severity	OR	95% CI	*P*-value	Adj. OR	Adj. 95% CI	*P*-value
Cognitive impairment	All	1.050	(0.627, 1.756)	0.854	0.968	(0.555, 1.686)	0.908
	LOC < 5 min	**2.304**	**(1.030, 2.304)**	**0.042**	**2.887**	**(1.152, 7.235)**	**0.024**
	LOC > 5 min	1.975	(0.528, 7.380)	0.312	2.155	(0.475, 9.773)	0.319
Abnormal perception or thought content	All	2.233	(0.602, 8.287)	0.230	2.060	(0.485, 8.743)	0.327
	LOC < 5 min	1.198	(0.275, 5.215)	0.809	1.261	(0.273, 5.829)	0.767
	LOC > 5 min	1.569	(0.202, 12.173)	0.666	1.001	(0.108, 9.265)	1.000
Affective dysregulation	All	0.984	(0.622, 1.556)	0.943	1.066	(0.653, 1.739)	0.799
	LOC < 5 min	0.941	(0.525, 1.688)	0.839	0.893	(0.486, 1.640)	0.714
	LOC > 5 min	1.132	(0.477, 2.683)	0.779	1.182	(0.476, 2.937)	0.718
Decreased motivation	All	1.289	(0.667, 2.493)	0.450	1.101	(0.541, 2.241)	0.790
	LOC < 5 min	**1.946**	**(1.005, 3.769)**	**0.048**	1.721	(0.866, 3.423)	0.121
	LOC > 5 min	**2.724**	**(1.085, 6.841)**	**0.033**	2.233	(0.848, 5.881)	0.104
Impulse dyscontrol	**All**	**1.614**	**(1.031, 2.528)**	**0.037**	1.509	(0.938, 2.429)	0.090
	LOC < 5 min	1.386	(0.775, 2.477)	0.271	1.290	(0.704, 2.364)	0.409
	LOC > 5 min	2.016	(0.844, 4.816)	0.115	1.728	(0.685, 4.358)	0.247
Social inappropriateness	**All**	**2.374**	**(1.035, 5.444)**	**0.041**	2.273	(0.929, 5.562)	0.072
	LOC < 5 min	1.304	(0.451, 3.774)	0.624	1.239	(0.419, 3.662)	0.698
	LOC > 5 min	**3.989**	**(1.286, 12.371)**	**0.017**	**4.034**	**(1.206, 13.493)**	**0.024**
MBI (any domain)	All	1.315	(0.869, 1.992)	0.195	1.370	(0.880, 2.131)	0.163
	LOC < 5 min	1.187	(0.664, 2.121)	0.563	1.109	(0.604, 2.033)	0.739
	LOC > 5 min	2.292	(0.887, 5.924)	0.087	2.482	(0.899, 6.856)	0.079

Note: Results of logistic regression are presented with unadjusted odds ratios for incidence of cognitive impairment/MBI in participants with TBI history (all severities), TBI with LOC < 5 minutes, and TBI with LOC > 5 minutes compared to those without TBI history. Adjusted odds ratios are presented including age, sex, race, type of dementia diagnosis, and years of education as covariates. Differences significant at the $P < 0.05$ level are denoted in bold.
Abbreviations: Adj., adjusted; CI, confidence interval; LOC, loss of consciousness; MBI, mild behavioral impairment; MCI, mild cognitive impairment; OR, odds ratio; TBI, traumatic brain injury.

< 5 minutes, LOC > 5 minutes, and the larger mixed-severity cohort) in the adjusted model, but impulse dyscontrol and social inappropriateness were not, despite significance of impulse dyscontrol in the univariate model. Interestingly, the abnormal perception/thought content domain was associated with more severe TBI (LOC > 5 minutes) in both univariate and adjusted models.

While, prior to dementia diagnosis, social inappropriateness was associated with LOC > 5 minutes, this was not observed in analyses incorporating the entirety of dementia progression. This earlier presentation of social inappropriateness may be explained by differing vulnerability of patients with more severe TBI to early neurodegenerative change in orbitomedial-frontal circuits, which are particularly vulnerable to damage in TBI and produce deficits in social cognition and disinhibition when lesioned.[17] Of note, disinhibition (as measured by the NPI-Q) has similarly been associated with atrophy in the orbitofrontal cortex in the context of dementia[34] and a previous study found lifetime TBI history (any severity with LOC) to be associated with an increased risk of disinhibition (a component NPS of the social inappropriateness MBI domain).[12] Notably, that study bore a shorter follow-up period, reporting outcomes 1.9 years after dementia diagnosis—earlier than the intersection of cumulative incidence curves noted here (Figure 2) and therefore may be consistent with this investigation. Loss of significance in late dementia may possibly indicate masking of disinhibited tendencies by other progressive symptoms such as abulia.

Looking across dementia progression, TBI of all severities was associated with decreased motivation in univariate and adjusted models. However, odds of decreased motivation prior to dementia onset were increased in the unadjusted model only. While this null finding preceding diagnosis may indicate more substantial decrements in later-stage dementia, it should also be considered that this may result from inadequate statistical power (particularly regarding participants with LOC > 5 minutes) or limitations of the TBI screening tool, as found in another study (which demonstrated poor sensitivity but good specificity).[35] Considering this, erroneous inclusion of participants with TBI history in the non-TBI cohort may artificially inflate means and confidence intervals of the control group, increasing risk of type II but not type I error. TBI has been associated with structural and functional decrements in the anterior cingulate cortex, which may progress and persist during the chronic phases of injury.[36–38] Subsequently, the association between TBI and decreased motivation may potentially indicate disruption of the underlying neural circuits mediating

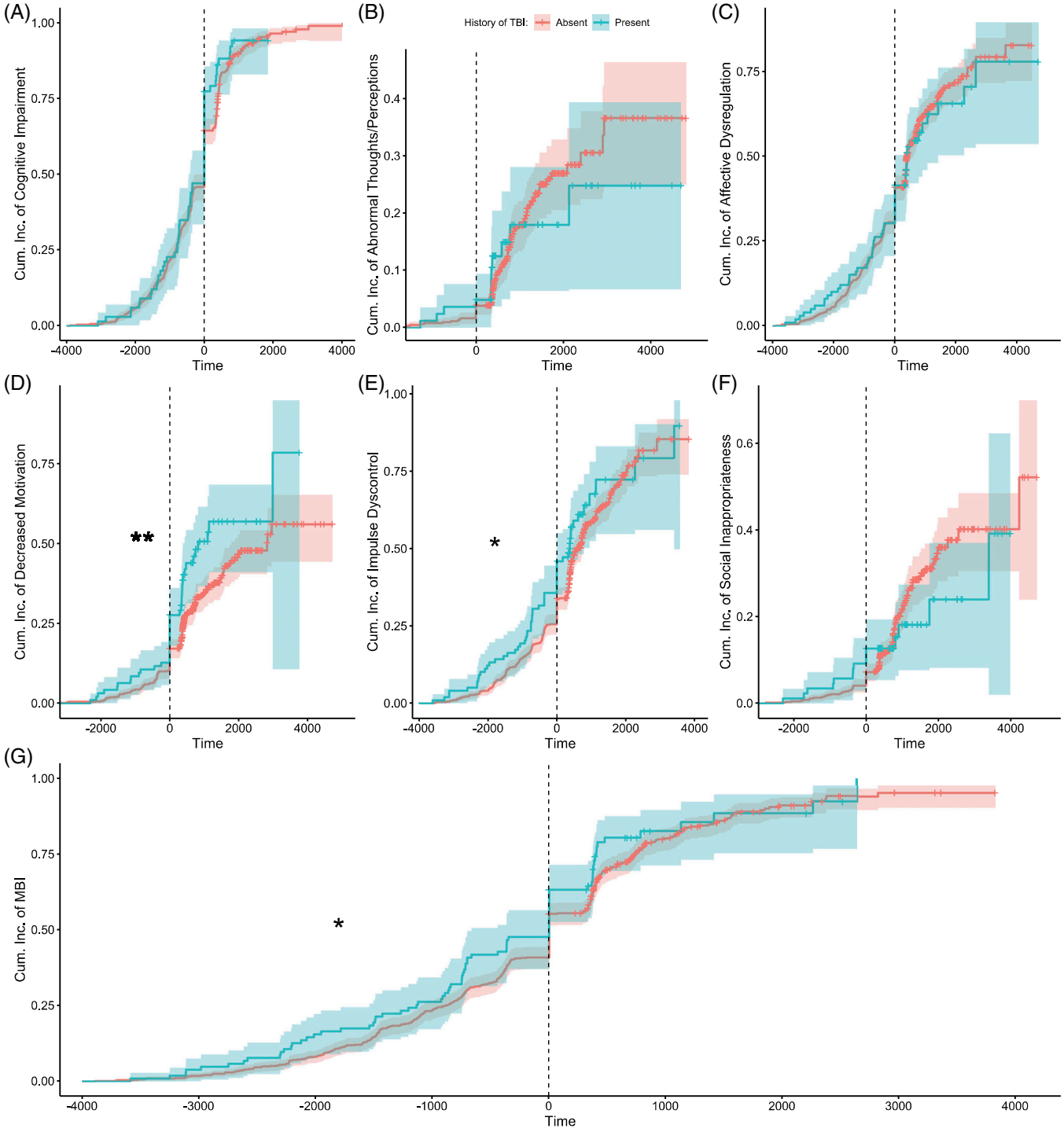

FIGURE 2 Cumulative incidence plots comparing development of cognitive impairment and MBI in participants with history of TBI (teal) and participants without TBI history (pink) regarding (A) cognitive impairment, (B) abnormal thoughts/perceptions, (C) affective dysregulation, (D) decreased motivation, (E) impulse dyscontrol, (F) social inappropriateness, and (G) MBI (any domain). Time at dementia diagnosis (time = 0) is indicated by the dashed line. Cum. Inc., cumulative incidence; MBI, mild behavioral impairment; TBI, traumatic brain injury. $^{*}P < 0.05$; $^{**}P < 0.01$

motivation, such as the anterior cingulate circuit,[39,40] warranting prospective study.

Delineating risk of decreased motivation is clinically important in this population, as apathy is both under-recognized and under-treated in the context of dementia.[41] Relevantly, decreased motivation in this patient population is frequently be mistaken for depression.[42] However, pharmacologic management differs between depression and decreased motivation, with first-line antidepressants like selective serotonin reuptake inhibitors potentially worsening outcomes.[42–45] Characterization of decreased motivation risk may lead to better

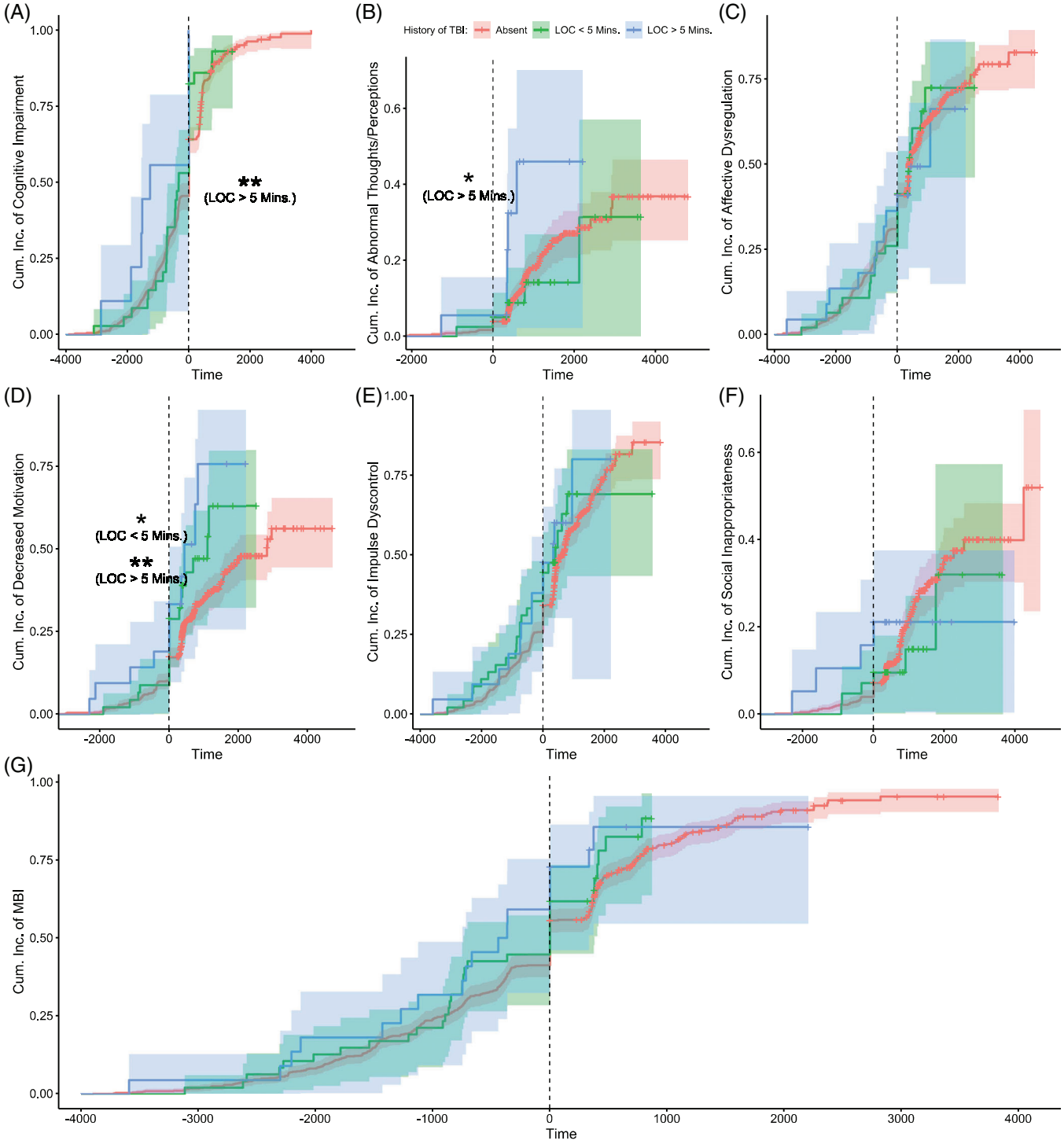

FIGURE 3 Cumulative incidence plots comparing development of cognitive impairment and mild behavioral impairment in participants with history of TBI with < 5 minutes LOC (green) and TBI with LOC > 5 minutes (blue) compared to participants without TBI history (pink) regarding (A) cognitive impairment, (B) abnormal thoughts/perceptions, (C) affective dysregulation, (D) decreased motivation, (E) impulse dyscontrol, (F) social inappropriateness, and (G) mild behavioral impairment (any domain). Time at dementia diagnosis (time = 0) is indicated by the dashed line. Cum. Inc., cumulative incidence; LOC, loss of consciousness; MBI, mild behavioral impairment; Mins., minutes; TBI, traumatic brain injury. $^{*}P < 0.05$; $^{**}P < 0.01$.

TABLE 3 Risk of developing MCI/MBI *across* the time-course of dementia progression

Cognitive/MBI domain	TBI severity	HR	95% CI	*P*-value	Adj. HR	Adj. 95% CI	*P*-value
Cognitive impairment	All	1.090	(0.832, 1.428)	0.534	1.033	(0.734, 1.275)	0.816
	LOC < 5 min	1.269	(0.881, 1.829)	0.202	1.185	(0.821, 1.711)	0.364
	LOC > 5 min	**2.440**	**(1.257, 4.737)**	**0.008**	**2.327**	**(1.197, 4.521)**	**0.008**
Abnormal perception or thought content	All	0.997	(0.530, 1.874)	0.992	1.202	(0.625, 2.312)	0.582
	LOC < 5 min	0.844	(0.342, 2.086)	0.714	0.921	(0.372, 2.285)	0.860
	LOC > 5 min	**3.010**	**(1.215, 7.458)**	**0.017**	**3.703**	**(1.470, 9.330)**	**0.005**
Affective dysregulation	All	1.002	(0.755, 1.330)	0.988	0.827	(0.619, 1.104)	0.197
	LOC < 5 min	1.039	(0.698, 1.547)	0.851	1.082	(0.726, 1.613)	0.697
	LOC > 5 min	0.927	(0.509, 1.689)	0.804	1.015	(0.553, 1.861)	0.962
Decreased motivation	**All**	**1.734**	**(1.240, 2.425)**	**0.001**	**1.546**	**(1.092, 2.188)**	**0.014**
	LOC < 5 min	**1.689**	**(1.063, 2.683)**	**0.026**	**1.643**	**(1.032, 2.618)**	**0.037**
	LOC > 5 min	**2.244**	**(1.220, 4.127)**	**0.009**	**2.048**	**(1.100, 3.814)**	**0.024**
Impulse dyscontrol	**All**	**1.372**	**(1.040, 1.811)**	**0.025**	1.045	(0.787, 1.388)	0.762
	LOC < 5 min	1.289	(0.858, 1.936)	0.221	1.269	(0.844, 1.908)	0.253
	LOC > 5 min	1.418	(0.815, 2.468)	0.217	1.261	(0.719, 2.211)	0.418
Social inappropriateness	All	0.946	(0.550, 1.627)	0.841	0.819	(0.471, 1.425)	0.479
	LOC < 5 min	0.753	(0.331, 1.717)	0.500	0.754	(0.330, 1.726)	0.504
	LOC > 5 min	1.304	(0.480, 3.542)	0.603	1.224	(0.445, 3.366)	0.695
MBI (any domain)	**All**	**1.270**	**(1.006, 1.603)**	**0.044**	1.063	(0.838, 1.347)	0.615
	LOC < 5 min	1.209	(0.858, 1.704)	0.278	1.231	(0.872, 1.737)	0.238
	LOC > 5 min	1.442	(0.901, 2.308)	0.127	1.487	(0.921, 2.400)	0.105

Note: Cox proportional hazard models are presented comparing participants with history of TBI to those without, with unadjusted hazard ratios and hazard ratios adjusted for age, sex, race, type of dementia diagnosis, and years of education. Differences significant at the $P<0.05$ level are denoted in bold.
Abbreviations: Adj., adjusted; CI, confidence interval; HR, hazard ratio; LOC, loss of consciousness; MBI, mild behavioral impairment; MCI, mild cognitive impairment; TBI, traumatic brain injury.

detection, treatment, and clinical outcomes for aging TBI survivors experiencing symptoms within this MBI domain.

Last, TBI with extended LOC (> 5 minutes) was associated with an increased prevalence of the abnormal perceptions/thought content MBI domain. This domain broadly encompasses NPS associated with positive psychotic symptoms. Interestingly, emerging literature has suggested that, in the chronic stages of moderate–severe TBI, progressive hippocampal atrophy may dysregulate amplitude of dopaminergic firing in mesolimbic circuits, increasing risk of positive psychotic symptoms in the years post-injury.[19,46] After moderate–severe TBI, hippocampal volumetric decrements have been observed and may continue to progress for years after the injury event.[47,48] In the context of dementia, TBI may introduce vulnerabilities to hippocampal neurodegeneration, such as vascular dysfunction,[49] thereby increasing risk of these NPS by similar mechanisms as have been proposed outside the context of dementia (see Bray et al.[19] and Grace[46]). The present study found that risk of this MBI domain was increased solely in the more severe group and that increased risk appeared to be more pronounced later in dementia progression; while these are in line with this possible explanation, evidence in support of this proposed mechanism is preliminary and further study is required. Furthermore, these results should be interpreted conservatively given the small sample size of the more severe TBI cohort.

The incorporation of MBI domains in the present study has the added novelty of grouping NPS by underlying network dysfunction. By informing future prospective investigation, these data may help elucidate long-term effects of TBI, including localized vulnerability to neurodegeneration as well as subsequent behavioral consequences, with implications for early detection of NPS, prognostication for aging TBI survivors, and clinical management. Through further research, this network-based approach to behavioral dysfunction in TBI and dementia may create opportunities for therapies targeted to specific networks, such as neuromodulation[50–52] and cognitive rehabilitative therapies.[53,54]

Interpretation of these results should consider certain limitations. First, TBI status was determined using a brief self-report tool which, despite high consistency of responses between assessments, may introduce recall bias and has lower sensitivity (50%) than other, more detailed assessments (despite adequate 90% specificity).[35,55] Thus, this may increase risk of type II but not type I error due to misallocation of TBI participants to the control group and falsely reduced between-group differences, warranting conservative interpretation of null findings. Further, it was not possible to stratify TBI exposure by number of injuries, chronicity, or mechanism due to the lack of available data in the NACC-UDS. This sample was limited regarding racial and ethnic diversity and therefore findings may not be

universally generalizable. The NPI-Q was used to determine MBI status and domain frequency, which may confer some limitations, notwithstanding incorporation of consecutive visit scores to increase specificity. Some aspects of MBI as captured by the MBI checklist (MBI-C)[22] are not described in the NPI-Q, potentially causing lower sensitivity, particularly for the motivation and social inappropriateness domains which include fewer NPI-Q NPS per domain. Future studies incorporating the MBI-C may address these limitations. Additionally, controlling for type of dementia diagnosis may be overly conservative, given the possibility that TBI may contribute to dementia misdiagnosis through altered behavioral phenotypes. This may increase risk of type II error and therefore conservative interpretation of null findings is warranted as well. Furthermore, it was not possible to evaluate whether participants had stable MBI prior to study enrolment. Thus, pre-existing MBI secondary to chronic post-TBI deficits could not be differentiated from incident MBI secondary to neurodegeneration. Future prospective studies should take concerted steps during baseline evaluation to allow accurate differentiation of these, addressing this limitation.

While the operationalization of cognitive impairment using the MMSE cut-off described has been shown to have high specificity and sensitivity for MCI in comparable populations,[26] this approach warrants conservative interpretation. For the purpose of this investigation, this cut-off likely provides adequate sensitivity to appreciate timelines of cognitive change within this sample and subsequently juxtapose timelines of behavioral change. This study was also limited by the number of participants with TBI history (particularly regarding those with more severe TBI). Additionally, participants with missing TBI data after the initial visit were included in analyses and therefore, the likely small number of individuals suffering unrecorded incident TBI during the study period may introduce some error. Last, specific directional hypotheses were made a priori for all statistical analyses and as such no corrections for multiple comparisons were made in line with the current statistical literature.[56] However, some increased potential for type I error should be considered given the separate analyses conducted in this investigation warranting conservative interpretation.

5 | CONCLUSION

Using a large national database examining older participants pre- and post-dementia onset, prior TBI was associated with social inappropriateness, decreased motivation, and abnormal perceptions/thought content MBI domains. This suggests that MBI domains may be useful, circuit-oriented indicators of behavioral disturbance throughout the course of dementia, rather than only preceding dementia diagnosis. Though necessitating further study, these findings suggest an altered clinical course and potentially altered underlying neurological vulnerabilities in TBI patients. These findings provide novel insight into TBI's impact on the development of behavioral symptoms in dementia, with the potential to improve surveillance, detection, and treatment of detrimental NPS.

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

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