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Neurological and neuropsychiatric disorders affecting military personnel and veterans

Edited by
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Neurological and neuropsychiatric disorders affecting military personnel and veterans

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Editorial: Neurological and neuropsychiatric disorders affecting military personnel and veterans

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Editorial on the Research Topic
Neurological and neuropsychiatric disorders affecting military personnel and veterans

Active Service Members (SM) and Veterans of the military face unique neurologic and neuropsychiatric challenges unique to this population compared to the public. SMs and Veteran populations have faced traumatic experiences that lead to both physical and mental consequences. Amongst the important challenges unique to this population include traumatic brain injury (TBI), increased risk of neurological disorders such as dementia and stroke, and comorbid neuropsychiatric conditions. Unfortunately, many of these challenges also have a negative feedback loop such as brain injuries leading to post-traumatic stress disorder (PTSD), which can increase risk of Alzheimer's Dementia. Currently, there are many gaps in the diagnosis, prevention, and treatment of conditions that affect this population disproportionately. There are many opportunities to improve our understanding of these challenges that SMs and Veterans face. The goal of this Research Topic was to shine a light and improve understanding of these challenges. We aimed to collect knowledge from a global network of researchers working on this special Research Topic.

Neurotrauma

Behavioral dyscontrol is a common sequela of TBI, even when severity is mild (mTBI), and can lead to community reintegration problems and increase risk for suicide. Stromberg et al. examined associations among PTSD symptom severity, deployment-related history of mTBI, and behavioral dyscontrol among SMs and Veterans. Findings showed that SMs and Veterans with PTSD and reduced social support systems are at greatest risk for behavioral dyscontrol. Higher self-efficacy was found to have a protective effect. Findings inform clinical screening strategies and show the need to monitor for behavioral dyscontrol difficulties after mild TBI even in the chronic stages.

The relationship between TBI, its acute and chronic symptoms, and the potential for remote neurodegenerative disease is a priority for military research. Structural and functional connectivity (FC) of the basal ganglia, involved in walking, are altered after TBI. Newsome et al. measured the FC from caudate and pallidum in SMs and Veterans with a history of deployment-related mTBI and their gait. When evaluating the association between FC from the caudate and gait, the non-deployment mTBI group showed a significant positive relationship between walking time and FC with the frontal pole, implicated in navigational planning. Their findings have implications for elucidating subtle motor disruption in SMs and Veterans with mTBI.

van der Veen et al. studied the influence of mTBI history on the relation between balance, gait and sensory function among Veterans and SMs with combat exposure. When sensory systems (vision, vestibular or proprioception) were compromised, the number of mTBIs sustained were associated with lower scores on the Computerized Dynamic Posturography balance assessment. Their findings indicate that processing of sensory information from the vision, proprioception, or vestibular systems were affected long-term after mTBI which in turn affects balance negatively.

After a TBI, the electroencephalogram (EEG) recordings are altered and remain disordered even years after the injury. However, it is still unclear how the changes in EEG recordings relate to cognitive difficulties experienced after TBI. Franke et al. studied 340 service members and veterans, EEG recordings taken 11 years after TBI showed that power in beta and alpha frequencies reflects both injury characteristics and cognitive difficulties, while power in delta frequencies is related to cognitive functions and psychological distress associated with poor long-term outcomes after mTBI.

TBI in Post-9/11 Veterans is concerning due to known associations between TBI and dementia. To avoid potential symptom over-reporting, researchers have used the Validity-10 metric to evaluate for symptom over-reporting. Because the Validity-10 was normed on a relatively healthy sample of young men on active duty, Swan et al. used patient self-report data from the VA comprehensive TBI evaluation to identify characteristics of Veterans with symptom validity failure. The primary factors associated with symptom validity failure were multi-morbidity and polypharmacy of medications affecting the central nervous system. Their findings suggest that use of the Validity-10 to exclude participants from research may be overly restrictive in populations with multimorbidity.

Dementia and neurodegenerative diseases

There is a growing use of cannabis to self-medicate many symptoms associated with TBI such as chronic pain, headache, insomnia, and cannabinoids may regulate some processes associated with neurodegeneration, Esmaeili, Dismuke-Greer et al. examined the association of cannabis use disorder (CUD) and subsequent diagnosis of diagnoses suggesting cognitive dysfunction. This population-based study of over 1.5 million Veterans found that cognitive disorders was most common among those with CUD and TBI. However those with TBI or CUD alone were also at elevated hazard cognitive dysfunction. Esmaeili, Pogada et al. also examined costs of care for Veterans with different constellations of CUD and cognitive dysfunction. Costs of care in the first 5 years after the TBI index date suggests that costs for those with CUD and dementia tend to emerge over time. Their findings suggest that those with dementia and CUD don't receive care early but that costs of care gradually accumulate over time.

Diagnosis of frontotemporal lobe disorders (FTD) is frequently delayed due to symptoms that are common in other conditions especially behavioral disorders. Hoffman et al. examined a case series of veterans with cognitive and behavioral disorders using epidemiological, clinical, cognitive, laboratory and radiological data. Using this multimodal approach to phenotyping, the authors found distinct symptoms based on etiology for the three primary FTD presentations including 16 different subsyndromes that were characterized by initial overriding and presenting symptoms/syndromes. These distinct subgroups likely require different treatments and inform future research focusted on treating these subsyndromes. Panahi et al. used a population-based approach and natural language processing to identify subsyndromes of FTD in Post-9/11 veterans. Their approach identified a variant with a mix of language and behavioral symptoms which is not typical of FTD presentations. This study suggests that FTD presentation also has a continuum of severity of symptom distress not only across variants but also within variants and may help in identifying FTD early.

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease that affects the Veterans at a greater rate compared to their civilian counterpart. Kudritzki and Howard reviewed critical aspects of advancing disease-modifying therapies for ALS. The authors also layered the rationale and feasibility of interventions that can potentially be integrated into Veteran Healthcare Services.

Pain syndromes

The association between headache and remote mTBI is not well established, and risk factors are understudied. Walker et al. demonstrated that headache is extremely common among formerly combat-exposed military personnel and that their remote mTBI history is associated with elevated odds of headache. Blast-related mTBIs were uniquely associated with a higher degree of headache impact on daily life. The findings highlight the

ramifications of lifetime mTBI history on headache conditions in the military population.

Non-invasive brain stimulation is gaining traction as a viable tratment approach for neurological and psychiatric conditions. Charvet et al. devised a clinical trial to examine whether at home remotely supervised transcranial direct current stimulation (RS-tDCS) can alleviate the severity and number of headache days in Veterans with persistent post-traumatic headache. The RS-tDCS intervention showed significant decrease in the severity and number of headache days along with high adherence rate. Their results are promising to further advance the utility of tDCS in TBI clinics.

Giakas et al. report the first systematic review and meta-analysis connecting suicidal behavior to chronic pain conditions. The meta-analysis showed that suicidal behavior is greatest in patients with migraine and significantly elevated in back/neck pain compared to a non-pain control group. The elevated risk of suicidal behavior in both migraine and neck/back pain patients underscores the critical need for suicide prevention in Veterans that experience chronic pain.

Sleep disorders and other conditions

Sleep is a critical pillar of health which is critical to performance of military service members. Rawcliffe et al. examined sleep patterns with wearable technology and self-reported sleep satisfaction in two cohorts of British Army recruits during basic training. The majority of recruits (over 80%) reported poor sleep quality. This led to interference with performance including daytime sleepiness which may impair both cognitive and physical functioning.

Detailed cognitive testing is rarely performed in clinical trials for multiple sclerosis (MS). Relating clinically meaningful measures of MS disability to easily obtainable MRI metrics of atrophy in progressive MS populations is important for clinical research and clinical care. This study (Spain et al.) details cross-sectional structure- cognitive function relationships in a large and well-characterized progressive MS Veteran population, and further compares those relationships between secondary and primary progressive MS.

As is evident by these articles, there is complex comorbidity in veterans with neurological and neuropsychiatric conditions. Caring for individuals with complex comorbidity is frequently associated with significant burden and stress. Rattray et al., used qualitative interviews including self-report measures to examine the impact of caring for Veterans recently separated from active military service over 2 years. This study suggest that when caring for Veterans with "invisible" injuries, systems that provide support to these unpaid care partners would benefit the health and wellbeing of both the care partner and the veteran.

Conclusion

Military personnel and Veterans suffer from unique conditions and thus require unique care. The articles that comprise this special Research Topic highlight the importance of collaborative efforts needed between healthcare professionals, researchers, caregivers, and funding agencies to support the care of this important population. We hope this Research Topic demonstrates the unique challenges that military personnel and Veterans face but also offers insight into the future potential for advancements in their care.

Author contributions

CL: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—original draft, Writing—review & editing. MP: Writing—original draft, Writing—review & editing. VK: Writing—original draft, Writing—review & editing. LK: Writing—original draft, Writing—review & editing. WW: Writing—original draft, Writing—review & editing.

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Risks of suicide in migraine, non-migraine headache, back, and neck pain: a systematic review and meta-analysis

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Objective: To conduct a systematic review and meta-analysis on suicidal ideation, attempts, and death in patients with head, neck, and back pain.

Method: Search was performed using PubMed, Embase, and Web of Science from the date of the first available article through September 31, 2021. A random effects model was used to estimate the pooled odds ratios (ORs) and 95% confidence intervals (95% CI) for the association between suicidal ideation and/or attempt and head, back/neck pain conditions. Articles describing non-migraine headache disorders and death by suicide were also reviewed but not included in the meta-analysis due to an insufficient number of studies.

Results: A total of 20 studies met criteria for systemic review. A total of 186,123 migraine patients and 135,790 of neck/back pain patients from 11 studies were included in the meta-analysis. The meta-analysis showed that the estimated risk of combined suicidal ideation and attempt in migraine [OR 2.49; 95% CI: 2.15–2.89] is greater than that in back/neck pain pain [OR 2.00; 95% CI: 1.63–2.45] compared to non-pain control groups. Risk of suicide ideation/planning is 2 folds higher [OR: 2.03; 95% CI: 1.92–2.16] and risk of suicide attempt is more than 3 folds higher [OR: 3.47; 95% CI: 2.68–4.49] in migraine as compared to healthy controls.

Conclusion: There is an elevated risk of suicidal ideation and attempt in both migraine and neck/back pain patients in comparison to healthy controls, and this risk is particularly higher among migraine patients. This study underscores the critical need for suicide prevention in migraine patients.

KEYWORDS

suicide, chronic back pain, chronic neck pain, migraine, headache

1. Introduction

Chronic pain is a leading cause of disability worldwide and affects upwards of 20.4% of adults in the United States (1). Headache disorders, especially migraine, are among the most common types of chronic pain conditions encountered by neurologists and psychiatrists. Migraine has a global negative impact on overall quality of life, cognitive, emotional health, and contributes to isolation, frustration, guilt, fear, avoidance behavior, and stigma (2). Individuals with migraine thus often learn to internalize symptoms with strict concealment, as the manifestations of migraine, as well as its degree of severity and disability, are

invisible: pain, cognitive impairment, nausea, vertigo, hypersensitivity to the environment, aura, etc. (3). Despite the prevalence and impact of migraines, 70% of migraine patients do not seek medical advice (4, 5).

Migraine has significant association with multiple mental health disorders. For example, bidirectional association exists between migraine and psychiatric disorders such as anxiety disorder, bipolar disorder, and depression (6–8). This is especially true for the military and Veteran population. In 2020, the suicide rate for Veterans was 57.3% greater than for non-Veteran U.S. adults when adjusted for demographic differences (9). Traumatic brain injury (TBI), PTSD, and depression are significant risk factors for chronic headache in Veterans (10). Veterans with chronic headache, especially those with comorbid TBI, PTSD, and depression, are at increased risk for suicidal behavior (10, 11). As such, there is a need to better understand the relationship between suicidality and head, neck, and back pain, and establishing interdisciplinary collaboration when caring for Veterans with migraine, which often go undiagnosed or not coded (12).

One cannot "split the brain"; therefore, improved understanding of increased suicide risk among headache disorders affords a unique opportunity for clinicians of various disciplines to proactively engage in dialogue to collaborate and advocate for better treatment. Currently, most of headache management is done by specialty care or primary care separately. We hope to bring awareness to the increased risk of suicide among headache disorders, which serves as an invitation for neurologists, psychiatrists, psychologists, and others involved in patient care to join the interdisciplinary care team.

Previous research has indeed associated migraines with an increased suicide risk (13, 14), but previous review and meta-analysis are lacking regarding the potential risk for suicide in both migraine and other pain disorders. There is also a lack of comprehensive review between different types of headache disorders and a spectrum of suicidal behaviors. As such, authors conducted a systematic review and meta-analysis to examine the risk of different types of suicidal behavior (i.e., ideation, attempts, and death) in patients with migraine, non-migraine headache conditions, and back/neck pain compared to healthy controls.

2. Methods

2.1. Literature search

Authors conducted the literature search using three databases (PubMed, EMBASE, and Web of Science) from the date of the first available article through September 31, 2021. Studies related to headache, back pain, or neck pain and suicide were identified using keywords "migraine AND suicide," "cluster headache AND suicide," "trigeminal autonomic cephalgia AND suicide," "post-traumatic headache AND suicide," "tension headache AND suicide," "trigeminal neuralgia AND suicide," "hemicrania continua AND suicide," "chronic back pain AND suicide," "back pain AND suicide," "lumbar pain AND suicide," "cervicalgia AND suicide," "chronic neck pain AND suicide," and "neck pain AND suicide." No other filters were used. The principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was used to further screen and filter studies. One reviewer screened studies to determine whether they meet the eligibility criteria as outlined below, and one independent reviewer confirmed that only papers that fully met these criteria were included in this study. The full text of all included studies was then examined by a third reviewer to ensure that data had been recorded accurately.

2.2. Eligibility criteria

To be included in the analysis, studies were required to meet all of the following criteria: (A) participants were adults 18 years of age or older; (B) the study defined the type of suicidal behavior being examined; (C) the study used healthy controls or controls without chronic pain conditions; (D) the study assessed the association of an individual headache disorder (migraine, cluster headache, tension headache, trigeminal autonomic cephalgia, and trigeminal neuralgia) or chronic back or neck pain with suicidal behavior or death by suicide as compared to healthy controls; (E) the study was published in the English language.

Studies were excluded if they met the following criteria: (A) inclusion of participants under 18 years of age; (B) published in the form of conference abstracts/posters, editorials, guidelines, or reviews; (C) insufficient data, such as raw data, mean or *p*-value; (D) lack of a healthy control group; (E) patients with chronic pain included in the control group.

2.3. Data collection and analysis

Data were extracted by the same researcher from each article and included the following items: year, population of interest, ICD codes and/or method of defining chronic pain, statistical method, sample size of the chronic pain and healthy control groups, odds ratio of risk of suicide in pain group compared to healthy control group, and confidence intervals. Unadjusted ORs were used due to inter-study variance in controlled factors. Authors used Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ, USA) to generate summary statistics and pooled adjusted ORs using a random effects model, as stratified by the suicidal behavior (suicide ideation, suicide attempt) and pain types (migraine, chronic neck/back pain).

3. Results

Initial search yielded 1,763 results, which were then screened for inclusion in the review and meta-analysis (Figure 1). Twenty studies met the criteria to be included in the systematic review. Two of these studies examined cluster headache disorder (15, 16) and two examined tension-type headache (17, 18) so meta-analysis was not conducted for these specific headache disorders due to limited study numbers. Similarly, only two studies examined death by suicide as an outcome, they were not included in the meta-analysis (19, 20). The meta-analysis was therefore conducted for migraine and back/neck pain with suicidal ideation/planning or suicide attempts as outcome measures. Three additional studies were lacking specific statistics and thus were not eligible for

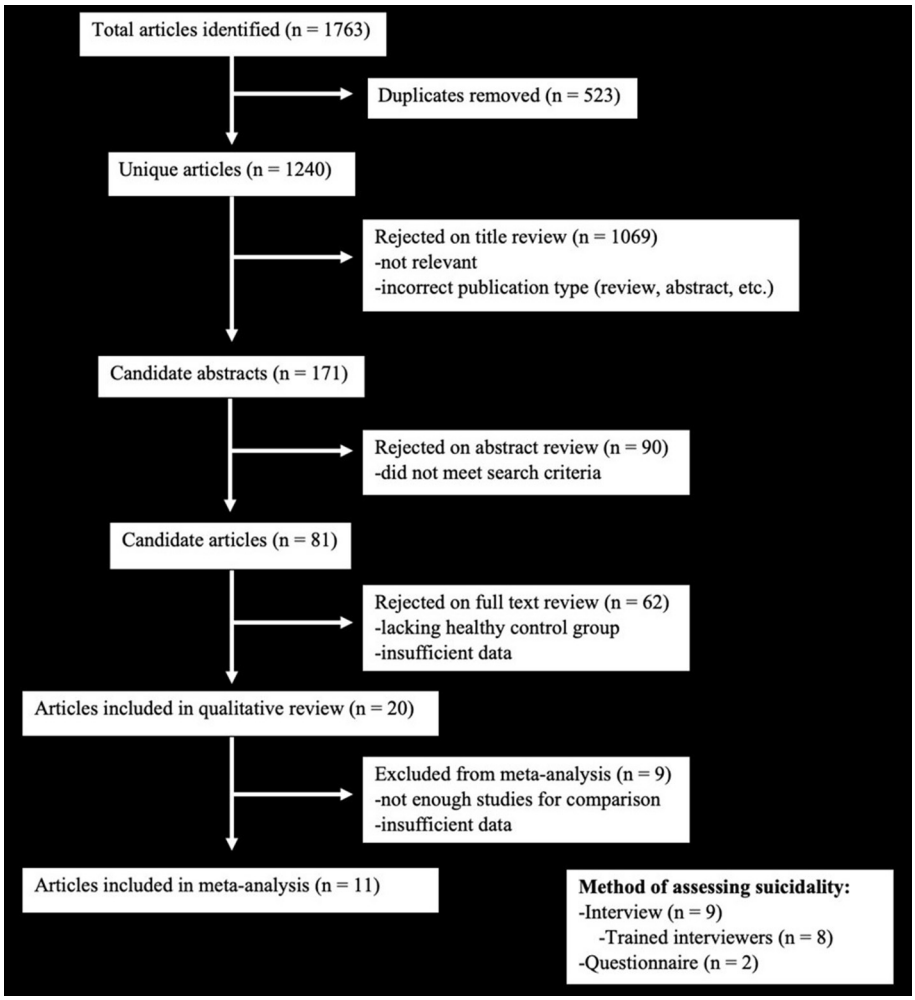


FIGURE 1
PRISMA inclusion diagram for meta-analysis, which demonstrates the process through which the studies used in the manuscript were selected from the total number of studies identified.

the meta-analysis (21–23). Therefore, a total of 11 studies were included in the meta-analysis.

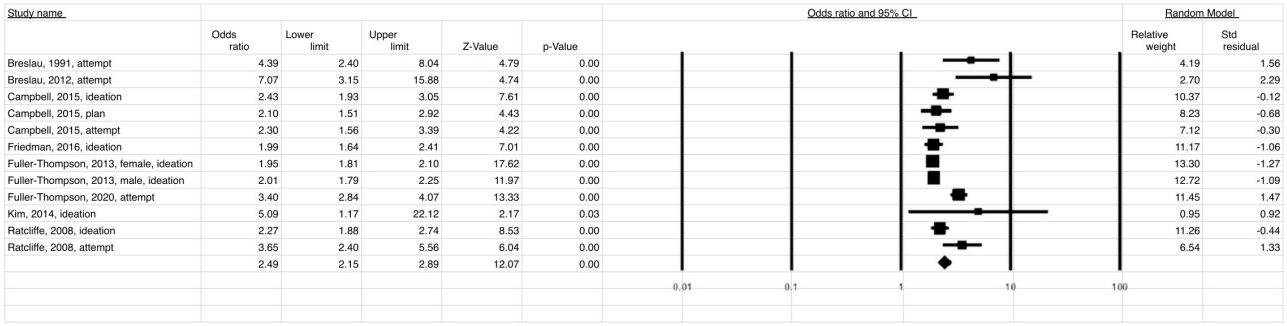
3.1. Meta-analysis results

A total of 186,123 migraine patients and 135,790 of back/neck pain patients were included in the meta-analysis. The meta-analysis showed that the estimated risk of suicidal ideation and/or attempt both in patients with migraine (OR 2.49; 95% CI: 2.15–2.89) (Figure 2) and in those with back/neck pain (OR 2.00; 95% CI: 1.63–2.45) (Figure 3) was significantly elevated when compared to healthy controls. Migraine was associated with a 2-fold higher risk of suicidal ideation/planning (OR: 2.03; 95% CI: 1.92–2.16) (Figure 4) and over three times higher risk of suicide attempt (OR: 3.47; 95% CI: 2.68–4.49) (Figure 5) when compared to controls. The odds of suicidal ideation/planning in back/neck pain were just under two times that of healthy controls (OR: 1.81; 95% CI: 1.39–2.36) (Figure 6). Chronic back/neck pain was associated with a 2.53 (95% CI: 2.05–3.12) times increased odds of suicide attempts (Figure 7), which was lower than that associated with migraine (z test, $p = 0.04$).

3.2. Reviews of studies not included in meta-analysis

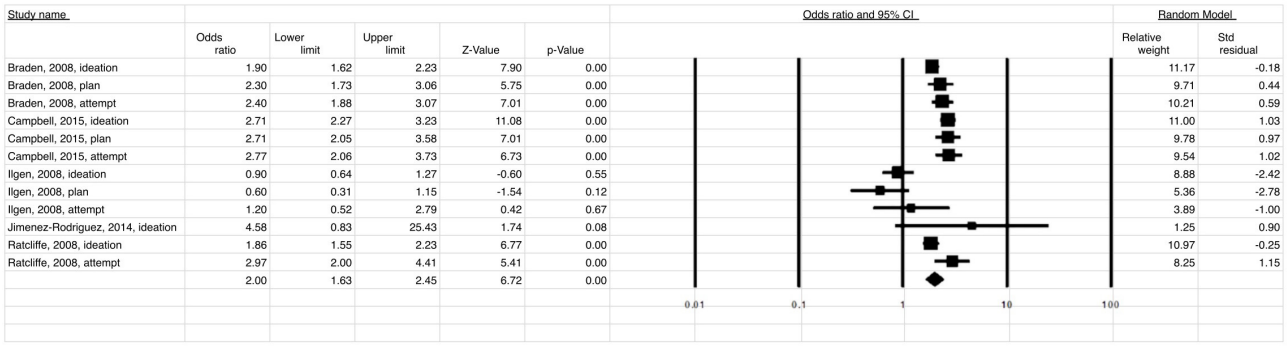
3.2.1. Death by suicide

Two studies identified in the present review examined death by suicide as an outcome measure. One study examined the association between migraine and both self-harm and suicide mortality. The authors reported an increased odds (hazard ratio = 2.18) of self-harm for those diagnosed with migraine but did not find an association between migraine and death by suicide (19). However, another study reported an increased risk of death by suicide associated with migraine (hazard ratio = 1.68), which persisted when controlling for psychiatric comorbidities (hazard ratio = 1.34) (17).



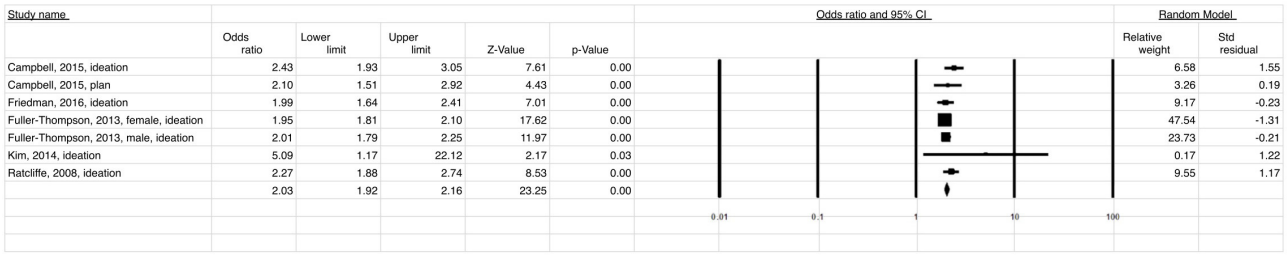
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std residual
Breslau, 1991, attempt	4.39	2.40	8.04	4.79	0.00	4.19	1.56
Breslau, 2012, attempt	7.07	3.15	15.88	4.74	0.00	2.70	2.29
Campbell, 2015, ideation	2.43	1.93	3.05	7.61	0.00	10.37	-0.12
Campbell, 2015, plan	2.10	1.51	2.92	4.43	0.00	8.23	-0.68
Campbell, 2015, attempt	2.30	1.56	3.39	4.22	0.00	7.12	-0.30
Friedman, 2016, ideation	1.99	1.64	2.41	7.01	0.00	11.17	-1.06
Fuller-Thompson, 2013, female, ideation	1.95	1.81	2.10	17.62	0.00	13.30	-1.27
Fuller-Thompson, 2013, male, ideation	2.01	1.79	2.25	11.97	0.00	12.72	-1.09
Fuller-Thompson, 2020, attempt	3.40	2.84	4.07	13.33	0.00	11.45	1.47
Kim, 2014, ideation	5.09	1.17	22.12	2.17	0.03	0.95	0.92
Ratcliffe, 2008, ideation	2.27	1.88	2.74	8.53	0.00	11.26	-0.44
Ratcliffe, 2008, attempt	3.65	2.40	5.56	6.04	0.00	6.54	1.33
	2.49	2.15	2.89	12.07	0.00		

FIGURE 2
Relationship between suicide ideation and attempt (OR = 2.49) in patients with migraine when compared to healthy controls.



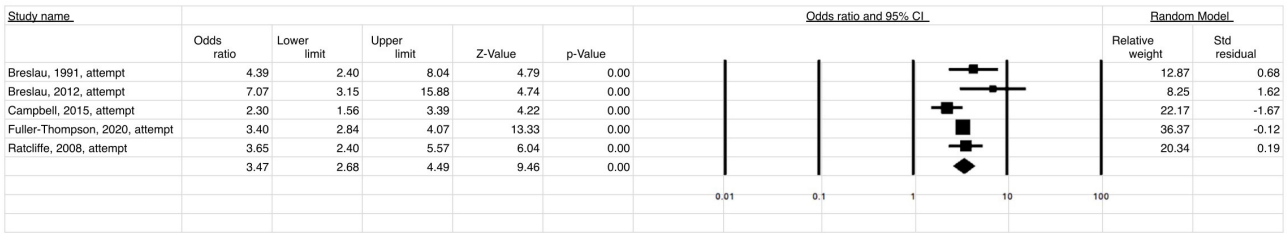
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std residual
Braden, 2008, ideation	1.90	1.62	2.23	7.90	0.00	11.17	-0.18
Braden, 2008, plan	2.30	1.73	3.06	5.75	0.00	9.71	0.44
Braden, 2008, attempt	2.40	1.88	3.07	7.01	0.00	10.21	0.59
Campbell, 2015, ideation	2.71	2.27	3.23	11.08	0.00	11.00	1.03
Campbell, 2015, plan	2.71	2.05	3.58	7.01	0.00	9.78	0.97
Campbell, 2015, attempt	2.77	2.06	3.73	6.73	0.00	9.54	1.02
Ilgen, 2008, ideation	0.90	0.64	1.27	-0.60	0.55	8.88	-2.42
Ilgen, 2008, plan	0.60	0.31	1.15	-1.54	0.12	5.36	-2.78
Ilgen, 2008, attempt	1.20	0.52	2.79	0.42	0.67	3.89	-1.00
Jimenez-Rodriguez, 2014, ideation	4.58	0.83	25.43	1.74	0.08	1.25	0.90
Ratcliffe, 2008, ideation	1.86	1.55	2.23	6.77	0.00	10.97	-0.25
Ratcliffe, 2008, attempt	2.97	2.00	4.41	5.41	0.00	8.25	1.15
	2.00	1.63	2.45	6.72	0.00		

FIGURE 3
Relationship between suicide ideation and attempt (OR = 2.00) in patients with back/neck pain when compared to healthy controls.



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std residual
Campbell, 2015, ideation	2.43	1.93	3.05	7.61	0.00	6.58	1.55
Campbell, 2015, plan	2.10	1.51	2.92	4.43	0.00	3.26	0.19
Friedman, 2016, ideation	1.99	1.64	2.41	7.01	0.00	9.17	-0.23
Fuller-Thompson, 2013, female, ideation	1.95	1.81	2.10	17.62	0.00	47.54	-1.31
Fuller-Thompson, 2013, male, ideation	2.01	1.79	2.25	11.97	0.00	23.73	-0.21
Kim, 2014, ideation	5.09	1.17	22.12	2.17	0.03	0.17	1.22
Ratcliffe, 2008, ideation	2.27	1.88	2.74	8.53	0.00	9.55	1.17
	2.03	1.92	2.16	23.25	0.00		

FIGURE 4
Relationship between the risk of suicide ideation/planning (OR = 2.03) in patients with migraine when compared to healthy controls.



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight	Std residual
Breslau, 1991, attempt	4.39	2.40	8.04	4.79	0.00	12.87	0.68
Breslau, 2012, attempt	7.07	3.15	15.88	4.74	0.00	8.25	1.62
Campbell, 2015, attempt	2.30	1.56	3.39	4.22	0.00	22.17	-1.67
Fuller-Thompson, 2020, attempt	3.40	2.84	4.07	13.33	0.00	36.37	-0.12
Ratcliffe, 2008, attempt	3.65	2.40	5.57	6.04	0.00	20.34	0.19
	3.47	2.68	4.49	9.46	0.00		

FIGURE 5
Relationship between suicide attempt (OR = 3.47) in patients with migraine when compared to healthy controls.

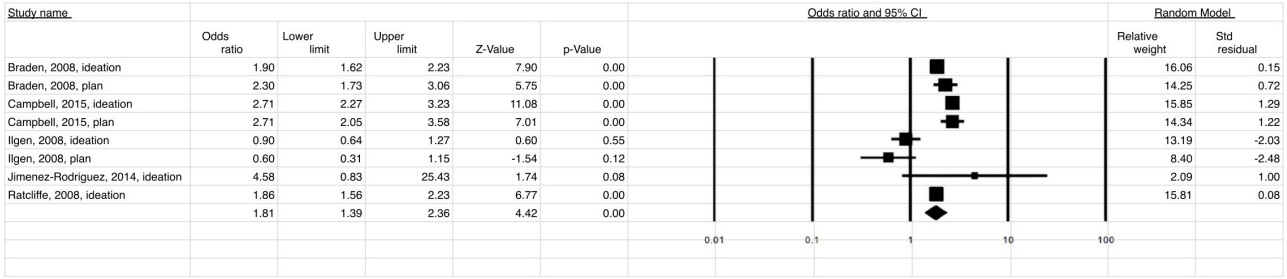


FIGURE 6
Relationship between risk of suicide ideation/planning (OR=1.81) in patients with back/neck pain when compared to healthy controls.

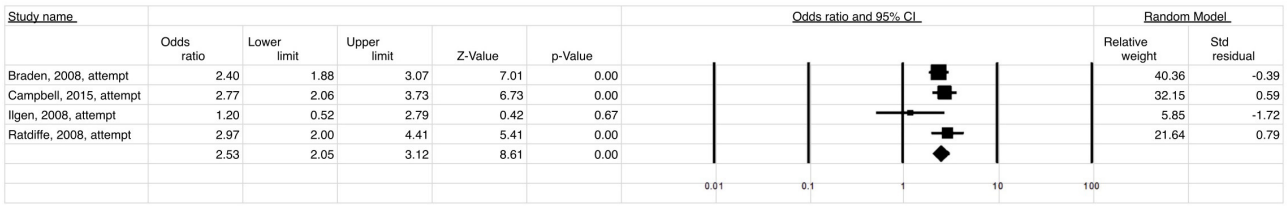


FIGURE 7
Relationship between risk of suicide attempt (OR = 2.53) in patients with chronic back/neck pain when compared to healthy controls.

3.2.2. Non-migraine headache disorders

Three studies identified in our search examined suicidality in relation to headache disorders distinct from migraine, specifically cluster headache and tension headache. Cluster headache was reported to increase the risk of suicidal ideation by 2.5 times [OR: 2.49, 95% CI: 1.91–3.25] (16) and around 2-fold [OR: 2.04, 95% CI: 1.08–3.85] (15) when compared to controls in two separate studies, even after accounting for depression and demoralization. A similar pattern was reported for tension headaches, which were associated with 2.39 times higher odds of suicidal ideation or attempt, defined as suicidal ideation and/or attempts (18). One study also reported an increased risk of death by suicide associated with headache or tension headache (hazard ratio = 1.38) (17). When distinguishing between chronic and episodic tension headache, only chronic tension headache was associated with increased suicidal ideation or attempt (18). In further comparison of headache conditions, another study reported an increased odds of suicide attempt for both migraine [OR: 7.21, 95% CI: 3.21–16.2] and non-migraine headache [OR: 8.38, 95% CI: 3.35–21.0] when compared to controls with no history of severe headache; however, there were no differences between migraine and non-migraine type headaches for odds of suicide attempts (24).

4. Discussion

This study sought to examine the risk of suicidality among patients suffering from migraine, non-migraine headache disorders, and back/neck pain. This meta-analysis demonstrates that suicidal ideation and attempts are both significantly increased among patients with migraine or back/neck pain compared to healthy controls, whereas systematic review demonstrates an increased risk of suicidality in patients with non-migraine headache disorders as well. Of note, the risk of suicide attempt in patients with migraine is statistically higher than in those with back/neck pain. The odds associated with suicide attempts in migraine were over 3-fold—the highest for any of the pain conditions and suicidal behaviors investigated in this study.

Previous literature reviews have described an increase in suicidal ideation and attempts associated with non-specific chronic pain (25–28). Our study provides additional evidence for increased risk of suicidality in patients with migraine and non-migraine headache disorders. Most importantly, our results shed light on a potentially higher risk of suicide attempt in patients with migraine than in those with back/neck pain.

It is worth noting that studies examining the association between mental health disorder diagnosis as it relates to chronic pain and suicidality reveal inconsistent results. Some studies suggested that the relationship between migraine or back/neck pain and suicidality persists when accounting for psychiatric comorbidities (24, 29–31) while others didn't find significant associations (21, 32, 33). Further discrepancies are present based on the type of suicidal behavior examined. For example, one study reported that, when controlling for mental health disorders, migraine remained associated with suicidal ideation but not planning or attempts (30), whereas another study noted a consistent association with suicidal ideation and planning but not attempts, which may be due to under diagnosis of mental health disorders (34). Regardless of the intensity of pain of migraine attacks, the frequency and duration have been found to have a strong association with the burden of psychiatric comorbidity [OR: 7.21, 95% CI: 3.21–16.2] (6).

TABLE 1 Clinical features assessed in meta-analysis articles.

References	Method	Diagnostic criteria of pain condition	Frequency/ chronicity of pain	Trained interviewer	Suicidality assessment details
Braden and Sullivan (33)	In-person interview for all questions other than suicidality. Suicidality questions were asked in a self-administered booklet rather than interview	Self-reported endorsement of: arthritis/ rheumatism, chronic back or neck problems, frequent or severe headaches, or "other" chronic pain	Frequency: not specified Chronicity: lifetime and in the past 12 months	Yes	Stand-alone questions regarding if they had "ever seriously thought about committing suicide, made a plan for committing suicide, or attempted suicide"
Breslau et al. (40)	In-person interview	Criteria adapted from the 1988 Headache Classification Committee of the International Headache Society diagnostic criteria for migraine	Frequency: at least 5 occurrences for classification of migraine Chronicity: lifetime prevalence	Unspecified	Single question on suicide attempts from National Institute of Mental Health's Diagnostic Interview Schedule
Breslau et al. (24)	In-person interview	Migraine: features from the ICHD-2 criteria Non-migraine severe headache: duration of >4 h, no history of migraine-like features, and minimum Headache Impact Questionnaire score of 38.05	At least 1 headache in the past year	Yes	Single question on suicide attempts from World Health Organization Composite International Diagnostic Interview
Campbell et al. (30)	In-person interview	WMH-CIDI with questions pertaining to arthritis, migraines, and neck/back pain	Frequency: not specified Chronicity: pain condition persisted for 6 months	Yes	Multiple questions on suicidal behavior (ideation, plans, attempts) from WMH-CIDI
Friedman et al. (31)	In-person interview	Migraine: meeting ICHD-III beta criteria administered in a Spanish-language questionnaire Probable migraine: Meet all but one of the migraine criteria	Frequency: not specified Chronicity: not specified	Yes	Suicidal ideation item from the Patient Health Questionnaire-−9
Fuller-Thompson et al. (41)	In-person interview	Self-report of having previously been diagnosed with migraine by a health professional	Frequency: not specified Chronicity: migraine had persisted or was expected to persist for 6 months or more	Yes	One stand-alone question on suicidal ideation: "have you ever seriously considered committing suicide or taking your own life?"
Fuller-Thompson and Hodgins, (42)	In-person interview	Migraine: self-report of having previously been diagnosed with migraine by a health professional Chronic pain: self-report of usual pain or discomfort that is of moderate or severe intensity	Frequency: not specified Chronicity: migraine had persisted or was expected to persist for 6 months or more	Yes	Single question on suicide attempts asking "if they had ever "attempted suicide or tried to take (their) own life"
Ilgen et al. (17)	In-person interview	A series of yes/no questions pertaining to: arthritis or rheumatism, chronic back or neck problems, frequent or severe headaches, and any other chronic pain	Frequency: not specified Chronicity: 12-month prevalence	Yes	Stand-alone questions regarding suicidal ideation, plans, and attempts (both lifetime and in the last 12 months)
Jimenez-Rodríguez et al. (43)	Questionnaire	Constant or intermittent non-specific low back pain	Frequency: not specified Chronicity: at least the past 3 months	N/A	Suicidal ideation assessed with question 9 of the Beck Depression Inventory and risk of suicide with the Plutchik Suicide Risk Scale

(Continued)

TABLE 1 (Continued)

References	Method	Diagnostic criteria of pain condition	Frequency/ chronicity of pain	Trained interviewer	Suicidality assessment details
Kim and Park (32)	In-person interview	Revised version of the ICHD-II	Chronic migraine was defined as frequency of ≥15 headache days per month in the prior 3 months, with at least 8 days per month meeting the criteria for migraine without aura. Those not meeting this definition were included as non-chronic migraine. Migraine patients were included as a single group in the analysis, regardless of chronicity.	Yes, trained neurologist	Beck scale for suicidal ideation
Ratcliffe et al. (29)	In-person interview	Self-report of chronic pain conditions (i.e., arthritis or rheumatism, back problems, migraine headaches, fibromyalgia) previously diagnosed by a health professional	Frequency: not specified Chronicity: condition had persisted or was expected to persist for 6 months or more	Yes, professional interviewers with "additional training to increase sensitivity on mental health issues"	Stand-alone questions regarding suicidal ideation and attempts (both lifetime and in the last 12 months)

Apart from Ratcliffe et al. (29), the type of training that interviewers received was unspecified (i.e., whether training was general to interview administration or specific to mental health). Although Fuller-Thomson et al. (41) and Fuller-Thompson and Hodgins (42) do not specify training type, data were obtained from the same national survey as Ratcliffe et al. (29) (i.e., the Canadian Community Health Survey), albeit from different years. ICHD, International Classification of Headache Disorders; WMH-CIDI, World Mental Health Survey Initiative version of the Composite International Diagnostic Interview.

It is imperative to note while migraine is strongly associated with elevated suicide risk, physicians should also be familiar with increased suicide risk in patients with cluster and chronic tension headaches. Very few studies examined non-migraine type headache disorders, and thus were not included in the meta-analysis. However, upon systematic review, the odds of self-inflicted injury, suicidal ideation and attempt, or death by suicide for cluster headache and chronic tension headache were similar to that of migraine (15–18). Cluster headaches have been linked with increased suicidal ideation, planning and attempts during attacks, which was found to predict increased suicidality in the interictal phase of cluster headache. In addition, longer disease burden, even with episodic cluster headaches, was associated with a similar increase in suicidality, prompting the need for preventative treatment (35). These results further parallel those of another study showing the risk of suicide attempts in migraine patients was equivalent to that in non-migraine type headaches (24).

Suicide Crisis Syndrome, or SCS, is a recently described acute suicidal mental state which may link migraines and suicidal behavior (36). Several SCS criteria have symptoms overlapping with migraine (36, 37). Of note, CDC report demonstrated that only a fraction of deaths by suicide expressed ideation before their death; >75% explicitly denied suicidal ideation prior to their death (38). One of the reasons for non-disclosure of suicidal ideation is that explicit suicidal intent may last less than 10 min preceding a suicide attempt, a very short period which is likely to occur outside the clinical setting. Another reason is that suicidal individuals would not admit to their suicidal intent out of fear of being hospitalized and losing their autonomy; this is potentially more likely to occur among military personnel and Veterans. SCS, on the other hand, is diagnosed indirectly, without asking about suicidal ideation or intent, and has consistently outperformed suicidal ideation for prediction of future suicidal behavior (13–16, 39). It is worth noting that all studies reviewed used a simple yes/no question to elicit suicidal behavior (Table 1). This represents a significant void in clinical research studying associations between migraine and suicidal behavior. Using SCS checklist may be an exceedingly useful tool for identifying individuals with migraine headaches who are at imminent risk for suicide.

Despite the novelty of this study, there are some limitations. As discussed above, there were very few studies that included patients with headache disorders other than migraine, thus we were only able to include patients with migraine and back/neck pain in the meta-analysis. This lack of existing literature limits the conclusions we are able to draw pertaining to non-migraine type headache disorders and highlights an important direction for future research to allow for broader and more detailed analysis of suicidality in headache disorders. Additionally, our meta-analysis pooled results were uncontrolled for different variables, such as psychiatric comorbidities. We chose to analyze uncontrolled results because of the variability between studies in their adjusted analyses. For example, some studies controlled for diagnosed psychiatric disorders (24, 33, 40), while others controlled for self-reported depression or anxiety scores (32) and adverse childhood experiences (42).

A national cohort study in the Veterans Health Administration for fiscal year 2008–2019 found that Veterans with headache were being seen at the emergency department at the same rate as at neurology clinics and at a larger rate than headache specialists (12). In patients who died by suicide, it has been elucidated

that one-third had contact with mental health services within a year and one-fifth had contact within a month of their suicide. Additionally, about three-quarters of patients were seen by their primary care physician within a year, and about one-half of patients were seen within the month, of their suicide (39). This further demonstrates the need for increasing awareness of suicide risks among Veterans with different types of pain conditions and for collaboration between specialties within VHA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

XMA contributed to the design, interpretation of results, and drafting of the study. All authors contributed to the interpretation of results, drafting, and the revision of the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Remotely supervised at-home tDCS for veterans with persistent post-traumatic headache: a double-blind, sham-controlled randomized pilot clinical trial

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Background: Currently, there are no FDA approved therapies for persistent post-traumatic headache (PPTH) secondary to traumatic brain injury (TBI). As such neither headache nor TBI specialists have an effective means to manage PPTH. Thus, the objective of the present pilot trial was to evaluate the feasibility and preliminary efficacy of a four-week at-home remotely supervised transcranial direct current stimulation (RS-tDCS) intervention for veterans with PPTH.

Methods: Twenty-five (m=46.6±8.7years) veterans with PPTH were randomized into two groups and received either active (n=12) or sham (n=13) RS-tDCS, with anodal stimulation over left dlPFC and cathodal over occipital pole. Following a four-week baseline, participants completed 20–sessions of active or sham RS-tDCS with real-time video monitoring over a period of four-weeks. Participants were assessed again at the end of the intervention and at four-weeks post-intervention. Primary outcomes were overall adherence rate (feasibility) and change in moderate-to-severe headache days per month (efficacy). Secondary outcomes were changes in total number of headache days, and PPTH-related functional outcomes.

Results: Adherence rate was high with 88% of participants (active=10/12; sham=12/13) fully completing tDCS interventions. Importantly, there was no significant difference in adherence between active and sham groups (p=0.59). Moderate-to-severe headache days were significantly reduced within the active RS-tDCS group (p=0.004), compared to sham during treatment (–2.5±3.5 vs. 2.3±3.4), and 4-week follow-up (–3.9±6.4 vs. 1.2±6.5). Total number of headache days was significantly reduced within the active RS-tDCS (p=0.03), compared to sham during-treatment (–4.0±5.2 vs. 1.5±3.8), and 4-week follow-up (–2.1±7.2 vs. –0.2±4.4).

Conclusion: The current results indicate our RS-tDCS paradigm provides a safe and effective means for reducing the severity and number of headache days in veterans with PPTH. High treatment adherence rate and the remote nature of our paradigm indicate RS-tDCS may be a feasible means to reduce PPTH, especially for veterans with limited access to medical facilities.

Clinical Trial Registration: ClinicalTrials.gov, identifier [NCT04012853].

KEYWORDS

veterans, tDCS, mTBI, post-traumatic headache, brain injury

1. Introduction

Persistent post-traumatic headache (PPTH) is one of the most common types of chronic pain conditions experienced among veterans with traumatic brain injury (TBI) (1, 2). PPTH is characterized as a chronic headache disorder lasting more than three months and is 1) a secondary headache disorder that develops or 2) a worsening primary headache disorder, in close temporal relation to a TBI (3). The prevalence and incidence of TBI and PPTH have increased dramatically in veterans, especially in those returning from Operation Enduring Freedom and Operation Iraqi Freedom (4). Although PPTH frequently manifests as migraine or chronic migraine, many patients fail to respond to conventional migraine therapies (5). Currently there is no FDA approved treatment for PPTH and the escalating opioid crisis raises concerns about medication overuse and abuse in this population. Co-existing PPTH with polytrauma triad (TBI, chronic pain, and PTSD) further complicates functional recovery and overall quality of life. Our research demonstrates veterans with comorbid TBI and persistent headaches is associated with a greater risk of suicide attempts than other types of chronic pain (6). Therefore, there is a critical need to identify and provide effective treatment for veterans with PPTH.

Transcranial direct current stimulation (tDCS), a safe and well-tolerated non-invasive brain stimulation technique, utilizes continuous, low-intensity direct electrical current to modulate resting membrane potential (7, 8). Although the exact effect of tDCS on neuronal behavior is largely unknown, it is believed to facilitate or inhibit neuronal firing rate by generating sub-threshold depolarization or hyperpolarization, depending on direction of current flow (7). In addition to the direct impact on the neuronal resting membrane potential, tDCS is also believed to elicit changes in neurotransmitter release, neuroinflammatory processes, as well as cerebrovascular behavior (9–11). Although the acute effects of tDCS only last approximately 1 hour, repeated sessions can produce cumulative and long-lasting modulations of neural activity and neuroplasticity (12, 13). Unsurprisingly, tDCS has gained attention as a potential therapeutic tool for use in a range of various neuropsychiatric conditions (14–20). Our systematic review and meta-analysis of tDCS for migraine found that repeated tDCS sessions can significantly reduce headache intensity and duration (21). However, to our knowledge, there are no randomized, sham-controlled, double-blind clinical trials published on the feasibility and efficacy of at-home remotely supervised tDCS (RS-tDCS) for with PPTH.

Until recently the clinical implementation of tDCS has been limited by logistical factors, however, modern tDCS devices are portable, programmable, and easy to operate. Furthermore, tDCS can be delivered to patients at home via telehealth applications with real-time clinical monitoring (22). Previous research has demonstrated that RS-tDCS interventions are feasible and effective in a number of clinical populations such as Parkinson's Disease, Multiple Sclerosis, Alzheimer's Disease, Stroke, and TBI (17, 23–26). At-home delivery of RS-tDCS offers an accessible and appealing option for veterans who may not be able to travel to clinics for regular treatments. Accordingly, our primary objectives were to evaluate the feasibility and preliminary efficacy of a four-week RS-tDCS intervention using real-time video monitoring in veterans with PPTH.

We conducted a randomized, double-blinded, sham-controlled pilot clinical trial comparing active RS-tDCS with anodal stimulation over left dlPFC and cathodal stimulation over occipital pole vs. sham RS-tDCS. More specifically, we compared the efficacy of 20-sessions of 20-min active, 2 mA anodal vs. sham RS-tDCS. Our primary outcome measures were adherence rate, and reduction in number of moderate-to-severe headache days during the intervention as well as four-weeks post-intervention. Our secondary and tertiary outcome variables were changes in total number of headache days, and headache-related disability during the intervention as well as four-week post-intervention. We hypothesized that our RS-tDCS intervention would have high adherence rates (greater than 80%) (23), and that individuals receiving active RS-tDCS at would report significant reductions in number of moderate-to-severe headache days, total number of headache days and headache related disability during treatment and at four-week follow-up compared to sham RS-tDCS.

2. Methods

The study procedures for this pilot randomized sham-controlled clinical trial (ClinicalTrials.gov Identifier: NCT04012853) were approved by Department of Veterans Affairs (VA) institutional review board in Columbia, South Carolina. All participants provided written informed consent prior to enrollment and were eligible for financial compensation. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines (27).

2.1. Study population

Participants were recruited through the Columbia VA Medical Center. Identified patients were contacted and pre-screened by members of the research team. Figure 1 illustrates recruitment and enrollment of included participants. All participants were active or retired military service members between the ages of 20–60 years ($m = 46.6 \pm 8.7$ years) with a verified mTBI, and who met the International Classification of Headache Disorders (ICHD III) diagnostic criteria for "persistent headache attributed to traumatic head injury" (28). Prior to randomization, enrolled participants were asked to complete a 28-day baseline headache diary to confirm headache characteristics/inclusion criteria.

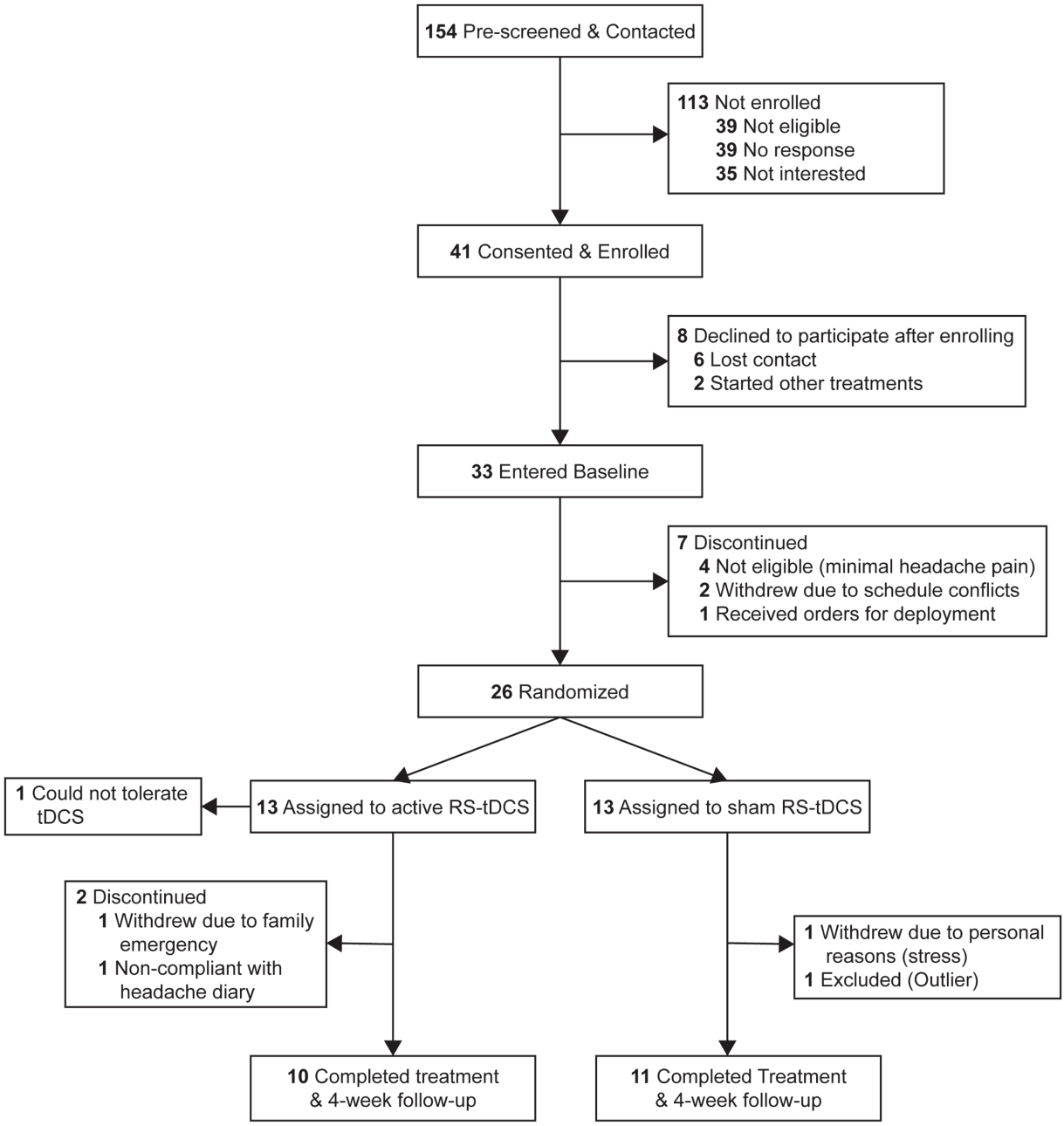

FIGURE 1
CONSORT flow diagram.

2.2. Study design

This randomized, double-blind, sham-controlled, pilot clinical trial consisted of an initial screening and recruitment phase, baseline observation phase (four-weeks), treatment phase (four-weeks), and post-treatment follow-up (four-weeks; Figure 2). During the baseline phase, participants who met inclusion and exclusion criteria (Supplementary material) were invited to complete a four-week headache diary. This was followed by an in-person introductory RS-tDCS training session and a tDCS stimulation tolerability test. A member of the study team provided initial training and ensured that each participant would be able to operate the equipment at home. Participants then completed the tDCS tolerability test to ensure that they could comfortably tolerate the tDCS stimulation. For the tolerability test, tDCS intensity was gradually ramped up to the target intensity of 2 mA. Participants were asked whether the intensity was tolerable and were prompted to report any adverse reactions. Participants were excluded if they did not tolerate the target stimulation intensity. Participants completed the first tDCS session in-person immediately following their tolerability test and the remaining 19-sessions were completed at home with remote supervision via VA Telehealth Video Connect (VVC).

Prior to the in-person tDCS session participants were randomized into either active or sham RS-tDCS conditions and completed a series of questionnaires (Figure 2). These questionnaires encompassed headache-related disability (Headache Impact Test; HIT-6), depression (Patient Health Questionnaire; PHQ-9), PTSD-related symptoms (DSM-5 PTSD Checklist; PCL-5), anxiety (Beck's Anxiety Inventory; BAI), sleep disturbances (Insomnia Severity Index; ISI), and post-concussive symptoms (Rivermead Post-Concussive Symptoms Questionnaire; RPQ). Participants repeated these questionnaires at the end of their respective intervention and at 4-week post-treatment follow-up.

2.2.1. Randomization and RS-tDCS stimulation protocol

Participants were randomized (1:1) using a random number generator (R Studio v3.4.1, Boston, MA). To maintain double blinding, a clinic nurse who is not part of the study team pre-programmed each device according to their group randomization assignment.

To ensure consistent electrode placement, each head strap was configured according to the international 10–20 system (29). We used our novel stimulation montage, based on computational modeling (see Figure 3) with the anodal electrode placed over the left dlPFC (F3) and the cathode placed over the occipital pole (Oz). Stimulation was delivered via the FDA approved for investigational use Mini-CT

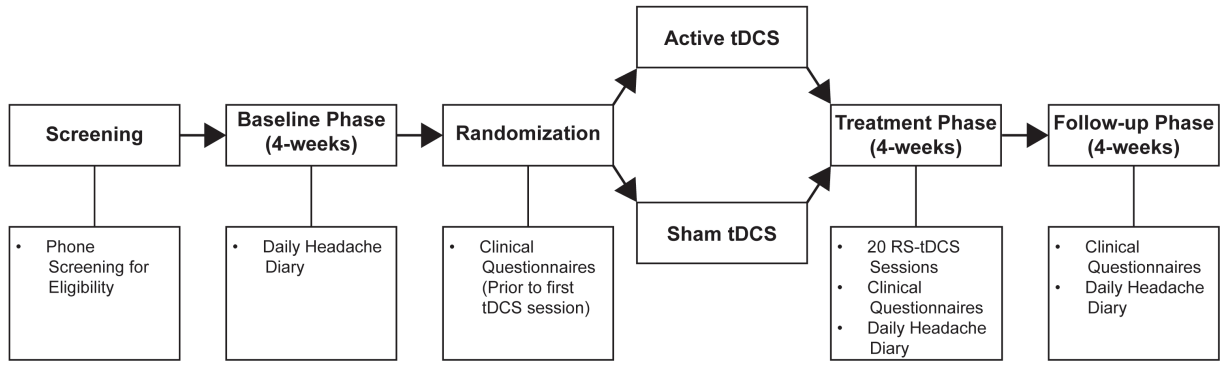

FIGURE 2
RS-tDCS intervention and treatment timeline.

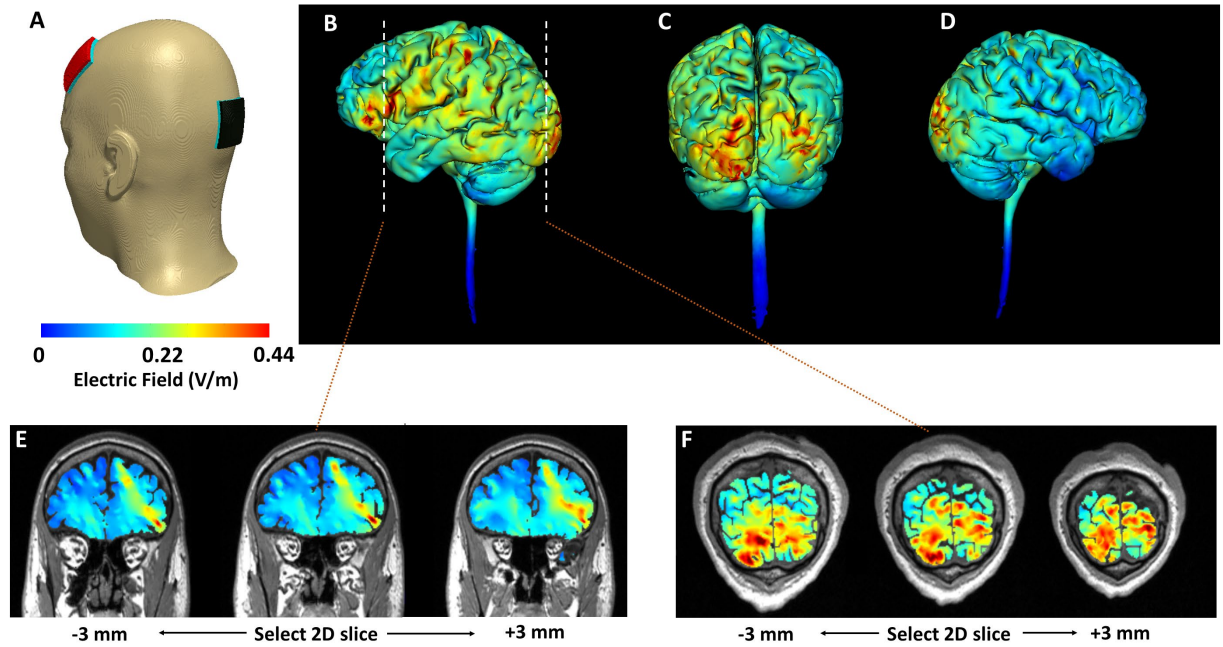

FIGURE 3
Computational simulation of electric field distribution. **(A)** Model geometry considered. Red electrode indicates placement of the anode (F3). Black electrode indicates placement of the cathode (Oz). Cortical surface (3D) plots are included in **(B–D)**. Cortical cross-sectional (2D) plots that highlight depth focality/flow in deeper subcortical regions are included in **(E,F)**. **(B)** Left lateral view. **(C)** Posterior view. **(D)** Right lateral view. The corresponding cross-sectional slices from the left dorsolateral prefrontal cortex and the occipital cortex (dashed line in **B**) are shown in **(E,F)**, respectively. Slices at +/−3mm from the selected 2D slice are also plotted to further highlight induced current flow patterns.

(Soterix Medical, Woodbridge, NJ); and patients were given a study kit consisting of customized headgear with electrodes, sponges, rechargeable batteries, and battery charger. The unique electrodes (SNAPpad) allow loading onto headgear (SNAPstrap) at fixed locations preventing incorrect electrode placement (see Figure 4).

We developed this novel electrode montage as both mTBI and migraine are linked to abnormal functional connectivity within frontal brain regions such as the left dlPFC (30–33). Previous research demonstrates that anodal stimulation over the left dlPFC is more effective than M1 for migraine (34). However, most studies utilize a reference (cathode) electrode placed over the supraorbital region. Because emotional reactivity and mood disturbance are common in mTBI and PPTH patients (35–38), we wanted to avoid inadvertently modulating cortical regions involved in behavioral and mood regulation (e.g., right PFC, inferior frontal gyrus) located near SO. Finally, migraine patients often demonstrate greater neuronal excitability within the occipital lobe (39), and cathodal stimulation over the lower occipital pole has shown to be effective in pain reduction in migraine (40).

Each at-home session was monitored by a member of the study team via HIPAA compliant VVC. At the beginning of each session, participants were given a code by the supervising researcher to unlock the tDCS device. Each tDCS device's stimulation parameters were uniquely programmed and could only be unlocked with a one-time code. For active tDCS, stimulation was gradually increased during the first 30-s to the target intensity (2 mA) and maintained for the remainder of the session (19-min) and then ramped down gradually during the last 30-s. For sham tDCS, the device was programmed to gradually ramp up to 2 mA and back down to zero in both the first and last minute of the session, with no current being delivered in between (41). All RS-tDCS sessions were paired with mindfulness meditation to serve as an attentional control consistent across participants and sessions. The meditation sessions were identical each day and consisted of voice-guided mindfulness exercises designed to promote awareness of body and breathing via the VA Mindfulness Coach app (US Department of Veterans Affairs). If participants missed treatment sessions during the week, they were allowed to "make up" the session on weekend or by extending the intervention timeline to a 5th week.

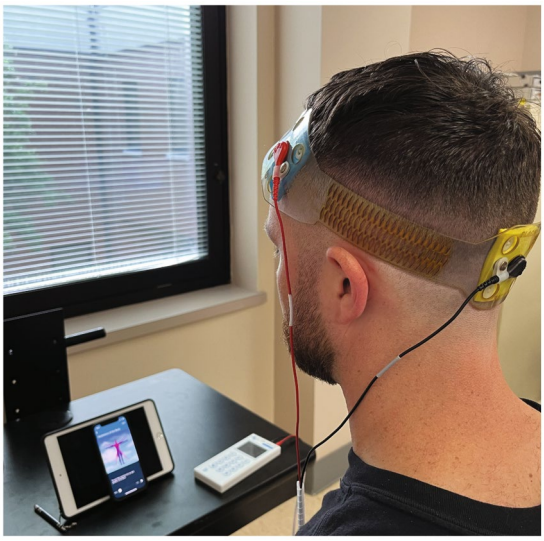

FIGURE 4
RS-tDCS montage.

2.2.2. Headache diary

A headache diary was used to capture individual headache characteristics throughout the duration of each four-week (28-days) phase of the intervention (baseline, treatment, and post-treatment). The headache diary was adapted from the VA Cognitive Behavioral Therapy for Headache manual (42). Due to variability in how individuals describe pain we adopted the following scale: mild (nagging, annoying headache with little to no interference with daily activity), moderate (headache that is bothersome, interferes significantly with daily activity, and usually requires medication), and severe (disabling or intolerable pain that causes inability to perform routine daily activity).

2.3. Clinical outcomes

2.3.1. Primary outcomes

Feasibility was defined by the participant's completion of ≥16 sessions (80% adherence) (43). Adherence rate and participant discontinuations were characterized and compared between the active and sham RS-tDCS conditions.

Efficacy was evaluated by comparing changes in number of moderate-to-severe headache days from the baseline to the end of treatment and at their four-week follow-up evaluation.

2.3.2. Secondary outcomes

Change in total number of headache days, headache disability (HIT-6), and days of acute pain medication use from the baseline to the end of treatment and at their four-week follow-up evaluation.

2.3.3. Tertiary outcomes

Change in depressive symptoms (PHQ-9), anxiety symptoms (BAI), PTSD-related symptoms (PCL-5), sleep disturbance (ISI), and post-concussive symptoms (RPQ) from the baseline phase to the intervention phase and follow-up phase.

2.3.4. Intervention related side effects/tolerability

Participants were asked to report any perceived treatment related side-effects at the end of each RS-tDCS session.

2.4. Statistical analyses

Independent two-tailed t-tests and Fisher Exact tests were used to compare continuous and categorical (respectively) group level demographics, TBI characteristics, and baseline headache features. To investigate measures of safety and tolerability, as well as feasibility and compliance, we compared group differences in self-reported treatment side-effects and intervention attrition using a series of Fisher Exact tests. To assess the efficacy of our RS-tDCS intervention change scores relative to baseline (Evaluation – Baseline) were computed for as well as tertiary outcomes and secondary outcome measures collected at each post-intervention evaluation. Normality was assessed using Shapiro–Wilk's test of normality and homogeneity of variance was assessed by Levene's test. Group outliers were identified as individual values that exceeded ±2.5 standard deviations at each evaluation timepoint for both primary and secondary outcome measures. Participants were one participant was excluded as he was consistently

identified as an outlier across primary and secondary outcomes from further analyses if they were consistently identified as an outlier across primary and secondary outcomes. Next, a series of group (SHAM, ACTIVE) × time (Post-Treatment, Follow-up) univariate analysis of variance (ANOVA) were computed for each outcome measure. All statistical analyses were conducted with an *a priori* alpha = 0.05. For significant interactions and main effects, Bonferroni corrections for multiple comparisons were applied.

3. Results

3.1. Participants

From December 2019 to March 2022, 154 patients were screened for eligibility. Forty-one participants who met inclusion and exclusion criteria were consented and enrolled in the study (Figure 1). Thirty-three participants completed baseline headache diaries, and 26 eligible participants were randomly assigned to either active ($n = 13$) or sham ($n = 13$) RS-tDCS treatment. One participant was unable to tolerate the target intensity and never began treatment. Twenty-two participants completed the full intervention (active $n = 10$; sham $n = 12$). One participant was determined to be an outlier and was removed leaving a total of 21 participants (active $n = 10$; sham $n = 11$) in the final analysis (see Supplementary Figure S1). There were no significant differences in demographics, or baseline TBI and clinical characteristic between groups (p's ≥ 0.08; Table 1). Participants were predominantly white (12/21), and male (18/21), adults and 10 of the 21 participants had at least some college or technical school education. There was no significant difference in the number of days to complete needed to complete the RS-tDCS treatment among SHAM ($m = 29.3 \pm 2.5$ days) or active ($m = 28.9 \pm 1.7$ days) groups ($p = 0.7$). Medication use was similar between groups and no participant was taking opioids or benzodiazepines (Supplementary Table S3).

3.2. Safety and tolerability

Supplementary Figure S2 shows the reported side-effects by treatment group. As expected, most side-effects reported were related to mild sensations at the electrode site. The three most common side-effects were: 1) tingling (active 70%/sham 91.7%), 2) warm sensation (active 30%/sham 58.3%), and 3) itching (active 20%/sham 25%). There were no significant differences in side-effect reporting between the active vs. sham RS-tDCS groups (p's > 0.08). Side-effects diminished shortly after the end of each training session, with no lasting side-effects reported by any participant. Importantly, no participant reported any side-effects or adverse events that required discontinuation of the treatment session or withdrawal from the intervention.

3.3. Primary outcomes

3.3.1. Feasibility

Eighty-eight percent (22/25) completed the intervention (active 10/12 vs. sham 12/13, Figure 1), and there was no significant difference in adherence rate between groups ($p = 0.59$).

TABLE 1 Baseline demographics and headache characteristics.

	Active RS-tDCS (n=10)	Sham RS-tDCS (n=11)	p-value
Age (years)	49.3 ± 8.5	42.6 ± 8.0	0.08
Sex (# men)	9 (90%)	9 (81.8%)	1.00
Body mass tndex (kg/m^2)	28.9 ± 4.9	29.9 ± 4.9	0.64
Race (n)			0.67
White	5 (50%)	7 (63.6%)	
Black or African American	5 (50%)	4 (36.4%)	
Marital Status (n)			0.82
Married	7 (70%)	8 (72.7%)	
Divorced	2 (20%)	2 (18.2%)	
Never married/domestic partnership	1 (10%)	1 (9.1%)	
Education Level (n)			0.61
High School graduate or GED	2 (20%)	1 (9.1%)	
Some college or technical school	4 (40%)	7 (63.6%)	
Bachelor's degree or higher	4 (40%)	3 (27.3%)	
Employment Status (n)			0.24
Employed (full or part time)	4 (40%)	7 (66.6%)	
Unemployed	3 (30%)	0	
Disabled	1 (10%)	2 (18.2%)	
Retired	2 (20%)	2 (18.2%)	
TBI characteristics			
Number of injuries	2.4 ± 1.0	2.3 ± 1.1	0.54
Years since first injury	16.6 ± 9.2	15.3 ± 9.8	0.75
TBI mechanism (n)[a]			
Blast	5	6	1.00
Mortar	3	2	0.62
Motor vehicle accident	4	3	0.65
Other	5	6	1.00
Headache characteristics			
Age at headache onset (years)	30.7 ± 9.2	30.6 ± 9.3	0.96
Number of headache days (out of 28 days)	25.6 ± 3.8	24.1 ± 5.0	0.45
Number of moderate to severe headache days (out of 28 days)	15.6 ± 8.8	15.7 ± 7.1	0.97
Headache phenotype			1.00
Migraine-like	9 (90%)	9 (81.8%)	
Tension-type	1 (10%)	2 (18.2%)	

(Continued)

TABLE 1 (Continued)

	Active RS-tDCS (n=10)	Sham RS-tDCS (n=11)	p-value
Acute pain medication use (days out of 28)	11.5 ± 11.3	9.5 ± 8.1	0.64
[b]Medication overuse (n)	4 (40%)	4 (36.4%)	1.00
Quality of life			
PHQ-9	14.3 ± 6.8	14.1 ± 5.0	0.94
HIT-6	64.5 ± 6.7	65.3 ± 6.1	0.79
BAI	30.6 ± 15.0	26.5 ± 15.4	0.54
PCL-5	47.6 ± 21.6	44.6 ± 19.3	0.74
ISI	18.1 ± 8.7	18.6 ± 5.9	0.87
RPQ	44.7 ± 14.6	43.5 ± 9.1	0.82

[a]Not mutually exclusive. Values reported as mean ± standard deviation unless otherwise indicated. GED, General Educational Development Test; TBI, Traumatic brain injury; PHQ-9, Patient Health Questionnaire; HIT-6, Headache Impact Test; BAI, Beck Anxiety Inventory; PCL-5, DSM-5 PTSD Checklist; ISI, Insomnia Severity Index; RPQ, Rivermead Post-Concussion Symptoms Questionnaire.
[b]Medication overuse is defined as taking one acute pain medication more than 15 days/month or 2+ acute pain medications more than 10 days/month.

3.3.2. Moderate-to-severe headache days

Figure 5A illustrates individual and group changes in moderate-to-severe headache days over the course of the RS-tDCS intervention. Omnibus analysis of changes in moderate-to-severe headache days revealed an effect for group ($F_{[1,38]} = 9.2$, $p = 0.004$, $\eta^2 = 0.19$), with the active RS-tDCS group reporting a greater reduction in moderate-to-severe headache days during the intervention and at 4-week follow-up (est. mean = −3.2 ± 1.2) compared to sham (est. mean = 1.7 ± 1.1). No other significant differences were observed (Table 2).

3.4. Secondary outcomes

3.4.1. Secondary headache outcomes

Figure 5B omnibus analysis of reduction in headache days revealed an effect for group ($F_{[1,38]} = 5.3$, $p = 0.03$, $\eta^2 = 0.12$), indicating that irrespective of timepoint, the active RS-tDCS group reported a greater reduction in total headache days (est. mean = −3.0 ± 1.2) compared to sham (est. mean = 0.7 ± 1.1). No significant reductions were observed for headache-related disability or acute pain medication usage (p's ≥ 0.57). No other significant differences were observed (Table 2).

3.5. Tertiary outcomes

3.5.1. PPTH-related functional outcomes

Omnibus analyses failed to detect any significant group or time differences in non-headache-related outcome measures (p's ≥ 0.06) among active or sham RS-tDCS groups (see Table 2). However, it should be noted that the active group exhibited a statistical trend towards reduced anxiety across timepoints ($p = 0.06$, $\eta^2 = 0.10$).

4. Discussion

Veterans with PPTH frequently present with migraine or chronic migraine phenotypes (82% in our cohort) (44). However, typical migraine therapies are often ineffective for managing headaches or reducing PPTH-related disability (45). Furthermore, traditional therapeutic approaches for TBI are minimally effective for managing chronic pain in veterans with PPTH (24). Unsurprisingly, veterans with PPTH have disproportionately poor outcomes relative to their peers, including increased rates of joblessness, homelessness, and suicidality (6). This double-blind, randomized, sham-controlled, pilot clinical trial provides preliminary evidence for the feasibility and efficacy of a novel at-home RS-tDCS with real-time monitoring protocol for veterans with PPTH.

In our first of its kind clinical trial, we demonstrated that a four-week RS-tDCS intervention was feasible (high adherence rate), and well tolerated by veterans with PPTH. Specifically, 88% of veterans that began treatment completed the intervention in its entirety, and there was no significant difference between groups. This further validates findings from broader tDCS literature, demonstrating tDCS is well tolerated by a wide-range of clinical populations (19, 46–48). Most importantly, compared to sham stimulation, veterans receiving active stimulation reported decreases in moderate-to-severe headache days and total number of headache days both during the intervention and at four-week follow-up; providing the first evidence that RS-tDCS is an effective treatment for veterans with PPTH.

The exact mechanisms by which tDCS reduces pain is not fully understood. However, tDCS is believed to modulate excitatory neurotransmitter release, post-synaptic N-methyl-D-aspartate (NMDA) receptor over binding, neuroinflammation, and the synchronous activity of neurons, all of which are key pathophysiological factors underlying both chronic mTBI, migraine, and PPTH (11, 49–51). Prior research demonstrates tDCS improves neuronal synchronization and reduces hyper-excitability in veterans with chronic TBI (45, 46) and reduces spectral perturbations in those with migraine (47, 48). However, whether the changes occur in those with PPTH is unknown. Future research employing biological and psychophysiological measures will help elucidate tDCS mechanisms of change in those with PPTH and help guide future interventions.

It should be noted that although we observed significant changes in our primary and secondary outcomes, common comorbidities associated with mTBI and chronic headache such as depression, anxiety, post-traumatic stress, and insomnia were not significantly different. Although perplexing, this could be due to several factors including our novel montage, which was purposefully selected to target and related functional outcome (headache severity associated disability). Thus, our targeted montage configuration may have resulted, as intended, in pain specific neuromodulations.

However, it is also possible that the small sample size could account for current null results in tertiary outcomes. Changes in anxiety were nearly significant ($p = 0.06$) across timepoints and the observed effect sizes were moderate ($\eta^2 = 0.10$). Given the extant literature on the efficacy of tDCS for modulating anxiety and its neural progenitors (44), it is possible with a larger sample size changes in anxiety would have been significant. However, research including more participants and longer duration interventions are necessary to gain a better understanding of the influence of our RS-tDCS protocol on anxiety in veterans with PPTH.

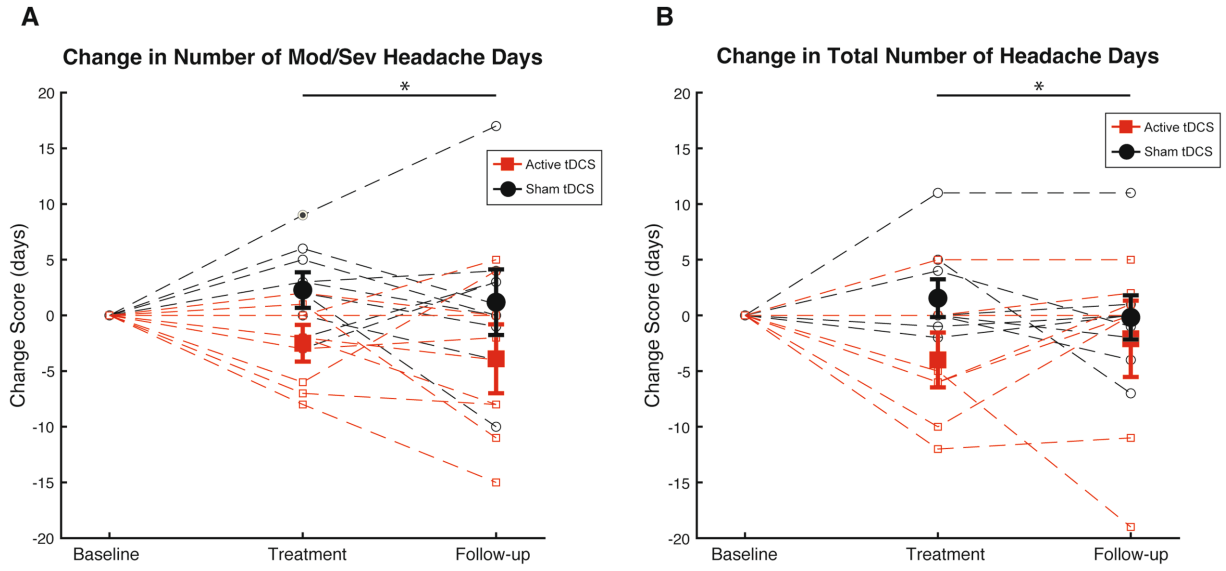

FIGURE 5
(A) Mean [SE] changes in moderate-to-severe headache days (Mod/Sev HA days) during treatment phase and follow-up among active RS-tDCS (red square) and sham (black circle) groups. **(B)** Mean [SE] changes in total headache days (HA days) during treatment phase and follow-up among active RS-tDCS (red square) and sham (black circle) groups. * Indicates a group difference at $p<0.05$.

TABLE 2 Change in primary and secondary outcomes among active vs. sham RS-tDCS groups.

				Effect size (η^2) [p-value]		
	Group	Treatment	Follow-up	Interaction	Group	Time
Primary Outcome						
Mod/Sev HA Days (n)	sham	2.3 ± 3.4	1.2 ± 6.5	<0.01 [0.92]	**0.19 [<0.01]**	0.01 [0.45]
	active	−2.5 ± 3.5	−3.9 ± 6.4			
Secondary Outcomes						
HA Days (n)	sham	1.5 ± 3.8	−0.2 ± 4.4	0.03 [0.27]	**0.12 [0.03]**	<0.01[0.96]
	active	−4.0 ± 5.2	−2.1 ± 7.2			
Tertiary Outcomes						
PHQ-9	sham	0.1 ± 4.4	−1.0 ± 5.6	0.01 [0.54]	<0.01[0.96]	<0.01[0.89]
	active	−0.6 ± 4.1	0.1 ± 4.2			
HIT-6	sham	0.8 ± 5.4	−5.4 ± 18.4	0.03 [0.33]	0.01 [0.57]	0.02 [0.41]
	active	−4.5 ± 6.5	−4.0 ± 7.3			
BAI	sham	1.9 ± 7.4	3.5 ± 10.8	<0.01[0.84]	0.10 [0.06]	<0.01[0.73]
	active	−3.2 ± 8.6	−2.8 ± 9.6			
PCL-5	sham	1.9 ± 10.5	−1.4 ± 17.2	<0.01[0.89]	<0.01[0.91]	0.03 [0.35]
	active	2.9 ± 9.3	−1.5 ± 12.4			
RVMD	sham	−4.2 ± 11.7	−4.0 ± 14.8	0.01 [0.57]	0.01 [0.46]	0.01 [0.54]
	active	−10.2 ± 19.1	−4.8 ± 10.6			
ISI	sham	0.2 ± 5.1	0.9 ± 8.4	<0.01[0.85]	0.01 [0.58]	<0.01[0.85]
	active	−0.5 ± 5.5	−0.5 ± 4.2			

Mod/Sev HA Days, Moderate-to-Severe Headache days; HA Days, Headache Days; PHQ-9, Patient Health Questionnaire; HIT-6, Headache Impact Test; BAI, Beck Anxiety Inventory; PCL-5, DSM-5 PTSD Checklist; ISI, Insomnia Severity Index; RPQ, Rivermead Post-Concussion Symptoms Questionnaire. Bold values indicate statistical significance at $p<0.05$.

Together, our results indicate that a relatively short term (1 month) RS-tDCS intervention can result in significant changes in moderate-to-severe headache days and total number of headache days. Furthermore, these benefits were maintained one-month post-intervention, suggesting the benefit extend beyond the intervention. Therefore, patients may be able to cycle RS-tDCS therapies while

maintaining efficacy. This is an important point as many patients undergoing tDCS find the prospect of long-term daily/regular stimulation as burdensome. Indeed, one of the current limitations of self-administrated neuromodulation therapy (e.g., Cefaly, Gammacore VNS) for headache is decreasing adherence rates over time (23) and being able to cycle neuromodulation therapies makes them a more realistic option from a patient and provider perspective. Additional research comparing various intervention lengths, stimulation intensities and duration are needed to create a standardized platform.

4.1. Limitations

Although our study is characterized by several strengths, there are limitations to consider. First, our final sample was relatively small and comprised of predominantly white, male military veterans. As such, our findings should not be generalized to female veterans, or non-military PPTH patients, and larger phase II clinical trials are necessary to confirm our findings. Second, tDCS is not FDA approved to treat PPTH or any other neurological condition. Accordingly, there are no guidelines for optimal parameter selection. Results of previous studies have been highly variable and direct comparisons are difficult due to these methodological differences. Also, parameters such as stimulation intensity and number of sessions are directly correlated to the duration of effects. While the parameters of our trial are consistent with existing literature, it is possible that more training sessions and/or higher stimulation intensities could result in greater benefits. Medication use is a key issue in clinical trials (52) and common preventative migraine medications (anticonvulsant, anti-depressants) are known to impact tDCS effects (53). Restricting medication use in veterans with mTBI with numerous comorbidities is often not clinically feasible. Consequently, we could not control for medication use in such a small trial. Fortunately, medication use was equally distributed between groups (Supplementary Table S3), and no participants were taking opioids or benzodiazepines. Future, more controlled research is necessary to determine the benefit of RS-tDCS independent of medication use. Finally, we had no true control group as all participants completed mindfulness meditation as an attentional control during their tDCS sessions. Although long-duration mindfulness meditation has shown to be an effective therapy for chronic migraine, the short durations have not (54). Furthermore, significant changes were only observed for active stimulation in both within and between groups analyses, suggesting mindfulness meditation did not significantly influence primary or secondary outcomes.

5. Conclusion

Our results indicate the combined feasibility and efficacy of RS-tDCS may provide a promising non-pharmacological alternative for veterans suffering from PPTH. Furthermore, having the option to conduct neuromodulation sessions remotely will greatly facilitate caring for veterans in more rural communities, where daily visits to medical facilities are impractical. Based on these promising preliminary results, larger clinical trials should be conducted to optimize the therapeutic benefit of RS-tDCS for veterans with PPTH secondary to mTBI. Furthermore, identifying the biological and psychophysiological changes that occur from RS-tDCS in this population is warranted.

Data availability statement

The datasets presented in this article are not readily available because, due to VA regulations and Veterans Health Administration ethics agreements, the analytical datasets used for this study are not permitted to leave the VA firewall without data-use agreement. Requests to access the datasets should be directed to XA, xiao.androulakis@va.gov.

Ethics statement

The studies involving human participants were reviewed and approved by U.S. Department of Veterans Affairs Institutional Review Board in Columbia, South Carolina. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Author contributions

LC conceived the project, assisted in device training and protocol development, participated in the manuscript writing process read, and approved the final manuscript. AH, KM, SG, and JZ participated in data analysis and interpretation of results, participated in the manuscript writing process read, and approved the final manuscript. RM participated in data analysis and interpretation of results. AD assisted in device training and protocol development, participated in the manuscript writing process, read and approved the final manuscript. XA conceived the project, obtained IRB approval, participated in data analysis and interpretation of results, participated in the manuscript writing process, read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AD was employed by Soterix Medical, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1184056/full#supplementary-material

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Processing speed and memory test performance are associated with different brain region volumes in Veterans and others with progressive multiple sclerosis

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Background: Cognitive dysfunction and brain atrophy are both common in progressive multiple sclerosis (MS) but are seldom examined comprehensively in clinical trials. Antioxidant treatment may affect the neurodegeneration characteristic of progressive MS and slow its symptomatic and radiographic correlates.

Objectives: This study aims to evaluate cross-sectional associations between cognitive battery components of the Brief International Cognitive Assessment for Multiple Sclerosis with whole and segmented brain volumes and to determine if associations differ between secondary progressive (SPMS) and primary progressive (PPMS) MS subtypes.

Design: The study was based on a baseline analysis from a multi-site randomized controlled trial of the antioxidant lipoic acid in veterans and other people with progressive MS (NCT03161028).

Methods: Cognitive batteries were conducted by trained research personnel. MRIs were processed at a central processing site for maximum harmonization. Semi-partial Pearson's adjustments evaluated associations between cognitive tests and MRI volumes. Regression analyses evaluated differences in association patterns between SPMS and PPMS cohorts.

Results: Of the 114 participants, 70% had SPMS. Veterans with MS made up 26% ($n = 30$) of the total sample and 73% had SPMS. Participants had a mean age of 59.2 and sd 8.5 years, and 54% of them were women, had a disease duration of

22.4 (sd 11.3) years, and had a median Expanded Disability Status Scale of 6.0 (with an interquartile range of 4.0–6.0, moderate disability). The Symbol Digit Modalities Test (processing speed) correlated with whole brain volume ($R = 0.29$, $p = 0.01$) and total white matter volume ($R = 0.33$, $p < 0.01$). Both the California Verbal Learning Test (verbal memory) and Brief Visuospatial Memory Test-Revised (visual memory) correlated with mean cortical thickness ($R = 0.27$, $p = 0.02$ and $R = 0.35$, $p < 0.01$, respectively). Correlation patterns were similar in subgroup analyses.

Conclusion: Brain volumes showed differing patterns of correlation across cognitive tasks in progressive MS. Similar results between SPMS and PPMS cohorts suggest combining progressive MS subtypes in studies involving cognition and brain atrophy in these populations. Longitudinal assessment will determine the therapeutic effects of lipoic acid on cognitive tasks, brain atrophy, and their associations.

KEYWORDS

progressive multiple sclerosis, veterans, processing speed, verbal memory, visual memory, clinical trials, brain volume changes, brain atrophy

1. Introduction

Accelerated brain volume loss is a frequently used imaging surrogate marker of relapse-independent disease progression in multiple sclerosis (MS) (1). Brain atrophy reflects multiple pathophysiological processes including axonal degeneration, neuronal loss, and loss of glial trophic support. Underlying chronic inflammation, mitochondrial dysfunction, oxidative stress, and loss of blood–brain barrier integrity are implicated in driving central nervous system neurodegeneration that occurs in MS faster than from aging alone (2). Because of strong correlations with clinical disease progression, whole brain atrophy is the primary outcome measure in Phase 2 progressive MS clinical trials (3). However, regional atrophy varies by MS phenotype and by the strength of association with clinical worsening (4). Analyses of total and segmented brain volumes are becoming available to researchers and clinicians by automated processing software packages available as open-source software and marketed commercially (5).

A consistent clinical correlation to brain atrophy in MS is cognitive impairment (6). Cognitive dysfunction, present from early relapsing-remitting MS (RRMS), increases in prevalence and severity with disease duration and in secondary progressive (SPMS) and primary progressive (PPMS) MS subtypes (7). Information processing speed deficits are particularly common (8). Deficits in additional cognitive domains including verbal fluency, verbal episodic memory, visuospatial construction, and executive dysfunction further distinguish progressive from relapsing MS, while visuospatial construction deficits may distinguish SPMS from PPMS (9). Rates of decline among cognitive domains also differ by MS phenotype (10). Because of the frequency of cognitive dysfunction in MS and its relevance to health-related quality of life, cognitive assessment and follow-up are recommended components of routine MS clinical monitoring (11).

Information processing speed tests such as the Paced Auditory Serial Addition Test (PASAT) and Symbol Digit Modalities Test (SDMT) are frequently the only cognitive assessment conducted in clinical practice and clinical trials (12). Batteries of cognitive tests are recommended to assess different cognitive domains. The Brief International Cognitive Assessment for MS (BICAMS) battery includes three short tests assessing information processing speed (SDMT), immediate verbal memory (California Verbal Learning Test, Second Edition; CVLT), and immediate visual memory [memory (Brief Visuospatial Memory Test-Revised; BVMT-R) (13)]. While the BICAMS does not test all cognitive domains, the battery was chosen as a balance between high-yield outcomes and administration efficiency. Studies to date of correlations between the BICAMS tests and brain volumes in progressive MS are limited by small sample sizes, inclusion of relapsing MS or limited to a single progressive MS subtype, or do not contain all three BICAMS tests (14, 15).

The objectives of this study were to determine cross-sectional associations between the components of the comprehensive BICAMS cognitive battery with standard whole and segmented brain volumes in people with progressive MS and to determine if the patterns of associations differ between SPMS and PPMS subtypes.

2. Materials and methods

2.1. Study design

This is a baseline analysis of an ongoing phase 2, double-blind, multi-center, randomized, placebo-controlled trial (RCT) of 1,200 mg daily oral lipoic acid (LA; Pure Encapsulations, Sudbury, MA) as add-on disease-modifying treatment to slow worsening of gait in progressive MS (NCT03161028). Participants were recruited from five Veterans Affairs Medical Centers as part of the MS Centers of Excellence Network, five United States University sites, and one Canadian study site between August 2018 and January 2022.

2.2. Participants

Inclusion criteria to the RCT were ages ≥18 years, prior diagnosis of RRMS or PPMS by 2010 revised McDonald criteria (16), current progressive MS defined as relapse-independent disability progression within the previous 2 years either while not taking disease-modifying therapy (DMT) or despite it, and an EDSS score between 3.0 and 6.5 at screening. Exclusion criteria were other medical or neurological conditions that would confound the assessment of gait, use of scheduled corticosteroid treatments in the year prior to enrollment, corticosteroid treatment for relapse within 60 days of enrollment, use of more than small amounts of LA in the prior 2 years, MRI constraints, pregnant or breastfeeding, significant active concurrent illness, uncontrolled or insulin-dependent diabetes, and lack of English fluency preventing the use of patient-reported outcomes.

Participants included in this baseline analysis were those having complete baseline data for all MRI measures and data from at least one cognitive test. Because of study recruitment from VA medical centers, veteran demographics are reported.

2.3. Standard protocol approvals, registrations, and patient consents

The study was approved by the Veterans Affairs Central Institutional Review Board (IRB), the University of Utah Single IRB, the University of Vermont IRB, the Swedish Medical Center IRB, and the Ottawa Research Ethics Board. Written consent was obtained from all the participants prior to performing the study procedures. The trial was registered at Clinicaltrials.gov (NCT03161028).

2.4. Cognitive tests

The site study staff were trained on how to administer the BICAMS by a psychologist with experience in neuropsychological assessment in people with MS (AT) at the beginning of the study with an in-person session that was recorded for ongoing study staff training. Cognitive testing was performed on the same day as the MRI acquisition. Cognitive testing was completed using the BICAMS which includes the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-Second Edition (CVLT) learning trials, and the Brief Visuospatial Memory Test-Revised (BVMT-R) learning trials (17–19). Raw scores were standardized relative to norms in the general population per the test manual guidelines. While the oral SDMT was the preferred format, some study sites used the written format until the error was noted and corrected. SDMT written was standardized for age and education, while SDMT oral was standardized for age, sex, and education (20). CVLT was standardized for age and sex, and BVMT-R was standardized for age only. Standardization yielded Z-scores for SDMT and T-scores for CVLT and BVMT-R. For Z-scores, the reference mean and standard deviation (sd) are 0 and 1, while for T-scores, the reference mean and sd are 50 and 10. A person with a Z-score of −1 is 1 sd below the reference mean, as is a person with a T-score of 40.

2.5. MRI acquisition protocol

3T MRI instruments were used to acquire the following anatomical series of the brain: (1) A magnetization prepared T1-weighted 3D sequence using a sagittally oriented gradient echo readout with a 1-mm isotropic spatial resolution and full brain coverage, as the basis for brain atrophy measures. (2) A fluid-attenuated inversion recovery (FLAIR) 3D T2-weighted series using a sagittally oriented turbo spin echo readout with 1 mm isotropic resolution and full brain coverage. Acquisitions across different 3T platforms were harmonized using the ADNI3 protocol (https://adni.loni.usc.edu/adni-3/) as a guide. Intravenous MR contrast was not administered. (3) The American College of Radiology (ACR) phantom scan was acquired within 7 days of each participant scan for quality control according to ACR protocols.

2.5.1. MRI volumetric analyses

MRI analyses used for study outcomes were analyzed by the Advanced Imaging Research Center at OHSU. T1-weighted and FLAIR Digital Imaging and Communications in Medicine (DICOM) image sets were converted to the Network Interface to File Transfer in the Internet (NIFTI) format, followed by signal intensity bias correction, skull stripped, de-noised, and co-registered. Brain volumetric and cortical thickness measures were extracted from image sets using Freesurfer software tools (v7.1.1) (5). The output using these tools of "total brain parenchymal brain volume" is the summation of normal appearing white matter, white matter hyperintensities, cortical and deep gray matter, and brainstem volumes and is referred to in this article as "whole brain volume." All tissue class volume masks were visually reviewed for gross errors. Additional brain measurements included total normal appearing white matter volume, total gray matter volume, deep gray matter volume, and cortical thickness. Intracranial vault size was estimated using a custom template generated in Montreal Neuroscience Institute (MNI)152 space followed by non-linear back-registration to native space images. Management of multiple MRI platforms and software was conducted by acquiring high-quality scans meeting quality control standards and by the use of a phantom at every study site.

2.6. Statistical analysis

Data analyses were completed using R version 4.2.0 and Stata version 15 (21, 22). Data were inspected to ensure normality and lack of extreme outliers.

Demographic variables (Table 1) and baseline cognitive scores and brain volumes (Table 2) were compared between SPMS and PPMS subtypes. *P*-values were obtained using a *t*-test for continuous variables, Fisher's exact test for dichotomous variables, and Mann–Whitney U-test for ordinal variables. We performed semi-partial correlations to characterize the age- and sex-adjusted

TABLE 1 Participant demographics for the full sample and by secondary progressive and primary progressive multiple sclerosis subtypes.

	Full sample ($n = 114$)	SPMS ($n = 80$, 70%)	PPMS ($n = 34$, 30%)	p-value
Age (years): mean (sd)	59.2 (8.5)	58.6 (8.2)	60.4 (9.2)	0.32
Female: *n* (%)	62 (54.4%)	48 (60.0%)	14 (41.2%)	0.10
White race: *n* (%)[a]	104 (91.2%)	72 (90.0%)	32 (94.1%)	0.72
Ever smoked: *n* (%)	53 (46.5%)	37 (46.3%)	16 (47.1%)	>0.99
Bachelor's degree or higher: *n* (%)	58 (50.9%)	42 (52.5%)	16 (47.1%)	0.81
Duration of disease since first symptom onset (years): mean (sd)	22.4 (11.3)	25.0 (11.0)	16.2 (9.5)	<0.01
EDSS: median (IQR)	6.0 (4.0–6.0)	6.0 (4.0–6.5)	5.5 (3.6–6.0)	0.06
Clinical and/or radiographic relapse in the 5 years prior to entry: *n* (%)	27 (23.7%)	18 (22.5%)	9 (26.5%)	0.63
Taking DMT: *n* (%)	63 (55.3%)	45 (56.3%)	18 (52.9%)	0.84
Interferons/glatiramer/teriflunomide: *n* (%)[b]	12 (19.0%)	11 (24.4%)	1 (5.6%)	0.15
DMF/fingolimod: *n* (%)[b]	14 (22.2%)	11 (24.4%)	3 (16.7%)	0.74
CD20 B cell therapy: *n* (%)[b]	32 (50.8%)	18 (40.0%)	14 (77.8%)	0.01
Natalizumab: *n* (%)[b]	5 (7.9%)	5 (11.1%)	0 (0.0%)	0.31

[a]Other races were Black (4.4%), more than one race (2.6%), Asian (0.9%), Unknown (0.9%).
[b]Percentage of those taking DMT.
DMF, dimethyl fumarate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; IQR, interquartile range; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; sd, standard deviation.

TABLE 2 Baseline cognitive scores and MRI brain volumes for the full sample and by secondary progressive and primary progressive multiple sclerosis subtypes.

	Full sample ($n = 114$)	SPMS ($n = 80$, 70.2%)	PPMS ($n = 34$, 29.8%)	p-value
SDMT Z-score (mean, sd)	−1.11 (1.52)	−1.14 (1.56)	−1.05 (1.46)	0.77
CVLT T-score (mean, sd)	53.75 (11.92)	53.96 (10.57)	53.24 (14.81)	0.80
BVMT-R T-score (median, IQR)[a,b]	44 (34–56)	44 (32.75–56.25)	45 (36–52)	0.78
Proportion with at least 1 impaired cognitive test[c]	48.2% (55)	48.8% (39)	47.0% (16)	>0.99
WBV (mL): mean (sd)	1053.39 (123.58)	1046.51 (128.52)	1069.58 (111.20)	0.34
Total gray matter vol (mL): mean (sd)	465.92 (58.49)	463.39 (62.74)	471.88 (47.30)	0.43
Deep gray matter vol (mL): mean (sd)	47.33 (5.05)	47.03 (5.38)	48.05 (4.15)	0.28
Total white matter vol (mL): mean (sd)	441.29 (73.97)	437.48 (78.70)	450.26 (61.56)	0.36
Mean cortical thickness (mm): mean (sd)	2.34 (0.21)	2.35 (0.22)	2.31 (0.17)	0.40

[a]BVMT-R sample size was $n = 113$ (80 SPMS, 33 PPMS).
[b]Mann–Whitney U-test was used for tests of the median due to the assignment of 19 for two participants getting BVMT-R scores at the lower bound of the standardization algorithm, giving them each a T-score of <20 rather than an exact T-score.
[c]Impaired defined as more than 1.5 sd below the standardized population mean.
BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT, California Verbal Learning Test, second edition; IQR, interquartile range; mL, milliliter; mm, millimeter; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; sd, standard deviation; SDMT, Symbol Digit Modalities Test; Vol, volume; WBV, whole brain volume.

correlations between each cognitive measure and each MRI measure. To adjust the MRI output, we regressed each MRI measure on age and sex and extracted the residuals. Sex and age adjustments were not made to cognitive scores as they were already standardized scores. Pearson's correlation coefficients between each set of MRI regression residuals and each cognitive measure were calculated. Correlations were calculated for the full sample, as well as for each subtype (SPMS and PPMS) separately. Although total normal appearing white matter volume, total gray matter volume, deep gray matter volume, and cortical thickness are all components of whole brain volume, there were no statistical accountings performed for the *a priori* correlations between whole brain volume and sub-volumes. Scatterplots visualizing these correlations were produced in R using the ggpubr package (23).

We also built age- and sex-adjusted linear regression models to characterize the strength of association between each cognitive measure and each MRI measure. Models including the MS subtype and the interaction between the MS subtype and each MRI

TABLE 3 Semi-partial Pearson's correlations (R) between cognitive tests and sex- and age-adjusted brain volumes for the full sample of participants and by secondary progressive and primary progressive MS subtypes.

Correlation pairings	Full sample ($n = 114$)		SPMS ($n = 80$, 70.2%)		PPMS ($n = 34$, 29.8%)	
	R	p_{raw}/p_{adj}	R	p_{raw}/p_{adj}	R	p_{raw}/p_{adj}
SDMT						
Whole brain vol	0.29	**<0.01/*0.01***	0.26	**0.02**/0.10	0.39	**0.03**/0.12
Total gray matter vol	0.13	0.18/0.46	0.05	0.69/0.85	0.40	**0.02**/0.12
Deep gray matter vol	0.22	**0.02**/0.06	0.22	**0.04**/0.15	0.20	0.27/0.45
Total white matter Vol	0.33	**<0.01/*<0.01***	0.34	**<0.01/*0.01***	0.27	0.12/0.22
Mean cortical thickness	0.10	0.28/0.60	0.03	0.79/0.81	0.34	**0.05**/0.19
CVLT						
Whole brain vol	0.00	0.99/0.99	−0.03	0.77/0.85	0.08	0.64/0.74
Total gray matter vol	0.04	0.70/0.95	−0.08	0.45/0.85	0.32	0.06/0.19
Deep gray matter vol	0.00	0.98/0.99	−0.02	0.85/0.85	0.07	0.71/0.76
Total white matter vol	0.00	0.99/0.99	0.05	0.67/0.85	−0.12	0.50/0.69
Mean cortical thickness	0.27	**<0.01/*0.02***	0.22	**0.05**/0.15	0.39	**0.02**/0.12
BVMT-R						
Whole brain vol	0.00	0.99/0.99	0.06	0.62/0.85	−0.18	0.30/0.45
Total gray matter vol	0.08	0.42/0.70	0.09	0.41/0.85	0.02	0.91/0.91
Deep gray matter vol	0.09	0.32/0.60	0.14	0.20/0.51	−0.08	0.64/0.74
Total white matter vol	−0.04	0.66/0.95	0.03	0.82/0.85	−0.30	0.09/0.19
Mean cortical thickness	0.35	**<0.01/*<0.01***	0.37	**<0.01/*0.01***	0.31	0.08/0.19

BVMT-R, Brief Visuospatial Memory Test-Revised; CVLT, California Verbal Learning Test, second edition; PPMS, primary progressive multiple sclerosis; SPMS, secondary progressive multiple sclerosis; SDMT, Symbol Digit Modalities Test; TBP, Total brain parenchymal; Vol, volume.
Raw (p_{raw}) and Benjamini–Hochberg adjusted (p_{adj}) *p*-values presented. Statistical significance was set at a *p*-value of ≤0.05.

measure were built to examine the association in each MS subtype independently. Reduced models, not including any MS subtype effects, were built to examine each association in the pooled population (SPMS and PPMS combined).

To adjust for multiple comparisons, we calculated Benjamini–Hochberg adjusted *p*-values with an overall false detection rate of 0.05. Both raw and adjusted *p*-values are presented in tables and plots, but the *p*-values mentioned in the body of the study are adjusted *p*-values.

2.7. Data availability

The datasets generated during the current study are not publicly available due to the ongoing status of the longitudinal study but are available from the corresponding author upon reasonable request.

3. Results

Of the original study sample size of 115 respondents, one participant was excluded from the analysis because excessive T2 lesion volume resulted in unreliable volume measurements. Participant demographics are listed in Table 1. Mean age was 59.2 (range: 34–73, sd 8.5) years, 54% were women, with mean disease duration of 22.4 (range: 3–49, sd 11.3) years, and median EDSS of 6.0 [interquartile range (IQR) 4.0–6.0]. Twenty-seven (23.7%) participants had active disease defined as clinical or radiographic (new, enlarging, or enhancing MRI lesions) relapses in the 5 years prior to study entry. Most (55.3%) were taking DMT at the baseline visit. The SPMS cohort ($n = 80$, 70.2%) had a longer duration of disease since the first MS symptom onset (mean 25.0 sd 11.0 vs. 16.2 sd 9.5 years, $p < 0.01$). The PPMS cohort had a higher proportion of those on DMT taking B cell-depleting therapies (77.8% vs. 40%, $p = 0.01$). Otherwise, MS subtypes were comparable. Veterans with progressive MS comprised 26% ($n = 30$) of the total sample, of whom 73.3% had SPMS. Mean age of veterans was 58.7 years (range: 34–73, sd 8.9), 23% were women, disease duration was 25.5 years (range: 3–49, sd 12.5), and median EDSS is 5.75 (IQR, 4.0–6.0). Aside from fewer women, veteran demographics and the proportion of SPMS were generally similar to that of the full sample.

Baseline cognitive scores and whole brain and segmented brain volumes including cortical thickness for the full sample and by MS subtype are shown in Table 2. Two participants had BVMT-R scores at the lower bound of the standardization algorithm, giving them T-scores of <20 rather than exact T-scores. Because of this, BVMT-R summary statistics are presented as median and IQR rather than mean and sd. For correlation and regression analyses, these individuals were assigned a T-score of 19. Baseline cognitive scores were similar between SPMS and PPMS subtypes. Defining

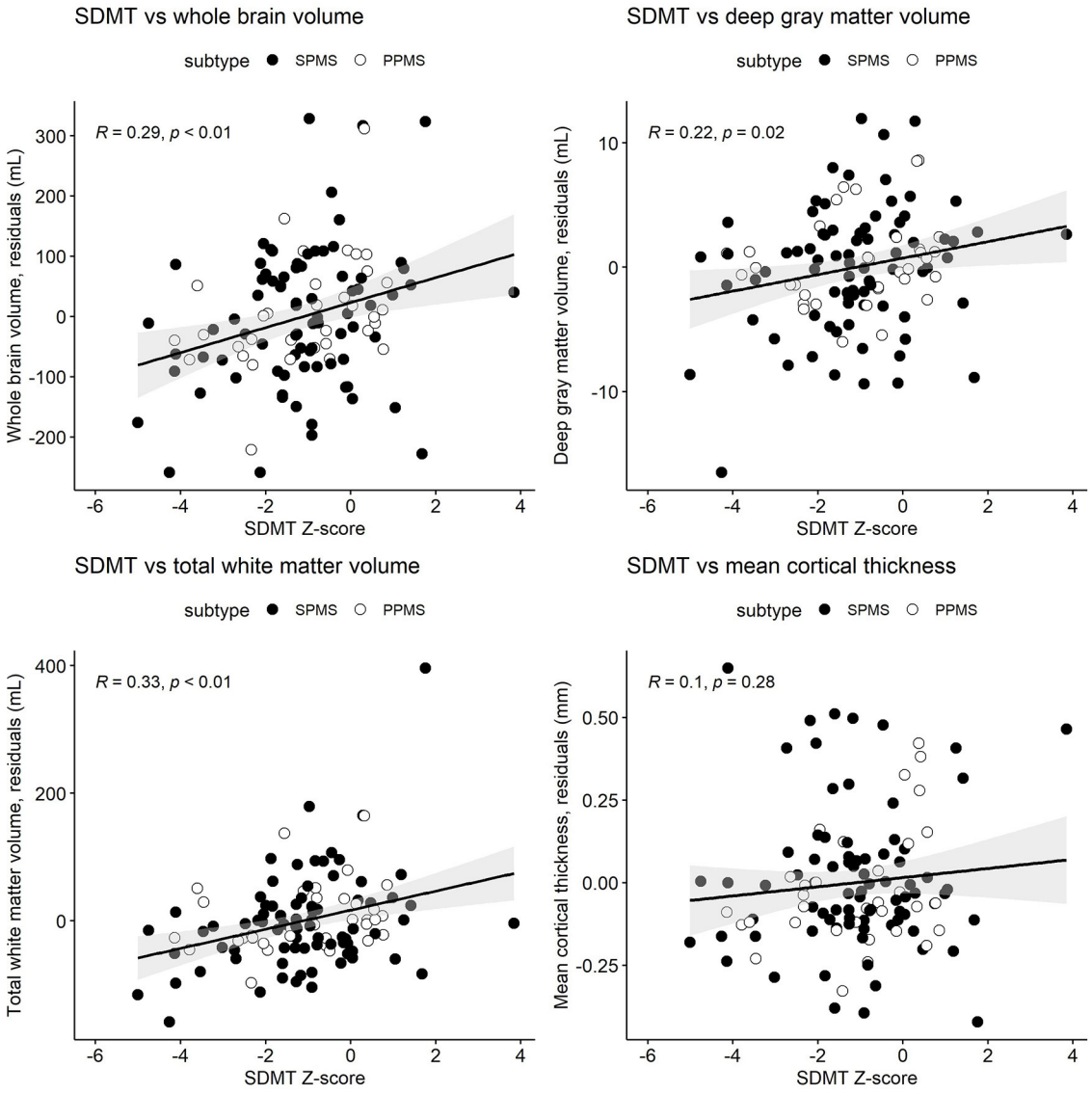

FIGURE 1
Semi-partial Pearson's correlations between the cognitive processing speed test Symbol Digit Modalities Test (SDMT) Z-scores and whole brain volume, deep gray matter volume, total white matter volume, and mean cortical thickness. MRI measures have been adjusted for age and sex, so what is presented here are the residuals (distance each participant is from the age- and sex-adjusted mean). Correlations are for combined secondary progressive (SPMS, filled circles) and primary progressive (PPMS, unfilled circles) multiple sclerosis cohorts. Statistical significance was set at a p-value of $\leq$0.05.

impairment as scoring more than 1.5 sd below the standardized population mean, 48.2% of all participants ($n = 55$) were impaired on at least one of the three cognitive tests. Half (53.3%) of veterans had an impaired cognitive test. For individual tests, 36.8% ($n = 42$) of all participants had impaired scores for SDMT, 4.4% ($n = 5$) for CVLT, and 25.7% ($n = 29$) for BVMT-R (24).

Table 3 and Figures 1–3 present semi-partial Pearson's correlations between cognitive tests and brain volumes with raw and Benjamini–Hochberg adjusted p-values. SDMT correlated modestly yet significantly with whole brain volume ($R = 0.29$, $p = 0.01$) and total white matter ($R = 0.33$, $p < 0.01$) (Figure 1, Table 3). SDMT had a smaller correlation with deep gray matter volume, losing significance after adjustment for multiple comparisons ($R = 0.22$, $p = 0.06$). SDMT had smaller and non-significant correlations with total gray matter volume ($R = 0.13$, $p = 0.46$) and mean cortical thickness ($R = 0.10$, $p = 0.60$). In contrast, both the CVLT and BVMT-R correlated modestly and significantly with mean cortical thickness ($R = 0.27$, $p = 0.02$, and R = 0.35, $p < 0.01$, respectively) but not with total brain parenchymal volume, total gray matter volume, or total white matter volume (all $p \geq 0.60$) (Figures 2, 3, Table 3).

Regression analyses did not reveal systematic differences between SPMS and PPMS subtypes in the correlations between cognitive tests and brain volume. Associations between cognitive

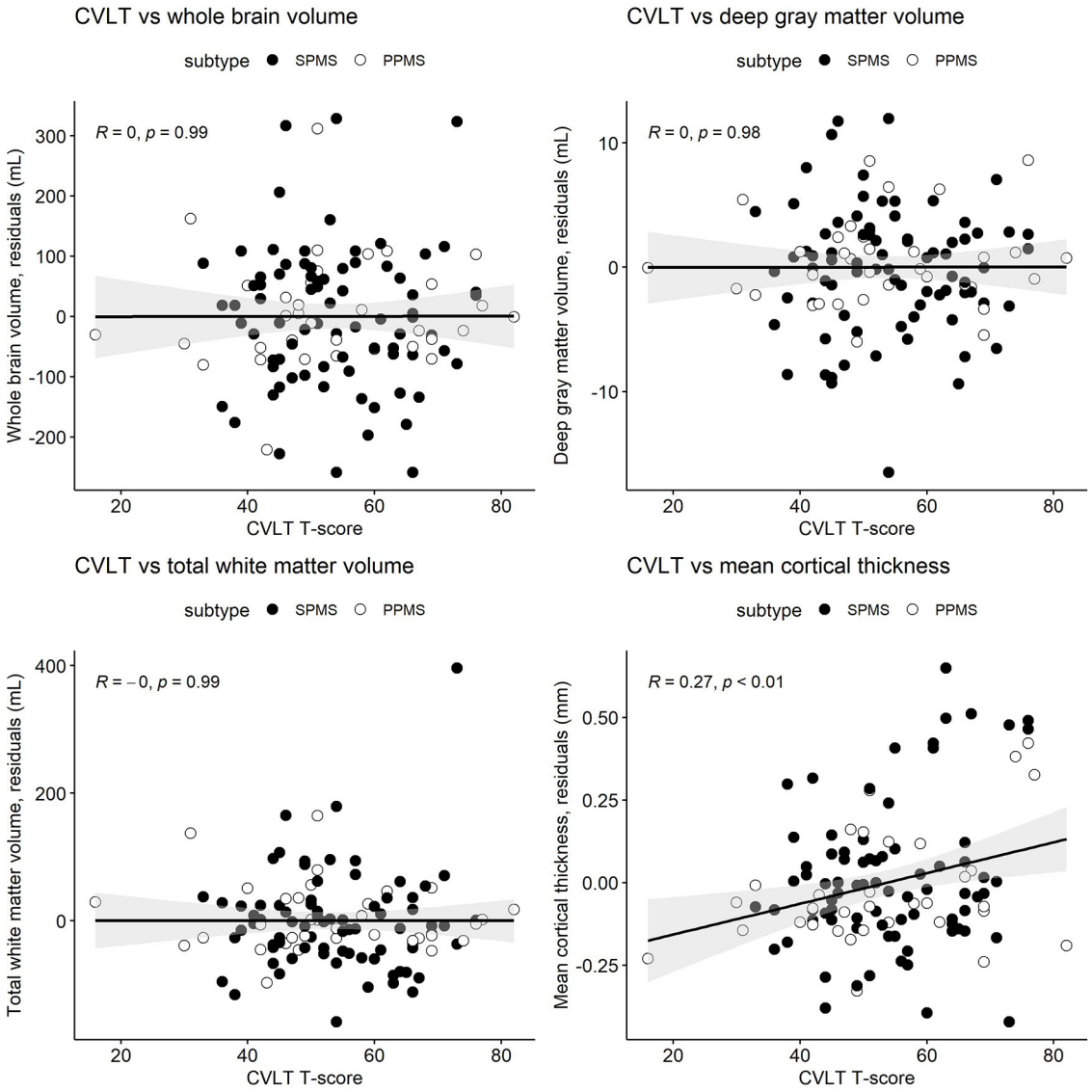

FIGURE 2
Semi-partial Pearson's correlations between the California Verbal Learning Test, second edition (CVLT) T-scores and whole brain volume, deep gray matter volume, total white matter volume, and mean cortical thickness. MRI measures have been adjusted for age and sex, so what is presented here are the residuals (distance each participant is from the age- and sex-adjusted mean). Correlations are for combined secondary progressive (SPMS, filled circles) and primary progressive (PPMS, unfilled circles) multiple sclerosis cohorts. Statistical significance was set at a p-value of ≤ 0.05.

scores and brain volumes are broadly similar within each MS subtype (Supplementary Table 1), and there was no evidence of a consistent subtype interaction effect (Supplementary Table 2).

4. Discussion

This study demonstrated that components of the comprehensive BICAMS cognitive battery had unique correlation patterns with brain volumes in people with progressive MS. Specifically, the information processing speed (SDMT) test correlated with normalized whole brain and total white matter volumes, while the verbal memory (CVLT) and visual memory (BVMT-R) tests correlated only with mean cortical thickness. Correlations were low to moderate ranging from $R = 0.22$ to $R = 0.35$. However, the unique patterns of correlations are suggestive of unique CNS pathways driving cognitive domains. While statistical significance suffered due to lower sample sizes, the overall patterns of correlations were similar between SPMS and PPMS cohorts as supported by regression analysis. The similar patterns of correlations support the broad overlap in the pathophysiology of SPMS and PPMS including injury to normal appearing white and gray matter and cortical lesions (25). This suggests combining SPMS and PPMS subtypes when analyzing associations between brain volumes and cognitive tests in the domains assessed. Given similar demographics and proportion with baseline cognitive impairment of veterans to the larger cohort, the conclusions of our analyses may apply to veteran populations.

The strength of correlation between SDMT and whole brain volume ($R = 0.29$) found in our population is slightly less than in similar studies in relapsing and mixed relapsing and progressive MS

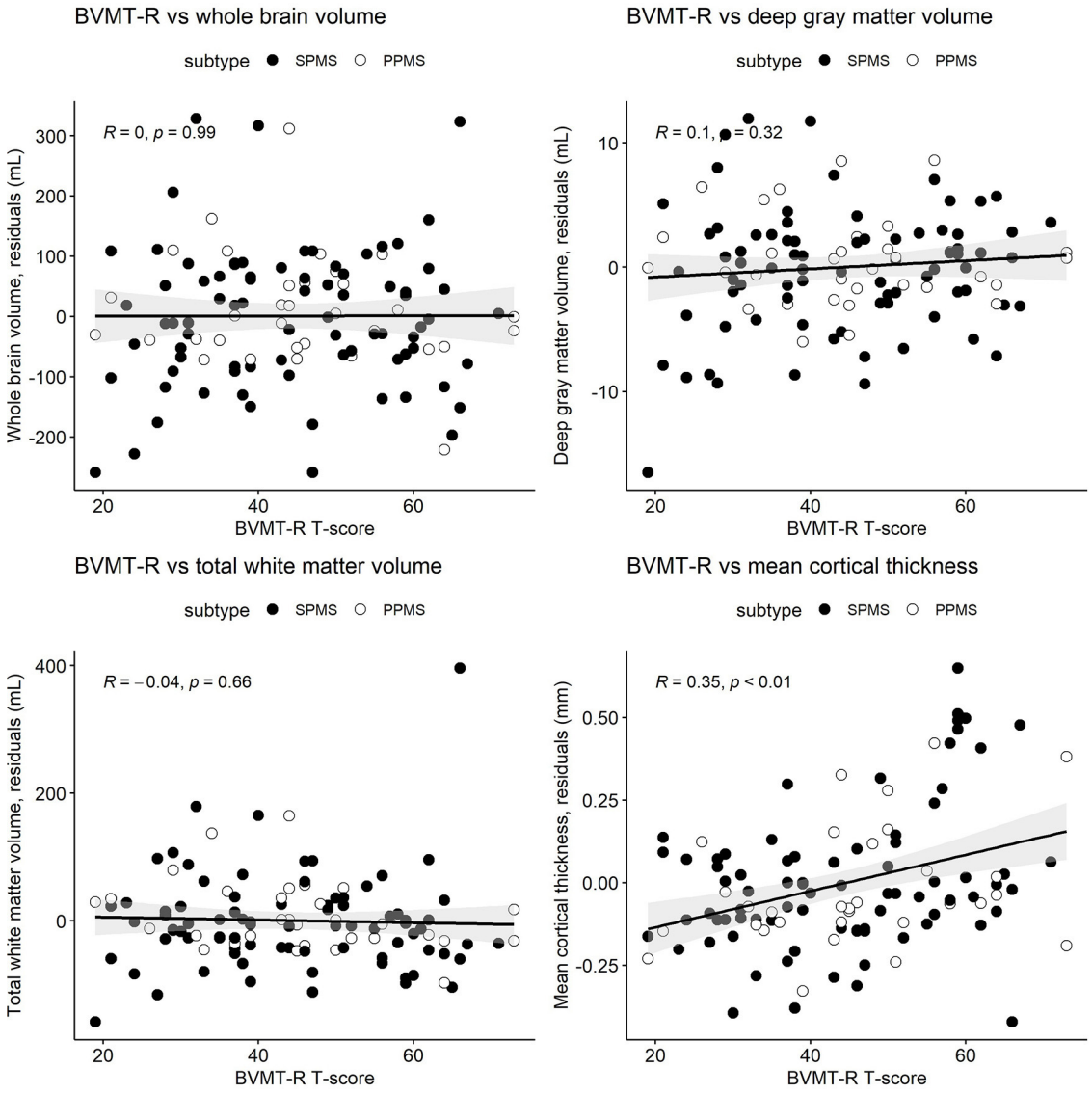

FIGURE 3
Pearson's correlations between the Brief Visuospatial Memory Test-Revised (BVMT-R) T-scores and whole brain volume, deep gray matter volume, total white matter volume, and mean cortical thickness. MRI measures have been adjusted for age and sex, so what is presented here are the residuals (distance each participant is from the age- and sex-adjusted mean). Correlations are for combined secondary progressive (SPMS, filled circles) and primary progressive (PPMS, unfilled circles) multiple sclerosis cohorts. Statistical significance was set at a p-value of $\leq$0.05.

cohorts. In purely relapsing MS cohorts, Fenu et al. report nearly identical Pearson's correlations between SDMT and whole brain volume ($R = 0.38$, $n = 195$) as D'hooghe et al. ($R = 0.4$, $n = 254$) and Calabrese et al. ($R = 0.41$, $n = 70$) despite different MRI segmentation methodologies (26–28). Interestingly and despite a smaller sample size, Fenu also found significant correlations between SDMT and total gray matter and mean cortical thickness ($R = 0.31$ and $R = 0.35$, respectively), while D'hooghe et al. did not find correlations with additional brain regions. Fenu et al. additionally reported significant correlations between both CVLT and BVMT-R and whole brain, total gray matter, and cortical thickness as reported with SDMT, and with similar correlation strengths (from $R = 0.24$ to $R = 0.36$) (25). In a mixed relapsing and progressive MS cohort, Benedict et al. also reported a modest correlation between SDMT and whole brain volume ($R = 0.40$) but no significant correlations between whole and segmented brain volumes with CVLT or BVMT-R (29).

We found only one study conducted in a purely progressive MS population relating BICAMS to brain volumes. Gueveia et al. reported significant correlations of both the SDMT and BVMT-R with deep gray matter volume ($R = 0.66$ and $R = 0.41$, respectively) in a PPMS cohort ($n = 55$), a finding we did not replicate, along with a significant correlation between BVMT-R and neocortical gray volume ($R = 0.39$) (15). This group did not evaluate whole brain volumes. Comparison of our findings to other progressive MS cohorts is anticipated given the growing numbers of treatment trials for progressive MS.

Differences in methodologies of studies associating cognitive tests and brain volumes in non-MS cohorts including small vessel disease, neuromyelitis optica, traumatic brain injury, and

normal aging limit direct comparisons to our results; however, heterogeneous findings suggest a lack of consensus regarding the clinical implications of whole or regional atrophy (30, 31). Brain atrophy in MS may represent a late-stage neurodegenerative phenomenon from demyelination and axonal and glial cell loss. Alternative imaging techniques such as diffusion tensor imaging and MR spectroscopy may detect structural and functional damage prior to irreversible atrophy, highlighting a treatment opportunity (32, 33).

Our participant population, although not selected for cognitive dysfunction, demonstrated a high prevalence (48.2%) of scores more than 1.5 sd below the standardized population mean on cognitive tests, highlighting the importance of identifying and treating cognitive dysfunction in progressive MS. While the SDMT had the highest percentage of abnormal scores (36.8%), 13 participants (11.4%) had abnormal scores in other cognitive domains that would have been missed if the SDMT was the only cognitive test utilized. This reinforces the value of screening across multiple cognitive domains when possible for clinical and research inquiries.

An unexpected finding of our study was the relative lack of impairment in CVLT performance compared to the SDMT and BVMT-R. Usually, impairment is found in all three domains tested in the BICAMS. While neither the CVLT nor BVMT-R gets corrected for education level, our highly educated study population may have had better auditory learning and biased the results. Interestingly, one study found the combination of SDMT and BVMT-R to be the most sensitive to cognitive impairment and had the strongest association with the full battery, suggesting that the CVLT performance may be less clinically relevant (34).

Strengths of the study include the relatively large sample of SPMS and PPMS participants from a large geographical area, trained personnel conducting cognitive testing, centralized blinded scoring of the CVLT and BVMT-R by two raters, and a centralized MRI processing site for brain volume analyses. Study limitations arise primarily from drawing the study sample from an interventional study and not based on the current analyses. The interventional trial required active disability worsening for study entry. As such, our results may not be applicable to stable, non-worsening MS populations. The sample size was not powered to detect differences between SPMS and PPMS in the measures investigated here. The SDMT was administered variously in oral and written formats which, although scored appropriately for the format, may have affected the analyses. The BICAMS battery does not include cognitive domains that may distinguish SPMS and PPMS (9). This analysis lacked healthy control or RRMS comparison populations thereby limiting conclusions about the uniqueness of our findings to progressive MS. Finally, regional cortical thickness and deep gray matter volume—both linked to cognitive dysfunction in some MS studies—were not outcomes of the interventional trial study but are ones that could be investigated in future (4, 35). The cross-sectional design of the current analysis limits conclusions about causality or influence. In fact, longitudinal data from a large interventional trial of natalizumab in SPMS did not find MRI volume changes associated with the worsening of SDMT or other measures of disability (36). Anticipated longitudinal studies including this one in progressive MS populations will clarify the clinical correlates of whole and regional brain atrophy.

5. Conclusion

In this cross-sectional study of veterans and other people with progressive MS, information processing speed was associated with whole brain and total white matter volumes, while verbal and visual memory tests were associated with mean cortical thickness. The strengths of associations were all modest though statistically significant. SPMS and PPMS subtypes appeared to have similar patterns of associations although small numbers precluded definitive confirmation. The planned longitudinal examination of this cohort will determine if changes in cognition and brain volume over time are associated. Advanced imaging techniques may determine if other measures are better predictors of cognitive or other disabilities change over time in progressive MS.

Data availability statement

The datasets presented in this article are not readily available because the datasets generated during and/or analyzed during the current study are not publicly available due to the ongoing status of the longitudinal study, but are available from the corresponding author on reasonable request. The study protocol and statistical analysis plan for the randomized controlled trial has not been attached as a Supplementary File because the methods and analyses for the current cross-sectional analysis are not included in those documents. The protocol and statistical analysis plan for the randomized trial will be included in the primary outcome paper. Requests to access the datasets should be directed to spainr@ohsu.edu.

Ethics statement

The studies involving human participants were reviewed and approved by VA Central IRB, University of Utah Single IRB, University of Vermont IRB, Swedish Medical IRB, Ottawa Research Ethics Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RS: conceptualization, methodology, investigation, writing, and reviewing and editing. AH: methodology, software, formal analysis, visualization, and writing. CW: investigation and data curation and writing. WR: methodology, data processing, and reviewing and editing. JE and DS: investigation and data processing. MF, MP, PR, AS, JR, MW, JH, OS, and RG: investigation and reviewing and editing. AT: conceptualization, methodology, and reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

AS contracted Research with Sanofi, Biogen, Novartis, Actelion, Genentech/Roche. Consulting fees from Octave Bioscience. Research support from Bristol Myers Squibb. Personal compensation for consulting for Genentech, Biogen, Alexion, Celgene, Greenwich Biosciences, TG Therapeutics and OctavemBioscience. Personal compensation non-promotional speaking for EMD Serono. Participationin ma Data Safety and Monitoring Board for NCT03073603, and NCT04877457. MF received a grant from Sanofi-Genzyme Canada. Honoraria or consultation fees from Alexion/Astra Zeneca, BiogenIdec, EMD Inc./EMD Serono/Merck Serono, Find Therapeutics, Hoffman La-Roche, Novartis, Quanterix, Sanofi-Genzyme, Teva Canada Innovation. Member of a company advisory board or board of directors for Alexion/Astra Zeneca, Atara Biotherapeutics, Bayer Healthcare, Celestra Health, EMD Inc./Merck Serono, Find Therapeutics, Hoffman La-Roche, Actelion/Janssen (J&J), Novartis, Sanofi-Genzyme, Setpoint Medical. Participation in a company sponsored speaker's bureau: Sanofi-Genzyme, EMD Serono. PR contracted research with Biogen, Genentech, Novartis, Sanofi. Consulting honoraria: Banner, BristolMyersSquibb, EMD Serono, Genentech, Novartis, Sanofi, TG therapeutics. Speaker honoraria: Biogen, BristolMyersSquibb, Genentech, Novartis, Sanofi, TG therapeutics. OS serves on the editorial boards of Therapeutic Advances in Neurological Disorders, has served on data monitoring committees for Genentech-Roche, Pfizer, Novartis, and TG Therapeutics without monetary compensation, has advised EMD Serono, Novartis, and VYNE, receives grant support from EMD Serono, is a 2021 recipient of a Grant for Multiple Sclerosis Innovation (GMSI), Merck KGaA, is funded by a Merit Review grant (federal award document number (FAIN) BX005664-01 from the United States (U.S.) Department of Veterans Affairs, Biomedical Laboratory Research and Development, is funded by RFA-2203-39314 (PI) and RFA-2203-39305 (co-PI) grants from the National Multiple Sclerosis Society (NMSS).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1188124/full#supplementary-material

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Comorbidity and polypharmacy impact neurobehavioral symptoms and symptom validity failure among post-9/11 veterans with mild traumatic brain injury

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Objective: The study aimed to examine the association between post-concussive comorbidity burdens [post-traumatic stress disorder (PTSD), depression, and/or headache] and central nervous system (CNS) polypharmacy (five or more concurrent medications) with reported neurobehavioral symptoms and symptom validity screening among post-9/11 veterans with a history of mild traumatic brain injury (mTBI).

Setting: Administrative medical record data from the Department of Veterans Affairs (VA) were used in the study.

Participants: Post-9/11 veterans with mTBI and at least 2 years of VA care between 2001 and 2019 who had completed the comprehensive traumatic brain injury evaluation (CTBIE) were included in the study.

Design: Retrospective cross-sectional design was used in the study.

Main measures: Neurobehavioral Symptom Inventory (NSI), International Classification of Diseases, Ninth Revision, and Clinical Modification diagnosis codes were included in the study.

Results: Of the 92,495 veterans with a history of TBI, 90% had diagnoses of at least one identified comorbidity (PTSD, depression, and/or headache) and 28% had evidence of CNS polypharmacy. Neurobehavioral symptom reporting and symptom validity failure was associated with comorbidity burden and polypharmacy after adjusting for sociodemographic characteristics. Veterans with concurrent diagnoses of PTSD, depression, and headache were more than six times more likely [Adjusted odds ratio = 6.55 (99% CI: 5.41, 7.92)]. to fail the embedded symptom validity measure (Validity-10) in the NSI.

Conclusion: TBI-related multimorbidity and CNS polypharmacy had the strongest association with neurobehavioral symptom distress, even after accounting for injury and sociodemographic characteristics. Given the regular use of the NSI in clinical and research settings, these findings emphasize the need for comprehensive neuropsychological evaluation for individuals who screen positively for potential symptom overreporting, the importance of multidisciplinary rehabilitation to restore functioning following mTBI, and the conscientious utilization of symptom validity measures in research efforts.

KEYWORDS

veterans, polypharmacy, multimorbidity, post-traumatic stress disorders, concussion, headache

Introduction

Traumatic brain injury (TBI) is a 'signature wound of war' among post-9/11 veterans, with more than 463,000 documented cases since 2000 (1). Although 80–85% of all cases are mild in severity (mTBI), TBI of any severity can result in long-term changes in physical, emotional, and cognitive functioning (1). As a result, exposure to TBI is possibly better described as the potential onset of a multifaceted disease process rather than a historical event (2). Multiple, concurrent, chronic physical, or mental health conditions (i.e., multimorbidity) and/or central nervous system (CNS) polypharmacy (i.e., 5 or more central nervous system medications) can have compounding adverse effects on wellbeing and functioning (3–5). The challenges veterans of the post-9/11 era face encompass not only recovery but also the stress of stigma and the logistics of care for ambiguous and common clinical complaints, cumulatively described as the "burden of adversity." (6).

The timely identification and treatment of TBI have the potential to prevent or delay the accumulation of related comorbidities, symptoms, and burdens (including CNS polypharmacy's adverse effects). In response, the Department of Veterans Affairs (VA) instituted mandatory TBI screening among all post-9/11 veterans in 2007 (7). Those who screen positively for TBI are referred for the comprehensive TBI evaluation (CTBIE), an in-depth structured interview, and physical assessment administered by a clinical specialist. Embedded within the CTBIE, the Neurobehavioral Symptom Inventory (NSI) assesses the impact of neurobehavioral symptoms commonly associated with TBI exposure (8).

TBI, however, is often followed by common mental and physical health symptoms, making it difficult to isolate TBI-related sequelae and symptoms from other causes. Given this complicated clinical picture, patients with a history of mTBI may present with an extensive medical history that includes treatment with multiple (sometimes concurrent) medications acting on the CNS (i.e., CNS polypharmacy) which can further exacerbate symptomology with medication-induced side effects (4, 9, 10).

To assess potential symptom overreporting, the Validity-10, an embedded measure of symptom validity, was developed leveraging low frequency or unusual symptom complaints on the NSI (11). Current guidance recommends that individuals who score 23 or greater on the Validity-10 should be referred for more comprehensive neuropsychiatric evaluation, presumably to evaluate psychological issues to which the symptom reporting might be better attributed. Its initial derivation, however, was in a sample of relatively healthy young men on active duty, from which those with neurological disorders were excluded. Although the Validity-10 is a valuable tool that has been praised for its clinical utility, concerns have emerged regarding its sensitivity among more clinically complex patient subgroups, particularly those with psychiatric conditions (12–14).

In this study, we examined the association between common comorbidities and polypharmacy with neurobehavioral symptom reporting among post-9/11 veterans with deployment-related mTBI. We first hypothesized that increasingly complex comorbidity would be associated with significantly greater neurobehavioral symptom burden and Validity-10 failure. Accounting for complex comorbidity, we also hypothesized that CNS polypharmacy would similarly have a significant association with increased neurobehavioral burden and Validity-10 failure. These findings are an important step toward increasingly sensitive estimates for symptom overreporting to account for the unique and complex needs of veterans experiencing multimorbidity associated with TBI exposure.

Methods

Sample

Following institutional review board approval, we used national health system data from the Departments of Defense (DoD) and Veterans Health Administration (VHA). The inclusion criteria were post-9/11 deployed veterans who a) had at least 3 years in the DoD (FY1999-FY2019) and b) at least 2 years of VHA care between fiscal year (FY) 2001 (1 October 2001) and the end of FY 2019 (30 September 2019). We further restricted this sample to those who completed the CTBIE after its institution in 2007 through 2018. The CTBIE is an in-depth clinical interview that includes a physical examination, a medical and psychiatric history, combat exposures, and the NSI. Finally, we limited the sample to veterans who were classified as having mTBI using a previously developed algorithm described elsewhere (15). For those who met

these inclusion criteria, we compiled and merged VHA inpatient and outpatient healthcare data and pharmacy records from FY 2001 to FY 2020.

Neurobehavioral symptom inventory

The NSI is a self-reported measure that assesses disruption over the past 30 days attributable to commonly observed symptoms after TBI (8). Response options for each item range from 0 (rarely or never present, not a problem at all) to 4 (almost always present, very severe problem) with total scores as the result of summing of all 22 items. Scores range between 0 and 88, where higher values indicate greater disruption of activities due to neurobehavioral symptoms. The NSI can also describe a more specific disruption due to affective, cognitive, somatosensory, and vestibular symptoms based on a recent factor analysis (16). Affective, cognitive, somatosensory, and vestibular subscale scores represent average responses to each item within the scale. To assess potential symptom overreporting, the Validity-10 was developed leveraging a subset of items of the NSI that are low frequency or unusual symptom complaints for healthy young active duty men (11). Scores of 23 or greater on the Validity-10 subscale are considered possible symptom overreporting, and clinical practice dictates that such patients should be referred for additional neuropsychiatric evaluation. Validity-10 status is therefore considered either "pass" (i.e., scores of 22 or lower) or "fail" (i.e., scores of 23 or greater).

Comorbidity burden

Depression, headache, and PTSD were used to assess the comorbidity burden based on their prominent association with TBI among military veterans (10). We used the International Classification of Diseases, Ninth and Tenth Revisions, and Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis codes to identify PTSD, depression, and headache (see Supplementary Table 1) within 1 year (before or after) of the CTBIE. We used an established and conservative approach of requiring at least two diagnosis codes assigned at least 7 days apart in VA outpatient care or a single inpatient diagnosis to identify qualifying diagnoses (17). We then created a composite score based on the number of qualifying diagnoses among each PTSD, depression, and/or headache. The resultant variable was zero ("none") for those with no history of PTSD, depression, or headache but otherwise equal to the count of these three diagnoses.

CNS polypharmacy

The VHA Pharmacy Benefits Management outpatient database was used to identify unique outpatient medications dispensed by the VA product name. Although there is no standardized definition for polypharmacy, the field has most frequently utilized a definition of five or more concurrent CNS medications for younger patients (18). We used an algorithm to identify veterans in receipt of five or more CNS-active medications (hereafter polypharmacy, "yes" or "no") within a year (before or after) of CTBIE administration (see Supplementary Table 2) (19).

Sociodemographic characteristics

We collected personal and military history information from VHA datasets. From the CTBIE, we included age, sex (men or women), marital status (married/partnered, divorced/separated/widowed, or single/never married), race/ethnicity (white, Black Hispanic, Black non-Hispanic, Asian American and Pacific Islander [AAPI], Native American, Hispanic, or other), and education (high school or equivalent, college graduate/post-graduate, some college, less than high school, or unknown). Age violated the assumption of normality and was subsequently categorized into 19–29, 30–39, 40–50, or 51 years and older. We also classified veterans according to military branch (army, air force, marine corps, or navy/coast guard), component (active duty, national guard, or reserve), and rank (enlisted or officer).

Statistical analyses

Descriptive statistics characterized the post-9/11 veteran sample by comorbidity burden. General linear modeling was used to predict NSI total and subscale (i.e., affective, cognitive, somatosensory, and vestibular) scores using comorbidity burden and polypharmacy variables while controlling for sociodemographic characteristics (age, sex, race/ethnicity, marital status, education, military branch, rank, and component). Model fits were measured by the coefficient of determination (R^2). Logistic regression was used to predict Validity-10 failure using comorbidity burden and polypharmacy status while controlling for sociodemographic characteristics (age, sex, race/ethnicity, marital status, education, military branch, rank, and component). We used a p-value of <0.01 as our level of significance and reported 99% confidence intervals for each analysis. All analyses were conducted using SAS® Version 9.3 (SAS Institute, Cary, NC).

Results

As shown in Table 1, on average, the sample was 31.9 (SD 8.2) years old, men (94%), white (63%), married/partnered (52%), and had a high school education or equivalent (60%). Most veterans were from the Army (72%) and served as enlisted members (96%). More than 28% of the sample met the criteria for polypharmacy. Approximately 91% of the sample had diagnoses of either PTSD, depression, headache, or some combination thereof diagnosed in VA care. Overall, 76.12% had diagnoses of PTSD, 53.59% depression, and 58.36% headache.

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TABLE 1 Characteristics of the post-9/11 veteran sample with deployment-related mild traumatic brain injury (mTBI) by comorbidity burden.

N (%)	Comorbidity burden*				Total sample *N* = 92,495
	None 7,664 (8.29)	One 22,894 (24.75)	Two 34,746 (37.57)	Three 27,191 (29.40)	
Polypharmacy	183 (2.39)	2,419 (10.57)	9,857 (28.37)	13,536 (49.78)	25,995 (28.10)
Age					
19–29	4,191 (54.68)	12,519 (54.68)	17,631 (50.74)	12,033 (44.25)	46,374 (50.14)
30–39	1,951 (25.46)	6,287 (27.46)	10,846 (31.22)	9,431 (34.68)	28,515 (30.83)
40–49	1,157 (15.10)	3,205 (14.00)	5,004 (14.40)	4,686 (17.23)	14,052 (15.19)
50+	365 (4.76)	883 (3.86)	1,265 (3.64)	1,041 (3.83)	3,554 (3.84)
Sex (F)	241 (3.14)	933 (4.08)	1,681 (4.84)	2,228 (8.19)	5,083 (5.50)
Race/ethnicity					
White	5,203 (67.89)	15,269 (66.69)	22,119 (63.66)	16,028 (58.95)	58,619 (63.38)
Asian American/Pacific Islander	562 (7.33)	1,851 (8.09)	3,465 (9.97)	3,196 (11.75)	9,074 (9.81)
Black Hispanic	34 (0.44)	90 (0.39)	113 (0.33)	135 (0.50)	372 (0.40)
Black non-Hispanic	951 (12.41)	2,838 (12.40)	4,748 (13.66)	4,323 (15.90)	12,860 (13.90)
Hispanic	767 (10.01)	2,325 (10.16)	3,514 (10.11)	2,860 (10.52)	9,466 (10.23)
Native American	130 (1.70)	460 (2.01)	715 (2.06)	608 (2.24)	1,913 (2.07)
Unknown	17 (0.22)	61 (0.27)	72 (0.21)	41 (0.15)	191 (0.21)
Marital status					
Married/partnered	3,564 (46.50)	11,440 (49.97)	17,796 (51.22)	15,186 (55.85)	47,986 (51.88)
Divorced/separated/widowed	1,446 (18.87)	4,691 (20.49)	8,129 (23.40)	6,799 (25.00)	21,065 (22.77)
Single, never married	2,638 (34.42)	6,713 (29.32)	8,761 (25.21)	5,149 (18.94)	23,261 (25.15)
Unknown	16 (0.21)	50 (0.22)	60 (0.17)	57 (0.21)	183 (0.20)
Education					
High school or equivalent	4,486 (58.53)	13,723 (59.94)	21,314 (61.34)	16,149 (59.39)	55,672 (60.19)
College grad/post graduate	563 (7.35)	1,396 (6.10)	1,884 (5.42)	1,591 (5.85)	5,434 (5.87)
Less than high school	108 (1.41)	291 (1.27)	491 (1.41)	383 (1.41)	1,273 (1.38)
Some college	2,405 (31.38)	7,052 (30.80)	10,285 (29.60)	8,424 (20.98)	28,166 (30.45)
Unknown	102 (1.33)	432 (1.89)	772 (2.22)	644 (2.37)	1,950 (2.11)
Military branch					
Army	5,170 (67.46)	15,671 (68.45)	25,191 (72.50)	20,657 (75.97)	66,689 (72.10)
Air force	251 (4.58)	935 (4.08)	1,352 (3.89)	1,042 (3.83)	3,680 (3.98)
Marine corps	1,534 (20.02)	4,706 (20.56)	6,311 (18.16)	4,127 (15.18)	16,678 (18.03)
Navy/coast guard	609 (7.95)	1,582 (6.91)	1,892 (5.45)	1,365 (5.02)	5,448 (5.89)
Military component					
Active	2,694 (35.15)	8,592 (37.53)	14,929 (42.97)	14,293 (52.57)	40,508 (43.79)
Guard	1,421 (18.54)	3,955 (17.28)	6,035 (17.37)	4,454 (16.38)	15,865 (17.15)
Reserve	3,549 (46.31)	10,347 (45.20)	13,782 (39.66)	8,444 (31.05)	36,122 (39.05)
Military rank (enlisted)	7,235 (94.40)	21,926 (95.77)	33,525 (96.49)	26,144 (96.15)	88,830 (96.04)

mild traumatic brain injury, mTBI; central nervous system, CNS.

*The comorbidity burden value is defined as "none" for those with no history of PTSD, depression, or headache, but otherwise equal to the count of these three diagnoses.

TABLE 2 Mean neurobehavioral symptom inventory (NSI) scores by comorbidity burden.

	Comorbidity burden*			
M (SD)	None	One	Two	Three
NSI measure				
Affective subscale	1.51 (0.88)	2.00 (0.95)	2.49 (0.87)	2.80 (0.81)
Cognitive subscale	1.36 (0.93)	1.73 (1.01)	2.13 (1.00)	2.45 (0.95)
Somatosensory subscale	0.91 (0.64)	1.21 (0.71)	1.46 (0.75)	1.75 (0.77)
Vestibular Subscale	0.78 (0.72)	1.00 (0.79)	1.24 (0.83)	1.49 (0.86)
Total NSI	25.46 (14.18)	33.13 (15.50)	40.66 (15.51)	47.01 (15.43)

*Comorbidity burden value is defined as "none" for those with no history of PTSD, depression, or headache but otherwise equal to the count of these three diagnoses.

Total NSI and subfactor scores

Table 2 describes the mean scores on the NSI subscales (i.e., affective, cognitive, somatosensory, and vestibular) by comorbidity burden. The reported neurobehavioral symptom burden was the highest on the affective subscale and the lowest on the vestibular subscale. Regardless of the NSI subscale, the reported neurobehavioral symptom burden increased as the comorbidity burden increased.

As shown in Table 3, comorbidity burden and polypharmacy were each significantly associated with increased neurobehavioral symptom reporting. Comorbidity burden demonstrated an increasing association on all examined aspects of neurobehavioral symptom burden as the number of comorbid conditions increased, which was also the single largest association among all covariates in the analysis. Even after accounting for the effects of comorbidity burden, polypharmacy had a significant association with neurobehavioral symptom reporting, which was the second strongest association in the fully adjusted analysis.

Older age, women (relative to men), veterans of non-white ethnicity (relative to white), married/partnered (relative to all other marital statuses), and enlisted service members (relative to officers) were each consistently associated with increased neurobehavioral symptom burden reporting. The various models ranged in variance were explained (R^2) by the series of models, ranging from 10% (NSI-vestibular subscale) to 21% (NSI-affective subscale).

Validity-10 failure

The results of the logistic regression predicting Validity-10 failure are shown in Table 4. Increasing comorbidity burden was associated with increased odds for Validity-10 failure, wherein those with PTSD, depression, and headache were more than six times more likely [Adjusted odds ratio = 6.55 (99% CI: 5.41, 7.92)]. to do so relative to those with none of those comorbidities. Similarly, those who met the criteria for polypharmacy were twice as likely to exceed the Validity-10 cutoff score. Consistent with the other NSI measures, older age, veterans of non-white ethnicity (relative to white), female veterans, and enlisted veterans (relative to officer) also had increased odds for Validity-10 failure.

Discussion

Among post-911 veterans with a history of mTBI, burdensome comorbidity, and CNS polypharmacy accounted for substantial variation in neurobehavioral symptom reporting after controlling for sociodemographic characteristics. This is consistent with previous studies, in that, while the NSI is a reliable and valid measure of post-concussive symptom distress, its scores are influenced by co-occurring psychiatric disorders such as PTSD, depression, and generalized anxiety (12, 20, 21). These analyses extend this effect to headache, a predominant complaint associated with TBI exposure. Perhaps more importantly, the Validity-10 failure rate was similarly affected by comorbidity burden and polypharmacy, revealing a need to account for TBI-related comorbidity in the utilization of the NSI. Patients with burdensome comorbidity following mTBI are likely best served by clinical and research contexts with increasingly holistic evaluation and care, particularly among those for whom potential symptom overreporting is a concern.

A history of mTBI exposure and psychological complaints are deeply and inextricably entwined (22). A clinical history of mTBI is emerging as a significant factor in the treatment for PTSD, influencing the type of treatment administered and how effective it may be (23, 24). It appears that, even though there are several treatments that are generally effective in treating PTSD symptoms, patients with a history of mTBI often have more persistent symptoms (25, 26). Given that Brenner et al. have similarly evidenced higher-than-expected rates of probable TBI among veterans seeking mental health services at the VA, a clearer understanding of how TBI and mental health are intertwined is critical (6). Therefore, although the Validity-10 symptom validity scale was initially derived from a clinically uncomplicated service member sample aside from deployment-related TBI status, its implementation could be adapted for use among the more complex patients often seen in polytrauma care. In fact, these findings emphasize the need for enhanced interdisciplinary clinical teams to ameliorate neurobehavioral symptoms and reduce polypharmacy (27). It is possible that clinical care teams with an eye for long-term adaptations in stress and mental health management could better enable sustainable reductions in symptom reporting and disability.

Increasingly advanced and sensitive statistical tools have recently made possible the identification of latent subgroups among clinic populations treating patients with TBI-related issues. For example, the polytrauma clinical triad describes a post-9/11 veteran patient subgroup that experienced TBI and grappled with pain and PTSD in its wake (28). Ensuing investigations have revealed that the constellation of clinical history and comorbid conditions encapsulated by the polytrauma clinical triad renders a substantially greater risk for prolonged symptomology, substance abuse, homelessness, and suicide-related behavior (3, 29, 30). Combined physical and health challenges experienced following TBI exposure can be enduring, progressive, and frequently diagnostically ambiguous, underscoring the need for

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TABLE 3 Results of the generalized linear model on each of the total score and subfactors of the Neurobehavioral Symptom Inventory (NSI).

B, SE	Affective $R^2 = 0.21$	Cognitive $R^2 = 0.14$	Somatosensory $R^2 = 0.16$	Vestibular $R^2 = 0.10$	Total NSI $R^2 = 0.20$
Comorbidity burden**					
None	Ref	Ref	Ref	Ref	Ref
One	0.45 (0.01)*	0.33 (0.01)*	0.27 (0.01)*	0.19 (0.01)*	6.92 (0.20)*
Two	0.86 (0.01)*	0.66 (0.01)*	0.46 (0.01)*	0.37 (0.01)*	12.97 (0.19)*
Three	1.07 (0.01)*	0.88 (0.01)*	0.67 (0.01)*	0.54 (0.01)*	14.44 (0.20)*
Polypharmacy					
No	Ref	Ref	Ref	Ref	Ref
Yes	0.37 (0.01)*	0.37 (0.01)*	0.25 (0.01)*	0.26 (0.01)*	6.66 (0.12)*
Age					
19–29	Ref	Ref	Ref	Ref	Ref
30–39	0.07 (0.01)*	0.07 (0.01)*	0.10 (0.01)*	0.08 (0.01)*	1.57 (0.12)*
40–49	0.01 (0.01)	0.04 (0.01)*	0.19 (0.01)*	0.13 (0.01)*	2.00 (0.16)*
50+	0.02 (0.02)	0.07 (0.02)*	0.23 (0.01)*	0.26 (0.01)*	3.00 (0.27)*
Sex					
Men	Ref	Ref	Ref	Ref	Ref
Women	0.03 (0.01)	0.00 (0.01)	0.15 (0.01)*	0.16 (0.01)*	1.29 (0.22)*
Race/ethnicity					
White	Ref	Ref	Ref	Ref	Ref
Asian American/Pacific Islander	0.03 (0.01)*	0.03 (0.01)*	0.03 (0.01)*	0.04 (0.01)*	0.68 (0.18)*
Black Hispanic	0.17 (0.04)*	0.12 (0.05)*	0.17 (0.04)*	0.18 (0.04)*	3.35 (0.78)*
Black non-Hispanic	0.15 (0.01)*	0.04 (0.01)*	0.17 (0.01)*	0.12 (0.01)*	2.73 (0.15)*
Hispanic	0.07 (0.01)*	0.03 (0.01)	0.09 (0.01)*	0.09 (0.01)*	1.58 (0.17)*
Native American	0.07 (0.02)*	0.07 (0.02)*	0.09 (0.02)*	0.08 (0.02)*	1.70 (0.35)*
Unknown	0.09 (0.06)	−0.01 (0.07)	0.04 (0.05)	0.01 (0.06)	0.63 (1.08)
Marital status					
Married/partnered	Ref	Ref	Ref	Ref	Ref
Divorced/separated/widowed	0.04 (0.01)*	0.01 (0.01)	−0.01 (0.01)	−0.01 (0.01)	0.27 (0.12)
Single, never married	−0.09 (0.01)*	−0.09 (0.01)*	−0.11 (0.01)*	−0.08 (0.01)*	−2.01 (0.13)*
Unknown	−0.18 (0.06)*	−0.24 (0.07)*	−0.19 (0.05)*	−0.25 (0.06)*	−4.40 (1.13)*
Education					
High school or equivalent	Ref	Ref	Ref	Ref	Ref
College grad/post-graduate	−0.05 (0.01)*	−0.05 (0.02)*	0.00 (0.01)	−0.01 (0.01)	−0.68 (0.24)*
Less than high school	0.03 (0.02)	0.06 (0.03)	0.04 (0.02)	0.06 (0.02)*	1.04 (0.42)
Some college	−0.02 (0.01)*	−0.01 (0.01)	0.00 (0.01)	0.00 (0.01)	−0.17 (0.11)
Unknown	0.20 (0.02)*	0.24 (0.02)*	0.21 (0.02)*	0.23 (0.02)*	4.52 (0.35)*
Branch					
Army	Ref	Ref	Ref	Ref	Ref
Air force	−0.04 (0.01)	−0.05 (0.02)*	0.00 (0.01)	0.03 (0.01)	−0.45 (0.26)
Marine corps	−0.03 (0.01)*	−0.03 (0.01)*	0.00 (0.01)	0.00 (0.01)	−0.19 (0.14)

(Continued)

TABLE 3 (Continued)

B, SE	Affective $R^2 = 0.21$	Cognitive $R^2 = 0.14$	Somatosensory $R^2 = 0.16$	Vestibular $R^2 = 0.10$	Total NSI $R^2 = 0.20$
Navy/coast guard	−0.06 (0.01)*	−0.08 (0.01)*	−0.03 (0.01)	0.01 (0.01)	−1.04 (0.22)*
Component					
Active	Ref	Ref	Ref	Ref	Ref
Guard	−0.03 (0.01)*	−0.02 (0.01)	−0.04 (0.01)*	−0.05 (0.01)*	−0.64 (0.15)*
Reserve	−0.03 (0.01)*	−0.02 (0.01)	−0.05 (0.01)*	−0.05 (0.01)*	−0.69 (0.12)*
Rank					
Officer	Ref	Ref	Ref	Ref	Ref
Enlisted	0.11 (0.02)*	0.07 (0.02)*	0.10 (0.01)*	0.06 (0.02)*	2.06 (0.28)*

*Statistically significant at the $p < 0.01$ level.
reference, Ref.
**The comorbidity burden value is defined as "none" for those with no history of PTSD, depression, or headache but otherwise equal to the count of these three diagnoses.

an interdisciplinary approach to rehabilitation following TBI, regardless of its chronicity.

CNS polypharmacy status was associated with neurobehavioral symptom reporting, even when controlling for the comorbidity burden and sociodemographic characteristics. CNS polypharmacy is an established concern among older individuals as the risk for multimorbidity or multiple concurrent chronic conditions becomes more common in older age (31, 32). Older veterans appear to be at a particular risk for adverse outcomes associated with polypharmacy, including morbidity, mortality, and suicide (5, 19, 32). Moreover, polypharmacy itself has been repeatedly associated with a greater risk for suicide-related behaviors (4, 19, 33). Similar to the existing literature on CNS polypharmacy among older adults, post-911 veterans were also susceptible to severe adverse reactions secondary to having multiple CNS-acting medications on hand to manage co-existing chronic conditions. Side effects of common CNS depressants (e.g., somnolence, fatigue, and poor concentration) and/or CNS stimulants (e.g., headache, insomnia, dizziness, and dizziness) potentially amplified under conditions of polypharmacy and can be indistinguishable from otherwise diagnostically ambiguous TBI sequelae.[4(p)] In fact, most patients subjected to polypharmacy are largely unaware of its existence or dangers, revealing that patient education may be an opportune path forward in ameliorating or preventing adverse outcomes to which this patient subpopulation may be particularly vulnerable (34). Our assessment of medication data in this effort is limited, however, to prescriptions filled at the VA and may underestimate the extent to which polypharmacy impacts military veterans. Fortunately, support for alternatives to pharmaceutical treatments for several post-concussive conditions (e.g., insomnia and headache), such as neurostimulation in its various incarnations, continues to mount in the literature (35–39). Given that more than 90% of the sample in the present study had mTBI and at least one other condition (i.e., PTSD, depression, and/or headache), the need for clinical practice guidelines sensitive to polypharmacy and multimorbidity is of great importance (40, 41).

Complex comorbidity and CNS polypharmacy impart a significant burden on the patient, provider, and healthcare system on the whole (41, 42). Heightened symptom reporting may influence clinical care pathways and affect patient engagement, particularly for racial/ethnic minorities or those with a lower socioeconomic status (43). In this analysis, minority status was associated with significantly greater neurobehavioral symptom distress and Validity-10 failure, even after accounting for many other socio = demographic and clinical characteristics. Although this effect was the most dramatic among Black Veterans, all minority veterans demonstrated a similar trend. Taken together with recent reports that extant barriers in the TBI screening process make the access and utilization of care more burdensome, renewed scrutiny and continued evolution of these programs are vital to enhancing long-term outcomes among veterans with mTBI (6, 9, 44). This finding may also underscore the continued need for diversity among clinical care providers, efforts to reduce stigma in the receipt of care, the enhancement of patient education efforts, and the coordination of complex care through social work and programmatic supports (45).

Consistent with the "burden of adversity" hypothesis, these findings have direct implications for the interpretation of neurobehavioral symptom burden scores captured by the NSI, particularly for patients with burdensome comorbidity (6). Landmark efforts to establish normative distributions (46) and develop the Validity-10 (11) for the NSI were undertaken among relatively homogenous clinical populations from which patients with neurological conditions were excluded. As a result, patients with more numerous and/or severe psychological, physical, or neurological comorbidities are not well characterized or represented by these initial efforts. Consistent with this gap, numerous reports have concluded that amended or refined thresholds for the Validity-10 may be critical to its implementation in more clinically complex populations (12, 13, 47–50). Moreover, the use of Validity-10 failure to exclude patients in research efforts may harm the generalizability of the findings and applicability to those most impacted by TBI-related neurobehavioral sequelae. Given that the potential symptom overreporting is presumably more consequential and prevalent in forensic settings (as opposed to clinical or research contexts, of which the VA is a unique entity given its role in service-connected disability adjudication), considering that the setting in which the NSI is collected could

TABLE 4 Results of the logistic regression predicting Validity-10 failure.

AOR (99% CI)	Validity-10 failure
Comorbidity burden**	
None	Ref
One	2.50 (2.06, 3.04)*
Two	4.30 (3.55, 5.19)*
Three	6.55 (5.41, 7.92)*
Polypharmacy	
No	Ref
Yes	2.06 (1.95, 2.18)*
Age	
19–29	Ref
30–39	1.26 (1.18, 1.34)
40–49	1.53 (1.42, 1.66)*
50+	1.94 (1.71, 2.20)*
Sex	
Men	Ref
Women	1.20 (1.08, 1.33)*
Race/ethnicity	
White	Ref
Asian American/Pacific Islander	1.20 (1.10, 1.31)*
Black Hispanic	1.64 (1.14, 2.37)*
Black non-Hispanic	1.58 (1.47, 1.69)*
Hispanic	1.45 (1.33, 1.57)*
Native American	1.39 (1.18, 1.65)*
Unknown	0.95 (0.50, 1.80)
Marital status	
Married/partnered	Ref
Divorced/separated/widowed	0.99 (0.93, 1.06)
Single, never	0.82 (0.77, 0.89)*
Unknown	0.54 (0.28, 1.04)
Education	
High school or equivalent	Ref
College grad/post-graduate	1.00 (0.89, 1.13)
Less than high school	1.13 (0.91, 1.39)
Some college	0.99 (0.94, 1.05)
Unknown	1.58 (1.35, 1.85)*
Military branch	
Army	Ref
Air force	1.08 (0.95, 1.23)
Marine corps	1.03 (0.95, 1.11)
Navy/coast guard	0.98 (0.87, 1.10)
Military component	
Active	Ref
Guard	1.02 (0.95, 1.10)
Reserve	0.99 (0.93, 1.05)
Military rank	
Officer	Ref
Enlisted	0.76 (0.66, 0.89)*

*Statistically significant at the $p < 0.01$ level.
**The comorbidity burden value is defined as "none" for those with no history of PTSD, depression, or headache but otherwise equal to the count of these three diagnoses.

be a principal factor in its interpretation (51). Given that a recent report noted a stark dearth of effort assessments among veterans in receipt of diagnoses of early-onset dementia, a reminder of the need for its comprehensive assessment appeared warranted (52). Cumulatively, this underscores a need for more dynamic and comprehensive ways of evaluating symptom overreporting among patients with complex comorbidity who are more likely to indicate greater disruption from neurobehavioral symptoms by virtue of that comorbidity status.

This study has some notable limitations. First, while the examined factors sought to comprehensively capture clinical and sociodemographic factors associated with neurobehavioral symptom burden, the list is not necessarily exhaustive. These nationwide data were also cross-sectional and, therefore, only examined associations rather than causal relationships on the neurobehavioral symptom burden. Our approach to approximating comorbidity burden selected among the most common TBI-related sequelae (i.e., PTSD, depression, and headache) as an exhaustive list was considered less feasible and interpretable with the statistical tools available. Another limitation to using clinical diagnoses from ICD codes instead of diagnostic instruments is that clinicians tend to use heuristics to minimize the number of diagnoses and/or to ensure access to certain clinics. Assessment of medications was limited to those prescribed in the VA and did not include medications from outside providers or over-the-counter medications that may similarly contribute to polypharmacy status. Moreover, medication-level data in this evaluation were not considered in this analysis but could be an opportune future direction. The generalizability of the findings may be limited to veterans actively engaged in VHA care as care outside the VHA in more representative samples was not captured. Moreover, we included only post-9/11 veterans who completed the CTBIE in this analysis; thus, generalizability is limited to veterans who were screened and evaluated.

Conclusion

This study sought to examine neurobehavioral symptom reporting among post-9/11 veterans with a history of deployment-related mTBI. Comorbidity burden (i.e., mTBI, PTSD, depression, and/or headache) and concomitant CNS polypharmacy provided

significant explanative power in reported neurobehavioral symptom distress and the evaluation of symptom validity (i.e., Validity-10), underscoring a potential benefit for adjusted thresholds for clinically complex patients to maintain its specificity for identifying potential symptom overreporting. The application of the Validity-10 in complex clinical populations outside of mTBI likely extends the use of the brief screening measure beyond its original scope. As such, it is strongly recommended that "failure" on a single symptom validity assessment prompt the examination of additional indicators of effort and/or symptom distress. Patients reporting substantial distress on the NSI would likely benefit from treatment through a coordinated, multidisciplinary lens for clinical care. Additionally, careful consideration and implementation of symptom validity metrics in research efforts could improve representation for those with burdensome neurobehavioral symptoms that may have otherwise been excluded from analyses by virtue of that status. Consistent with the onus for and promising early evidence from the VA-funded Intensive Evaluation and Treatment Programs (IETP) project (53), there is a need for increasingly nuanced clinical practice guidelines and utility for interdisciplinary clinical teams to serve subpopulations of patients at a greater risk for multimorbidity or polypharmacy. Future efforts could expand on this line of inquiry to identify particularly deleterious combinations of CNS-active medications, particularly burdensome drug effects, or interactions that reveal opportunities for enhanced patient education and facilitate clinical care pathways that connect patients with clinical specialists in consideration of the totality of their rehabilitative journey.

Cumulatively, this study broadly invokes renewed consideration for the "burden of adversity," a hypothesis that highlights the far-reaching effects of physical, mental, and functional disability that TBI-related multimorbidity can impart and highlights psychosocial, stigmatizing, and logistical challenges endemic to the pursuit of rehabilitation following TBI.

Data availability statement

The datasets presented in this article are not readily available because the dataset is owned by the Department of Veterans Affairs and is subject to Federal restrictions. Requests to access the datasets should be directed to alicia.swan@va.gov.

Ethics statement

The studies involving human participants were reviewed and approved by Salt Lake City VA IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AS, MP, EK, and MA contributed to conception and design of the study. MA organized the database and performed the statistical analysis. AS wrote the first draft of the manuscript. AS, MP, EK, JM, DC, AV, and ML wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1228377/full#supplementary-material

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Telehealth-based exercise in amyotrophic lateral sclerosis

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The Veterans Health Administration (VHA) has served as a leader in the implementation of telerehabilitation technologies and continues to expand utilization of non-traditional patient encounters to better serve a geographically and demographically diverse population. Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease impacting Veterans at a higher rate than the civilian population and associated with high levels of disability and limited access to subspecialized care. There is growing evidence supporting exercise-based interventions as an independent or adjunctive treatment to maintain or restore function for this patient population; many of these interventions can be delivered remotely by telehealth. The recent advancements in disease-modifying therapies for neuromuscular disorders will likely increase the importance of rehabilitation interventions to maximize functional outcomes. Here, we review the evidence for specific exercise interventions in ALS and the evidence for telehealth-based exercise in neuromuscular disorders. We then use this existing literature to propose a framework for telehealth delivery of these treatments, including feasible exercise interventions and remote outcome measures, recommended peripheral devices, and an example of a current remote group exercise program offered through VHA.

KEYWORDS

amyotrophic lateral sclerosis, telehealth, telemedicine, rehabilitation, exercise

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease with an estimated lifetime prevalence of one in 400 adults in the United States (1). Veterans experience an even greater risk of developing ALS, with nearly twice the rate of their civilian counterparts (2). As a result, the Veterans Healthcare Administration made ALS a 100% presumptively service-connected condition in 2008 (3).

The standard of care for ALS consists of multidisciplinary care visits quarterly (4), however, interval therapy follow-ups are frequently needed. With over 50% of persons with ALS in the United States living >50 miles away from the nearest ALS specialty center (5), there is a significant barrier for persons with ALS to access a therapist for the multiple visits generally required to follow through a treatment plan.

Physical therapy (PT) is an important component of care for persons with ALS. The role of the physical therapist in the ALS specialty program is to support prevention of secondary complications, restoration of strength and function when possible, and provision and training in strategies and durable medical equipment to compensate for lost function. Therapist expertise in ALS is needed to avoid exacerbation of symptoms such as fatigue, weakness, dyspnea, or injury related to falls. Additionally, an understanding of the typical progression of ALS allows the therapist to anticipate disease progression to ensure appropriate durable medical equipment

(DME) provision, which will meet both the current and future needs of the patient-saving time and cost to both patient and the healthcare system by avoiding redundant prescriptions of equipment as the degree of disability advances. Unfortunately, community-based outpatient physical therapists may have limited experience in providing care to patients with ALS.

Advances in disease-modifying therapies have the potential to slow progression and extend life expectancies in ALS, thereby shifting even more focus on the therapist's role in overseeing a rehabilitative exercise program to enhance functional outcomes. With this change, the ability to access PT for interval care between quarterly visits will become more critical for the person with ALS to ensure adequate supervision and progression toward the goals of treatment. Unsupervised home exercise programs for ALS have been studied, and while patients benefit with improved function, a high drop-out rate has been reported (6).

Use of telehealth for provision of specialized services for persons with ALS has been found to be efficient and economical means to deliver evidence-based interdisciplinary care (7), however, best practices for delivery of interval PT rehabilitative interventions for this population remain undefined. In this narrative review, we will provide an overview of the literature on exercise in ALS, which will be followed by discussion on implementation of exercise modalities to a virtual care setting based upon existing evidence in neuromuscular disease. Remote outcome measures, exercise interventions which can be delivered by telehealth, and peripheral devices used to enhance the collection of remote assessments on the patient's end will be explored.

Specific exercises and adaptability to telehealth

Range of motion exercises

Throughout all stages of ALS, maintenance of range of motion is important to improve mobility, self-care, posture, and wheelchair seating and reduce pain, spasticity, and risk of wounds. Range of motion exercises are considered foundational in ALS care due to the anticipated loss of strength and function. For this reason, range of motion has not been studied as a stand-alone exercise intervention but is often included as part of intervention and control arms for exercise-based studies in ALS.

Guiding patients and their caregivers through a passive or active range of motion program via telehealth is feasible and can be augmented with printed information or videos. Patients and caregivers benefit from detailed instructions for stretching technique and dosing, as well as caregiver hand position, location in reference to the patient, and body mechanics may also be taught, but may be most effective if the therapist can demonstrate on another individual. Successful telehealth-based stretching programs have been described in the orthopedic literature (8).

Aerobic exercises

Persons with ALS have reduced aerobic capacity related to loss of lean muscle mass and this may be compounded by physical deconditioning (9). Fatigue, declining function, and decreased activity tolerance are the most commonly reported secondary symptoms in the ALS population and may indicate reduced efficiency and aerobic capacity. There is conflicting evidence regarding the effect of aerobic exercise as compared to standard neurorehabilitation interventions in persons with ALS in regard to outcomes including function, quality of life, aerobic capacity, strength, respiratory function, fatigue, and pain (10, 11). High intensity exercises are not advised in ALS due to literature from animal-based studies suggesting worsening rate of progression related to overexertion (12).

Aerobic exercise may be the most amenable to remote service delivery or supervision by telehealth as it can generally be performed and monitored with inexpensive or no equipment. Stationary peddlers or walking programs are commonly used in this population. The intensity of aerobic exercise may be monitored by heart rate or subjective ratings of patient tolerance [e.g., Borg or rate of perceived exertion (RPE) scale]. Braga et al. (13) reported a successful feasibility study in 10 patients with ALS involving a telerehabilitation-based walking program using a treadmill or outdoors walking for persons with ALS, with remote vital signs monitoring (heart rate and pulse oximetry) to ensure safety.

Resistance exercises

Resistance exercises have been frequently studied in ALS due to weakness being usually the primary impairment associated with this disease. However, several precautions are commonly followed when prescribing exercise to persons with ALS to avoid injury, including avoidance of strengthening exercises to muscles with less than anti-gravity strength (14), and avoidance of eccentric strengthening exercises (15). Moderate intensity for strengthening exercises is gaged by the ability of the patient to complete a high number of repetitions with good form (16). There are mixed results of studies evaluating the effect of resistance exercise as an isolated intervention as compared to "usual care" on functional outcome measures in ALS (10, 11).

Resistance exercise also translates well to remote service delivery, given that equipment is generally inexpensive and widely available. A trial of telehealth-supervised resistance exercise has been described in a population of young adults with cystic fibrosis (17), but not as an isolated intervention in persons with ALS.

Combined interventions

Combined exercise interventions usually describe programs including both aerobic and resistance exercises. Research on combined interventions in persons with ALS show more promising results than aerobic or resistance exercise alone impacting not only limb strength and aerobic capacity, but also positive effects on function, quality of life, and reduced pain (11, 18). Based upon data from a review of 10 randomized control trials, Ortega-Hombradros (19) concluded that combined resistance and aerobic exercise programs should be completed at a moderate intensity, 2x/week to maximize benefits and reduce risk of worsening fatigue. Effective telehealth multimodal telerehabilitation exercise programs have been described in the Parkinson's (20) and Duchenne muscular dystrophy (21) populations.

Respiratory exercises

Dyspnea, orthopnea, hypoventilation, and poor airway clearance are common indications of respiratory dysfunction resulting from neuromuscular weakness in ALS. Respiratory exercises may include lung volume recruitment (breath stacking, glossopharyngeal breathing), muscle strengthening (inspiratory/expiratory muscle training), and airway clearance techniques [manually assisted cough (MAC), huff or squeeze coughing]. Clinical trials of respiratory muscle strengthening exercises in ALS have yet to show significant impact on meaningful endpoints, such as survival, hospitalization, or initiation of invasive mechanical ventilation. In a recently published systematic review (22), respiratory training was not shown to have a significant impact on ALS Functional Rating Scale-Revised (ALSFRS-R) scores or forced vital capacity (FVC). That said, techniques such as lung volume recruitment and airway clearance techniques may be lifesaving in the case of a medical emergency for a person with neuromuscular respiratory weakness.

Respiratory exercises require very little equipment and are easily adaptable to a telehealth setting. Telehealth video instructions for respiratory exercises were well-received by families of young men with Duchenne Muscular dystrophy during the COVID-19 pandemic (23).

Balance exercises

Persons with ALS are at a high risk of falls and serious fall-related injury (24), therefore, effective balance and fall prevention interventions are of great potential value in this population. Decreased lower limb strength in ALS correlates to increased risk of falls (25), however, specific exercises interventions to mitigate the risk of falls in isolation has not been studied in this population.

Telehealth evaluations for fall prevention are advantageous because of the ability to assess the patient in their home environment, which allows the clinician to identify environmental risk factors for falls as well as assist in appropriate DME prescription for fall prevention. Telehealth-based balance interventions have been found to be feasible and effective in stroke survivors (26) and community-dwelling elderly with balance impairments (27, 28).

Implementation of telerehabilitation-based exercise for ALS

The Veterans Health Administration (VHA) is well poised for innovation and delivery of specialized therapy services remotely through telehealth. Common barriers impacting the private sector, such as insurance coverages and interstate licensing for telehealth, do not exist in VHA (29). In the sections to follow, pragmatic considerations for further development of programs to serve Veterans with ALS will be explored.

Asynchronous telerehabilitation

Asynchronous care through emails, text messages, mobile device applications, or through transfer of video files provides the most flexibility for both the clinician and patient and has been used to support physical therapy exercise interventions (30). This flexibility of asynchronous exercise videos may lend to higher utilization as compared to live workshops, as described in one study performed in a population of patients with Duchenne muscular dystrophy and caregivers—the live session reported 16 total participants, whereas the recorded workshop received 132 views within 1 month (31). One limitation to this approach, however, is the inability to resolve concerns, adapt exercises, or obtain additional information in real time when needed.

Automated exercise reminders or check-ins, such as the VHA's mobile application "Annie," can further support adherence to the prescribed exercise program or elicit outcomes from Veterans for safety and tolerability monitoring (32). App-based asynchronous combined exercise programs have demonstrated improved functional outcomes for persons with multiple sclerosis (33). There is evidence which demonstrates the effectiveness of asynchronous interventions to support adherence to exercise programs in ALS and ensure safety through monitoring of heart rate and pulse oximetry during exercise sessions (13).

Synchronous telerehabilitation

Both telephone and clinical video telehealth have been described for synchronous care delivery for ALS. Telephone calls can be used to assess adherence and address any concerns regarding an individualized the exercise program (34). Video telehealth allows interactive and real-time streaming of individual or group therapy interventions to the patient, which may facilitate necessary adaptations to the prescribed exercise program based upon the patients function and tolerance of treatment. VHA served as early adopters of telerehabilitation specifically for physical therapy to facilitate access to rural-dwelling patients (35). One study examining telerehabilitation for persons with ALS during the COVID-19 pandemic confirmed that the highest utilization for synchronous telerehabilitation services was for physical therapy (53.7% of all visits) and that patient satisfaction with this modality was high (>94% "very good" or "excellent") (36).

Outcome measurements

Baseline and interval assessments ensure progress is being made toward functional improvements during treatment. In addition, these measures ensure adequate tolerance and safety to participate in exercise-based interventions. Many commonly performed assessments, both objective and subjective measures, have been adapted to use with telehealth. Examples of commonly used measures are included in Table 1.

Peripheral devices and technology

Peripheral devices may support teletherapy services by supplementing the physical examination with additional objective data. Technology innovations may assist clinicians in processing data collected from peripheral devices or may enhance the exercise interventions to improve user engagement (37). Although not an exhaustive list, representative examples of peripheral devices and technology which may be applied to the care of persons with ALS are presented in this section.

TABLE 1 Sample remote outcome measures for telerehabilitation in ALS.

Objective measures	Subjective measures
Two minute step test	ALS-FRS
Five times sit to stand	Fatigue severity scale
Pulse oximetry	ALS-specific quality of life
Spirometry	Pain visual analog scale
Heart rate	Rate of perceived exertion (Borg)

Wearable technology

Pulse oximeters can support safe exercise for persons with ALS by monitoring oxygen saturation and pulse before, during, and after a remote exercise session. Patients with ALS who have no co-morbid lung disease should be instructed in the oximetry feedback protocol described by Bach et al. (38), which prescribes use of assisted cough device and non-invasive ventilatory support for oxygen saturation below 95%.

Stand-alone heart rate monitors can be used to assess the intensity of exercise to ensure safety and therapeutic dose of exercise for the participant before and during exercise sessions. Target heart rate of 50–70% maximum heart rate is generally advised for moderate intensity exercise in ALS (39).

Wearable sensors present opportunities for additional objective data at both the impairment and the functional level. Electrogoniometers may be worn to quantify range of motion and/or detect changes in available range of motion over time. Accelerometers are commonly used for fall detection purposes and can also be used for remote monitoring of physical activity levels (40, 41). In addition, wearable sensors can provide information about gait characteristics (42).

Spirometers

Home spirometry is a convenient means of monitoring respiratory function for patients enrolled in virtual exercise programs and is more informative than pulse oximetry for monitoring neuromuscular respiratory failure (43). In addition to monitoring effects of an exercise program, earlier detection of respiratory compromise through more frequent monitoring at home with or without clinician supervision may also lead to earlier initiation of supportive interventions such as non-invasive ventilatory support (44).

Exergaming

Single camera video game peripherals have been used to measure reachable workspace related to upper body function in ALS (45). Exergames, or video games utilized for therapeutic rehabilitation purposes to improve adherence, must be adaptable for persons with disability to accommodate for progressive change in physical function. When this is taken into account, patients with neuromuscular disease and low functional abilities report satisfaction and enjoyment from engaging in this treatment (46). Virtual reality has been described as an adjunct technology to assist with upper body exercises in persons with ALS by customizing and gamifying tasks within the reachable workspace of the individual (47).

Artificial intelligence

Artificial Intelligence and machine learning will be critical components to process data elements derived from wearable technology to filter results and alert the medical team to notable changes in the patient's medical condition. One recent study described the use of machine learning to predict ALS-FRS scores based upon electrogoniometer and speech recording results (48). Digital health technology for ALS must be vetted by subject matter experts in the field to ensure accurate interpretation.

Program example: ALS HOPE

The ALS Holistic OutPatient Exercise (HOPE) program is a synchronous video telehealth-based exercise group designed for Veterans with ALS receiving care at the VA Puget Sound. Implemented in December 2022, this group is directed toward individuals with independent mobility, greater than anti-gravity strength in at least one limb, and ALS-FRS >32. Veterans participate in group exercise incorporating range of motion, strengthening, balance, and respiratory exercises, adapted for their individual level of function, under the supervision of a specialized ALS team physical therapist and physical therapy assistant. Outcomes assessed include all measures listed in Table 1 and are assessed at baseline and repeated at 6, 12, and 24 weeks. The group meets twice per week for 1 h per session and enrollment occurs on an ongoing basis. Follow-up assessments were conducted for practice improvement. This operational analysis was reviewed jointly by the Human Research Protection Program and Quality, Safety & Value service line at the VA Puget Sound Health Care System and determined to not constitute human subjects research.

During the 6-month pilot phase of this program, seven Veterans enrolled in the exercise group on a rolling basis. One Veteran discontinued after moving into a facility which offered an exercise program, the remainder continued participation with an average of 25 sessions (range 10–31). Average travel saved per participant for each session was 42 miles. No serious adverse events were reported in this timeframe. Participants report high levels of satisfaction with the program, citing ease of use, experiencing different points of view of a shared experience, and the ongoing connection to the ALS team between quarterly visits.

This program serves as an example of an intervention to increase access and support with the aim of reducing symptoms and maximizing function for Veterans with ALS, regardless of their geographic location.

Limitations and future directions

There is still ambiguity of the safety and efficacy of exercise for persons with ALS. Heterogeneity of participants and studies, small sample sizes, and presence of bias have created inconsistent results and unclear guidance on how to implement exercise into the healthcare plan.

Group telehealth exercise interventions may be an efficient way to improve access and efficiency of care, not only for PT, but also for all other subspecialized ancillary clinical services needed for optimal ALS care. During the COVID-19 pandemic, the VHA's Gerofit group exercise program rapidly and successfully adapted protocols for physical function assessments and group exercise treatments to a

telehealth, accommodating up to 24 geriatric patients in a virtual session (49). A similar transformation for other specialized services in ALS, such as assistive technology, or driver's rehab, for example, could have significant impact on the quality of life for persons with ALS.

Discussion

Most exercises described for persons with ALS fall into one of the following categories: range of motion (stretching), strengthening, or combined exercises. The strongest evidence supports combined exercise interventions, which have demonstrated improved outcomes, including increased aerobic capacity, strength, function, and quality of life for affected persons. Most of these interventions involve widely available and low-cost equipment, making them relatively simple to translate to the virtual care setting. Supervision of an exercise program by a physical therapist with knowledge of ALS is critical to ensure appropriateness of exercise modalities, necessary adaptations for the patient's functional level, and ensure safety, tolerability, and efficacy. Given the geographic limitations on specialty ALS centers, telehealth-based exercise is an attractive option for care service delivery in this population.

Innovative approaches to telerehabilitation, including asynchronous app-based and synchronous clinical video telehealth have been promoted by VHA and were accelerated outside of the VHA by the COVID-19 public health emergency. The ALS HOPE group exercise program is an example of a promising model of care, which could potentially improve the efficiency of delivery of care by providing interval subspecialized therapy beyond the usual quarterly multidisciplinary team visit. Further work is needed to confirm the effectiveness of telerehabilitation for persons with ALS and to compare the efficacy of telerehabilitation group-based interventions to individualized treatment in this population.

Even with the modest evidence of benefit for exercise for persons with ALS, the low risk and low cost associated with this treatment favors routine implementation of a combined exercise program for persons at early stages of disease.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

IH and VK decided the idea and structure, and contributed to research, writing, revision, and reading. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Long-term resting EEG correlates of repetitive mild traumatic brain injury and loss of consciousness: alterations in alpha-beta power

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Objective: Long-term changes to EEG spectra after mild traumatic brain injury (mTBI, i.e., concussion) have been reported; however, the role of injury characteristics in long-term EEG changes is unclear. It is also unclear how any chronic EEG changes may underlie either subjective or objective cognitive difficulties, which might help explain the variability in recovery after mTBI.

Methods: This study included resting-state high-density electroencephalography (EEG) and mTBI injury data from 340 service members and veterans collected on average 11 years after injury as well as measures of objective and subjective cognitive functioning. The average absolute power within standard bands was computed across 11 spatial regions of the scalp. To determine how variation in brain function was accounted for by injury characteristics and aspects of cognition, we used regression analyses to investigate how EEG power was predicted by mTBI history characteristics [number, number with post-traumatic amnesia and witnessed loss of consciousness (PTA + LOC), context of injury (combat or non-combat), potentially concussive blast exposures], subjective complaints (TBIQOL General Cognitive and Executive Function Concerns), and cognitive performance (NIH Toolbox Fluid Intelligence and premorbid IQ).

Results: Post-traumatic amnesia (PTA) and loss of consciousness (LOC), poorer cognitive performance, and combat experience were associated with reduced power in beta frequencies. Executive function complaints, lower premorbid IQ, poorer cognitive performance, and higher psychological distress symptoms were associated with greater power of delta frequencies. Multiple regression confirmed the relationship between PTA + LOC, poor cognitive performance, cognitive complaints, and reduced power in beta frequencies and revealed that repetitive mTBI was associated with a higher power in alpha and beta frequencies. By contrast, neither dichotomous classification of the presence and absence of mTBI history nor blast exposures showed a relationship with EEG power variables.

Conclusion: Long-term alterations in resting EEG spectra measures of brain function do not appear to reflect any lasting effect of a history of mTBI or blast exposures. However, power in higher frequencies reflects both injury characteristics and subjective and objective cognitive difficulties, while power in lower frequencies is related to cognitive functions and psychological distress associated with poor long-term outcomes after mTBI.

KEYWORDS

mild traumatic brain injury, military, EEG, loss of consciousness, chronic effects, post-traumatic amnesia, cognition

1. Introduction

Resting EEG power spectra are sensitive to mental states and to changes in neural coordination hypothesized to follow mild traumatic brain injury (mTBI) in the chronic phase (1, 2). While EEG spectra have been studied as an evaluative measure of TBI for the past 75 years, much is still unknown concerning the natural history and the clinical significance of spectral changes, as detailed below. These measures were therefore included as exploratory predictors in a prospective cohort study, Long-term Impact of Military Brain Injury Consortium—Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC), designed to assess mid- and long-term outcomes from mTBI and the contributing neurobiological processes.

1.1. EEG spectra and mTBI

Early studies of visible alterations in the EEG showed rapid resolution of acute abnormalities after an mTBI, which include power bias toward low frequency and reduction in beta power (3, 4). In mild-to-severe TBI, post-traumatic amnesia (PTA) lasting more than a few hours has been acutely associated with visible EEG abnormalities that are resolved within a longer timeframe of 6 months (5, 6). More severe injuries with a skull fracture and sustained impaired or loss of consciousness (>2 min) also produce a similar diffuse slowing, but to a greater degree (6, 7). Modern quantitative EEG (qEEG) similarly shows increased low-frequency power during PTA also resolving by 6 months postinjury (8). However, the natural history beyond this timeframe is uncertain. Findings of long-term effects (>6 months post-mTBI) have been reported in group studies. Consistently, an increase in low-frequency activity is observed (9–14). Such alterations are reminiscent of the acute changes reported, suggesting a continuity between acute injury and late effects. Enhanced low-frequency oscillations are associated with brain damage, neurodegenerative disease, and loss of or reduced consciousness (15–17) as well as recovery from these states (18). Less consistently, other chronic alterations such as increased gamma activity (19) and reduced alpha and beta coherence (13), and reduced beta power (20) are reported.

While it is clear that mTBI and loss of consciousness (LOC)/PTA especially cause immediate disturbances in the cortical function that typically resolve, it is still unclear whether EEG changes observed in the chronic phase reflect an ongoing, mTBI-specific process. In most studies, it is not clear whether any chronic EEG effects are likely attributable to the mTBI, because of all or some of the following: unvalidated retrospective mTBI classification, small samples, observational design, PCS as study group inclusion criterion, and limited clinical history. mTBI samples can differ significantly from well-matched controls in life experience and functioning (21), and current mental state may confound both EEG and retrospective mTBI classification. However, large samples with carefully detailed and documented history such as LIMBIC-CENC allow the testing of the impact of injury variables, including PTA and LOC, blast exposure, and repetitive injury, which can refine any findings associated with the simple dichotomous classification of mTBI.

1.2. EEG spectra and subjective cognitive complaints

While most (~90%) cases are thought to completely resolve, in a small minority of cases complaints persist. However, these complaints are not specific to mTBI–PCS symptoms and are equally observed in non-brain-injured groups with other injuries (22) and military controls (23). Additionally, postconcussive complaints persisting after the acute phase can sometimes be predicted by initial levels of anxiety (24). Yet, there is some indication that subjective cognitive complaints have a neurophysiological basis akin to acute mTBI effects. With routine EEG, abnormal diffuse low-frequency oscillations were observed among a large subset of military airmen with persistent symptoms after TBI, most commonly in those with subdural injuries, but only rarely in those with no symptoms (6). Also shown in that study, slow oscillations tracked the reappearance of symptoms after apparent recovery. With qEEG, similar findings have been reported: increased delta and reduced alpha power with PCS vs. healthy controls 1 year later (12) and acutely declining theta power tracking the PCS symptom abatement 6 weeks later (25). Studies examining the neurophysiologic basis of subjective cognitive complaints in other populations report a similar pattern: higher delta and lower alpha activities differentiate older adults with subjective memory problems from healthy controls (26). Furthermore, the positive relationship between complaints and theta power in EEG (27) and MRI abnormalities (28) is more pronounced in the older adults and TBI groups. In conclusion, it appears that subjective cognitive problems and acute mTBI share a neurophysiology of higher delta–theta power and lower alpha, and this has not been systematically examined in the chronic phase. It is thus not clear to what degree subjective complaints related to or independent of mTBI history are contributing to findings in the chronic phase.

1.3. EEG spectra and cognitive ability

A related issue is to what degree mTBI effects lead to objective cognitive problems. Many cohort studies including LIMBIC have examined this, and although not uniform, the results typically indicate no long-term cognitive impairment, on average (29, 30). However, resting EEG indices may track mTBI severity and cognitive function and could indicate a lasting vulnerability, or help explain the persistence of cognitive complaints in some individuals. As might be expected, EEG spectral power is sensitive to general cognitive ability in a myriad of ways. For instance, a large body of studies support that alpha power and theta power are associated with cognitive development, cognitive load, and intelligence (31–33). Others have shown baseline delta and beta power to relate to temporal prediction (34), speed of resting alpha to predict visual attention deficits that in turn strongly predict global cognition (35), and baseline theta to inversely relate to cognitive control (36). Whether chronic changes in EEG after mTBI reflect cognitive dysfunction is not clear.

The present study took advantage of the large sample size and the structured assessment of mTBI history as part of the LIMBIC-CENC study to investigate important predictors of EEG

power in chronic mTBI. A second goal was to clarify the extent to which resting oscillatory brain activity was related to subjective complaints and objectively measured cognition in individuals with mTBI.

2. Methods

2.1. Participants

All participants were enrolled in a large, multi-site, prospective study of long-term outcomes from military mTBI, the LIMBIC-CENC. Participants were all enrolled through either VA or DoD medical facilities. Eligibility criteria were deployment to a post-911 conflict, combat exposure as defined by the Deployment Risk and Resilience Inventory section D (DRRI2) (37) score >1, and 18 years of age or older. Exclusion criteria were any TBI of moderate or higher severity (defined as GCS <13, loss of consciousness >30 min, post-traumatic amnesia >24 h, or any positive finding on post-injury CT) or major neurologic/neuropsychiatric disorder such as stroke or schizophrenia. More information about the parent study including recruitment is available in prior descriptive publications (38). Eligibility for inclusion in the present analysis was determined by the availability of at least 4 min of artifact-free baseline resting EEG collected from study initiation in 2013 to March 2020. In total, 340 participants met the eligibility criteria. Eligible participants had been enrolled at three different study sites: VA Medical Centers in Richmond, Virginia, and Minneapolis, Minnesota, and DoD site Ft. Belvoir, Virginia.

2.2. mTBI assessment

TBI was characterized via validated structured interviews. Trained interviewers conducted the in-person interview, which first assesses all lifetime potential concussive events using a modified version of the Ohio State University TBI Identification (39), and then proceeded with in-depth structured questioning about each event using the VCU Concussion Diagnostic Instrument (40) to determine whether it met the criteria for mTBI as defined by the DoD/VA Clinical Management Guideline (41). Algorithmic mTBI determination was compared with free responses and any corroborating clinical documents to make the final determination. Based on the context of mTBIs incurred, there were five study groups: unexposed, pre-combat mTBI only, combat mTBI only, post-combat mTBI only, and combat and non-combat mTBI. Because of the high demographic and symptom similarity between the groups with combat only and combat plus non-combat, these were combined into one group for the present analysis, as were the pre- and post-combat TBI groups for the same reason; thus, three TBI classification groups resulted: unexposed, combat mTBI, and non-combat mTBI. The interview also generated standardized classifications of injury features for each mTBI: the occurrence of PTA and LOC; whether the LOC was confirmed by a witness; and blast involvement. PTA and LOC with witness corroboration were selected as the primary measure of injury severity, due to the greatest robustness with regard to issues with self-report and memory.

2.3. EEG collection and processing

EEG was collected using the Compumedics Neuroscan SynAmpsRT 64 Ag/AgCl channel system at two sites (Richmond/Ft. Belvoir), and the Brain Products ActiChAmp 128 Ag/AgCl channel system at one (Minneapolis), as part of a full day of assessment for the parent study. During recording, EEG was sampled at a rate of 500 Hz (Richmond/Ft. Belvoir) or 1,000 Hz (Minneapolis), and all impedances were kept below 5 kΩ. Participants were instructed to rest quietly with their eyes closed for 10 min, or alternate between 2 min of closing eyes and 2 min of opening eyes, resulting in at least 10 min of eyes-closed EEG. Eyes-open EEG was discarded for this analysis. Participants were monitored to prevent their falling asleep to ensure a common state of relaxed wakefulness. Raw data files were processed using a combination of automated and supervised processing by an investigator (LMF) blinded to all participant information other than the study site. All files were re-referenced to the averaged mastoid channels, DC offset-corrected, and low-pass filtered at 70 Hz using a Hanning window. Bad blocks of large movement artifacts were removed, and bad channels were interpolated with an average of four nearest valid neighbors. Epochs of 4 s (Richmond/Ft. Belvoir) or 1.2 s (Minneapolis) were created, and then any remaining epochs with large amplitude fluctuations (exceeding ±200 uV) were removed. The remaining EEG epochs were each subjected to FFT with a Hanning window with a width of 10%, and then, the results were averaged to produce average spectra for each channel for the entire recording period. The multichannel data were averaged to create regional averages within standard power bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12.5 Hz), beta (12.5–35.0 Hz), and gamma (35.0–70 Hz). Because the 128-channel system used is based on the same 10–20 standard as implemented in the 64-channel system, the same channel landmarks could be used to define the scalp regions: anterior of FCz = anterior; posterior of CPz = posterior; remaining central region between FCz and CPz, inclusive of these=central; midline electrodes (*z) = midline; left of midline = left; right of midline = right. For temporal regions, landmarks were as follows: lateral of C5 = left temporal; lateral of C6 = right temporal.

2.4. Cognitive functioning and other measures

Participants completed self-administered questionnaires to measure subjective cognitive functioning after TBI: TBIQOL General Cognitive Concerns (42) and psychological symptoms of depression via PHQ-9 (43), and PTSD via PCL-5 (44). Participants' military status, pay group, combat duty history, and service-connected disability were self-reported. Cognitive performance was measured using the validated NIH Toolbox Fluid Intelligence Measure, a combination of performance on several tests of fluid ability (processing speed, efficiency, and working memory): the Dimensional Change Card Sort test of executive function, the Flanker inhibitory control and attention Test, a Picture Sequence memory test, a List Sorting working memory test, and a Pattern Comparison processing speed test (45). Premorbid intellectual

ability was assessed using the Test of Premorbid Function (TOPF) (46).

2.5. Statistical methods and analysis

Descriptive statistics for the overall group and TBI subgroups were produced, and group differences were evaluated using independent *t*-tests for continuous variables or chi-square tests for categorical variables. EEG effects were evaluated with unadjusted (simple) linear single-step regression and adjusted (multiple) single-step linear regression models for each of the 11 regions and 5 bands. Before conducting regressions, it was verified that EEG power by band did not vary by data collection site, and all hypothesized predictors were verified to have a VIF < 5 to prevent issues due to multicollinearity. Time since injury/index date was removed due to VIF > 5; only age was included as a demographic predictor due to known effects of age on EEG and small numbers of women in the sample. Predictor correlations are given in Table 1. The final set of predictors included in the regression models were as follows: DRRI2 combat experience, TBIQOL Cognitive Concerns, TBIQOL Executive Function, NIH Toolbox Fluid Cognition Composite, TOPF, Age, PCL-5, PHQ-9, TBI (unexposed; exposed combat; and exposed non-combat), number of blast potential concussive events (PCEs), number of mTBIs, number of mTBIs with witnessed LOC and PTA). Statistical significance was determined using an alpha of 0.05 adjusted by the Benjamini–Hochberg method (47) to control the false discovery rate for each family of tests defined by EEG band and regression type (simple or multiple); for example, all simple regressions of delta band constituted a family.

3. Results

Demographic information for the entire sample and the key TBI study groups is presented in Table 2. While similar in age and other demographic characteristics, groups differed in terms of combat experience and psychological functioning. Both TBI groups reported higher psychological and cognitive complaints. Psychoactive-CNS medication information for the sample is presented in Table 3. While medication use, especially serotonin modulators, was very common, there was no difference in usage rates between the study groups.

3.1. Unadjusted analysis

There was no statistically significant effect of TBI classification (unexposed vs. combat vs. non-combat) or the number of blast PCEs on EEG power. However, significantly increased delta power accompanied higher scores on the PHQ-9 (unstandardized

TABLE 1 Predictor correlations.

	DRRI2	TBIQOL cognition	TBIQOL executive function	Fluid cognition	TOPF	Age in years	PCL-5	PHQ-9	Number of blast PCEs	Number of positive mTBIs	Number mTBIs with PTA and witnessed LOC
DRRI2	1										
TBIQOL cognition	−0.32	1									
TBIQOL executive function	−0.23	0.84	1								
Fluid cognition	−0.07	0.27	0.27	1							
TOPF	−0.01	0.12	0.18	0.33	1						
Age in years	−0.2	0.05	0.03	−0.41	−0.09	1					
PCL-5	0.31	−0.65	−0.67	−0.35	−0.27	0.03	1				
PHQ-9	0.26	−0.7	−0.72	−0.3	−0.23	−0.02	0.84	1			
Number of blast PCEs	0.5	−0.19	−0.12	0	0.05	−0.07	0.1	0.1	1		
Number of positive mTBIs	0.31	−0.25	−0.24	−0.09	0.01	0	0.18	0.18	0.34	1	
Number mTBIs with PTA and witnessed LOC	0.18	−0.11	−0.15	−0.15	−0.09	−0.01	0.19	0.18	0.15	0.42	1

Predictor correlations were computed as regression model diagnostics and not for focal hypothesis testing; thus, no *p*-values were assessed for significance.
DRRI, Deployment Risk and Resilience Inventory; TBIQOL, TBI Quality of Life inventory; PCL-5, PTSD Checklist 5; PHQ-9, Patient Health Questionnaire-9; PCE, potential concussive event; PTA, post-traumatic amnesia; LOC, loss of consciousness.

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TABLE 2 Demographic and descriptive statistics.

	Overall	Unexposed	Combat mTBI	Non-combat TBI	*p*-value
n	328	82	151	95	
DRRI2 combat experience [mean (SD)]	34.84 (14.63)	27.90 (9.21)	42.28 (15.32)	28.99 (11.46)	<0.001
Currently in the military?					
Yes (%)	63 (19.2)	11 (13.4)	38 (25.2)	14 (14.7)	0.04
Combat role (%)					
Combat	77 (23.5)	14 (17.1)	49 (32.5)	14 (14.7)	0.04
Combat service support	80 (24.4)	20 (24.4)	33 (21.9)	27 (28.4)	
Combat support	150 (45.7)	43 (52.4)	60 (39.7)	47 (49.5)	
Other	21 (6.4)	5 (6.1)	9 (6.0)	7 (7.4)	
Pay group (%)					
No response/missing	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0.318
Enlisted	258 (78.7)	63 (76.8)	125 (82.8)	70 (73.7)	
Officer	69 (21.0)	19 (23.2)	25 (16.6)	25 (26.3)	
Most recent pay grade[mean (SD)]	5.61 (1.61)	5.44 (1.48)	5.86 (1.59)	5.43 (1.72)	0.108
Service branch (%)					
No response/missing	1 (0.3)	0 (0.0)	1 (0.7)	0 (0.0)	0.435
Air force	24 (7.3)	8 (9.8)	8 (5.3)	8 (8.4)	
Army	246 (75.0)	62 (75.6)	115 (76.2)	69 (72.6)	
Marine corps	35 (10.7)	4 (4.9)	19 (12.6)	12 (12.6)	
Navy	22 (6.7)	8 (9.8)	8 (5.3)	6 (6.3)	
Service-connected disability (%)					
No response/don't know	2 (0.6)	0 (0.0)	1 (0.7)	1 (1.1)	0.073
N/A	63 (19.2)	11 (13.4)	38 (25.2)	14 (14.7)	
No	34 (10.4)	11 (13.4)	9 (6.0)	14 (14.7)	
Yes	229 (69.8)	60 (73.2)	103 (68.2)	66 (69.5)	
Service-connected disability (%)					
N/A	104 (31.7)	22 (26.8)	52 (34.4)	30 (31.6)	0.005
0%	1 (0.3)	1 (1.2)	0 (0.0)	0 (0.0)	
10%	15 (4.6)	7 (8.5)	0 (0.0)	8 (8.4)	
20%	9 (2.7)	3 (3.7)	1 (0.7)	5 (5.3)	
30%	13 (4.0)	9 (11.0)	2 (1.3)	2 (2.1)	
40%	15 (4.6)	3 (3.7)	7 (4.6)	5 (5.3)	
50%	14 (4.3)	3 (3.7)	6 (4.0)	5 (5.3)	
60%	30 (9.1)	7 (8.5)	14 (9.3)	9 (9.5)	
70%	24 (7.3)	7 (8.5)	10 (6.6)	7 (7.4)	
80%	23 (7.0)	4 (4.9)	13 (8.6)	6 (6.3)	
90%	33 (10.1)	9 (11.0)	16 (10.6)	8 (8.4)	
100%	47 (14.3)	7 (8.5)	30 (19.9)	10 (10.5)	
TBIQOL cognitive concerns [mean (SD)]	33.38 (10.33)	37.44 (9.64)	30.39 (10.36)	34.65 (9.45)	<0.001
TBIQOL executive function [mean (SD)]	37.76 (8.27)	40.46 (7.30)	35.59 (8.40)	38.89 (8.03)	<0.001
Fluid cognition [mean (SD)]	99.23 (12.70)	101.02 (12.96)	98.04 (12.32)	99.52 (13.00)	0.236

(Continued)

TABLE 2 (Continued)

	Overall	Unexposed	Combat mTBI	Non-combat TBI	*p*-value
TOPF [mean (SD)]	42.95 (11.97)	42.88 (12.04)	42.42 (12.04)	43.87 (11.88)	0.655
Sex = male (%)	286 (87.2)	70 (85.4)	138 (91.4)	78 (82.1)	0.089
Age in years [mean (SD)]	43.65 (9.99)	43.99 (10.56)	42.65 (9.82)	44.95 (9.70)	0.201
Education (%)					
Grade 12 or GED (high school graduate)	39 (11.9)	11 (13.4)	22 (14.6)	6 (6.3)	0.174
College 1 year to 3 years (some college or technical school)	112 (34.1)	28 (34.1)	55 (36.4)	29 (30.5)	
College 4 years or more (college graduate)	177 (54.0)	43 (52.4)	74 (49.0)	60 (63.2)	
Ethnicity = not Hispanic or Latino (%)	304 (93.5)	78 (95.1)	138 (92.6)	88 (93.6)	0.759
Marital status (%)					
Never married	47 (17.6)	16 (22.5)	18 (15.7)	13 (16.0)	0.443
Married	220 (82.4)	55 (77.5)	97 (84.3)	68 (84.0)	
Divorced	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Race = white (%)	222 (67.7)	51 (62.2)	105 (69.5)	66 (69.5)	0.471
PCL-5 [mean (SD)]	23.96 (19.79)	17.16 (17.45)	30.23 (20.16)	19.87 (18.23)	<0.001
PHQ-9 [mean (SD)]	7.32 (6.25)	5.42 (5.03)	8.65 (6.36)	6.83 (6.59)	0.001
Number of PCEs [mean (SD)]	5.26 (2.85)	3.44 (2.16)	6.34 (2.93)	5.11 (2.40)	<0.001
Number of blast PCEs [mean (SD)]	3.19 (2.21)	2.51 (1.86)	3.82 (2.40)	2.77 (1.90)	<0.001
Time since the injury or index date in years [mean (SD)]	10.71 (5.85)	11.69 (6.74)	10.45 (5.18)	10.30 (6.00)	0.215
Number of mTBIs [mean (SD)]	1.82 (1.81)	0.00 (0.00)	2.85 (1.76)	1.76 (1.37)	<0.001
Number mTBIs with PTA and LOC [mean (SD)]	0.33 (0.61)	0.00 (0.00)	0.54 (0.74)	0.27 (0.51)	<0.001

p-values are the result of ANOVA with factor of group, or chi-square test with group, as appropriate.
DRRI, Deployment Risk and Resilience Inventory; TBIQOL, TBI, Quality of Life inventory; PCL-5, PTSD Checklist 5; PHQ-9, Patient Health Questionnaire-9; PCE, potential concussive event.

coefficient range across all electrode locations 0.01–0.036, all *p*-values of <0.01) and PCL-5 (coefficient range 0.01–0.06, all *p*-values of <0.001), higher levels of executive cognitive complaints (coefficient range −0.02 to −0.07, all *p*-values of <0.02), and poorer current (coefficient range −0.02 to −0.08, all *p*-values of <0.01), and premorbid cognitive function (coefficient range −0.02 to −0.08, all *p*-values of <0.01). Furthermore, significantly reduced beta power accompanied more mTBIs with PTA+LOC (coefficient range −0.01 to −0.09, all *p*-values of <0.003), and higher levels of combat experience (coefficient range −0.002 to −0.003, all *p*-values of <0.003). Full regression parameters for models with significant effects after FDR alpha adjustment are shown in Table 4. All regression models are available in the Supplementary material.

3.2. Adjusted analysis

In the adjusted analysis, there was no statistically significant effect of TBI classification (unexposed vs. combat vs. non-combat) or the number of blast PCEs on EEG power. Delta power was found to increase for persons with poorer current cognitive function (unstandardized coefficient range −0.06 to −0.07, all *p*-values of <0.002) and greater PCL-5 symptoms (coefficient range 0.03–0.04, all *p*-values of <0.003). Alpha power was found to be higher with an increasing number of mTBIs (coefficient 0.396, $p = 0.004$) and PCL-5 severity (coefficient range 0.04–0.06, all *p*-values of <0.003). Alpha was lower with PHQ-9 severity (coefficient range −0.06 to −0.2, all *p*-values of <0.005). Beta power was reduced with higher PTA + LOC (coefficient range −0.07 to −0.1, all *p*-values of <0.006), cognitive concerns (coefficient −0.006, $p = 0.005$), and combat experience (coefficient −0.003, $p = 0.005$), and with poorer cognitive function (coefficient range 0.003–0.004, all *p*-values of <0.007). Beta was higher with an increasing number of mTBIs (coefficient range 0.02–0.03, all *p*-values of <0.007). Standardized effect sizes ranged from 0.2 to 0.5, in the small to moderate range. Significant effects after FDR correction with standardized coefficients are shown in Table 4. The topographies of adjusted effects are shown in Figure 1.

3.3. Sensitivity analyses

Sensitivity analyses were conducted *post-hoc* to assess the impact of differences across site/EEG system and collection procedures and the effect of PTA exposures without LOC. For the site, mixed-effects models confirmed zero or near zero variance for

the site random effect, indicating no impact of the site on outcomes. For the number of mTBI with PTA in those without LOC, there was no relationship with EEG outcomes in either simple or multiple regression, and multiple regression effects of the original set of predictors were not meaningfully changed with the addition of the PTA but no LOC variable.

4. Discussion

We found that resting EEG power in the chronic phase of mTBI was not affected by simple mTBI history, regardless of combat context or blast exposures. Instead, higher frequency (alpha–beta) oscillations were related to mTBI dose-severity variables, as well as cognitive performance. Low-frequency oscillations were related to distress symptoms and current cognitive functioning accounting for premorbid IQ.

4.1. Traumatic brain injury features are related to alpha–beta changes

The central finding of this analysis was that two injury features were independently associated with chronic changes in the alpha and beta bands. Alpha activity and beta activity are putatively involved in the top-down modulation of sensorimotor processing (48) and control of attention (49). PTA + LOC was associated with a widespread reduction in beta power, even after accounting for differences in other contributors, including the current fluid cognitive ability. This finding extends to the chronic phase observations of beta reduction in acute mTBI (4) and subacute mTBI (20), as well as with moderate–severe injury with attentional deficits (50) and beta coherence reduction in chronic mTBI (13). Similarly, subacute PTA with object feature binding dysfunction exhibited a bias away from middle-frequency power toward low frequency (8). Together with the present result, these provide convergent evidence that acute disruptions underlying observable disturbances of orientation and consciousness can persist, especially with repeated exposure. Presently, the reduction in beta power was also independently associated with poorer fluid cognition and cognitive concerns and so is consistent with a chronic neurophysiologic alteration that can produce true cognitive dysfunction and accurate complaints. The beta reduction may indicate reduced activity in the self-referential resting-state network and/or more activity in the sensory areas, especially auditory (51), and a lower level of attentional engagement and focus (52, 53).

Repetitive mTBI, after taking into account symptom level and PTA + LOC, was associated with higher resting posterior alpha. Higher posterior alpha is generally found with deactivation of the posterior cortex, especially visual, and a lower sampling rate of the focus of attention. Higher resting alpha predicted longer attentional blink (52), global perceptual bias (54), and increased susceptibility to interference in a Flanker task (53). High resting alpha is negatively related to sensory cortices rCBF, especially visual (51). Repetitive mTBI was also associated with a higher beta, indicating that multiple mTBIs may result in an abnormal imbalance of activity in the alpha–beta bands, i.e., in the alpha–beta ratio. Previous research would suggest an imbalance would accompany attentional effects that are more subtle than detectable by standard neuropsychological assessment: the alpha/beta ratio was related to the scope of attention in time and space (52, 54).

In summary, PTA + LOC exposures and repetitive mTBI appear to have different long-term effects on the resting alpha–beta activity previously related to attention and selection. This finding was somewhat unexpected because both repetitive mTBI and LOC are considered features, which may increase the risk for poor outcomes. However, these two injury variables thus should be considered independent risk factors, with different chronic effects as presently observed. Alpha–beta resting activity should be a focus of future research into chronic mTBI biomarkers; notably, recent findings convergently highlight these two bands as a discriminant for mTBI vs. PTSD (55). Beta power reduction in particular may be a useful biomarker because of its strong relationship with PTA + LOC, with and without statistical controls, and with objective

TABLE 3 Medications by study group.

	Unexposed	Combat mTBI	Non-combat TBI	*p*-value
n	82	151	95	
SSRI (%)	15 (51.7)	43 (53.1)	21 (47.7)	0.848
Atypical antipsychotic (%)	6 (20.7)	13 (16.0)	2 (4.5)	0.095
Opioid (%)	11 (37.9)	21 (25.9)	10 (22.7)	0.334
Adrenergic antagonist (%)	1 (3.4)	5 (6.2)	2 (4.5)	0.829
Barbituate-stimulant analgesic (%)	1 (3.4)	7 (8.6)	2 (4.5)	0.513
Hypnotic (non-benzodiazepine; %)	3 (10.3)	10 (12.3)	5 (11.4)	0.956
Serotonin agonist (%)	3 (10.3)	15 (18.5)	6 (13.6)	0.532
SNRI (%)	1 (3.4)	8 (9.9)	5 (11.4)	0.484
Antiepileptic (%)	5 (17.2)	25 (30.9)	9 (20.5)	0.238
Tricyclic antidepressant (%)	1 (3.4)	5 (6.2)	3 (6.8)	0.821
Anxiolytic (non-benzodiazepine; %)	3 (10.3)	10 (12.3)	5 (11.4)	0.956
Benzodiazepine (%)	2 (6.9)	12 (14.8)	4 (9.1)	0.427
Stimulant (%)	0 (0.0)	5 (6.2)	5 (11.4)	0.154
Caffeine (%)	1 (3.4)	5 (6.2)	2 (4.5)	0.829
Adrenergic agonist (%)	1 (3.4)	4 (4.9)	3 (6.8)	0.808

Percentages reported are based on the number of medications reported. *p*-values are the result of ANOVA of the group factor.
SSRI, selective serotonin reuptake inhibitor; SNRI, selective norepinephrine reuptake inhibitor.

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TABLE 4 Regression models for each scalp region and power band with significant effect after alpha correction for multiple comparisons.

Measure	Location	Unadjusted				Adjusted				
		Est.	SE	*t*	*p*-value	Est.	SE	*t*	*β*	*p*-value
A. Delta band										
Fluid cognition	Anterior R	−0.071	0.015	−4.591	0.000	−0.069	0.019	−3.666	−0.250	0.000
	Anterior mid	−0.083	0.018	−4.575	0.000					
	Anterior L	−0.065	0.015	−4.346	0.000	−0.062	0.018	−3.467	−0.235	0.001
	Central R	−0.036	0.010	−3.797	0.000					
	Central L	−0.035	0.010	−3.630	0.000					
	Central mid	−0.053	0.015	−3.462	0.001					
	Temporal R	−0.020	0.007	−3.102	0.002					
	Posterior mid	−0.020	0.007	−2.759	0.006					
PCL-5	Central R	0.032	0.006	5.338	0.000	0.043	0.012	3.553	0.392	0.000
	Central L	0.031	0.006	5.189	0.000	0.040	0.012	3.294	0.364	0.001
	Anterior mid	0.058	0.011	5.159	0.000					
	Posterior R	0.019	0.004	5.090	0.000	0.033	0.008	4.291	0.477	0.000
	Central mid	0.047	0.009	5.051	0.000	0.040	0.012	3.294	0.352	0.002
	Posterior mid	0.026	0.004	5.813	0.000	0.043	0.009	4.613	0.508	0.000
	Posterior L	0.018	0.004	4.798	0.000	0.036	0.008	4.705	0.520	0.000
	Anterior L	0.038	0.009	4.130	0.000					
	Anterior R	0.039	0.010	4.093	0.000					
	Temporal R	0.016	0.004	3.816	0.000					
	Temporal L	0.013	0.004	3.533	0.000					
PHQ-9	Anterior mid	0.125	0.036	3.460	0.001					
	Posterior mid	0.047	0.015	3.221	0.001					
	Central R	0.058	0.019	3.016	0.003					
	Central L	0.058	0.019	3.009	0.003					
	Central mid	0.091	0.030	2.993	0.003					
	Anterior L	0.089	0.030	2.965	0.003					
	Anterior R	0.091	0.031	2.937	0.004					
	Posterior R	0.033	0.012	2.746	0.006					
Executive function TBIQOL	Posterior mid	−0.033	0.011	−2.932	0.004					
	Anterior mid	−0.076	0.027	−2.824	0.005					
	Central R	−0.038	0.014	−2.638	0.009					
	Central L	−0.037	0.014	−2.606	0.010					
	Posterior R	−0.023	0.009	−2.519	0.012					
	Anterior L	−0.054	0.022	−2.486	0.013					
TOPF	Anterior mid	−0.083	0.019	−4.410	0.000					
	Central R	−0.044	0.010	−4.379	0.000					
	Central mid	−0.066	0.016	−4.155	0.000					
	Central L	−0.042	0.010	−4.133	0.000					
	Anterior L	−0.060	0.016	−3.846	0.000					
	Anterior R	−0.059	0.016	−3.669	0.000					

(Continued)

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TABLE 4 (Continued)

Measure	Location	Unadjusted				Adjusted				
		Est.	SE	*t*	*p*-value	Est.	SE	*t*	*β*	*p*-value
	Posterior L	−0.019	0.006	−2.965	0.003					
	Posterior mid	−0.022	0.008	−2.871	0.004					
	Temporal R	−0.020	0.007	−2.836	0.005					
	Posterior R	−0.017	0.006	−2.739	0.007					
B. Alpha band										
Number mTBIs	Posterior R					0.396	0.137	2.896	0.227	0.004
PCL-5	Central mid					0.038	0.013	2.985	0.373	0.001
	Posterior mid					0.059	0.018	3.250	0.362	0.001
	Anterior mid					0.049	0.016	3.066	0.353	0.002
	Central R					0.038	0.013	2.985	0.342	0.003
	Central L					0.037	0.012	2.953	0.339	0.003
	Anterior L					0.036	0.012	2.909	0.335	0.004
	Anterior R					0.036	0.013	2.770	0.320	0.006
PHQ-9	Posterior mid					−0.214	0.059	−3.621	−0.414	0.000
	Posterior L					−0.175	0.052	−3.359	−0.386	0.001
	Central mid					−0.133	0.041	−3.228	−0.394	0.001
	Temporal R					−0.071	0.021	−3.338	−0.390	0.001
	Central R					−0.133	0.041	−3.228	−0.380	0.001
	Temporal L					−0.064	0.020	−3.203	−0.377	0.002
	Central L					−0.127	0.040	−3.151	−0.371	0.002
	Anterior mid					−0.154	0.051	−3.005	−0.355	0.003
	Anterior L					−0.119	0.040	−2.982	−0.352	0.003
	Anterior R					−0.123	0.042	−2.930	−0.347	0.004
C. Beta band										
DRRI2	Posterior L	−0.003	0.001	−3.235	0.001					
	Posterior mid	−0.003	0.001	−3.106	0.002					
	Posterior R	−0.002	0.001	−3.078	0.002					
	Temporal L					−0.003	0.001	−2.823	−0.204	0.005
Fluid cognition	Posterior mid	0.004	0.001	4.281	0.000	0.004	0.001	3.425	0.229	0.001
	Posterior R	0.004	0.001	3.891	0.000	0.003	0.001	2.893	0.196	0.004
	Posterior L	0.004	0.001	3.809	0.000	0.003	0.001	2.782	0.187	0.006
	Temporal L					0.003	0.001	2.847	0.190	0.005
Number mTBIs	Temporal R					0.027	0.009	3.103	0.245	0.002
	Central R					0.028	0.010	2.780	0.216	0.006
	Temporal L					0.024	0.009	2.767	0.212	0.006
Number PTA + LOC	Central L	−0.085	0.021	−4.042	0.000	−0.107	0.025	−4.231	−0.263	0.000
	Posterior mid	−0.076	0.019	−3.914	0.000	−0.075	0.023	−3.219	−0.197	0.001
	Posterior L	−0.006	0.007	−0.844	0.000	−0.083	0.024	−3.476	−0.214	0.001
	Central R	−0.080	0.021	−3.712	0.000	−0.100	0.025	−3.987	−0.248	0.000
	Posterior R	−0.070	0.019	−3.682	0.000	−0.072	0.023	−3.102	−0.193	0.002

(Continued)

TABLE 4 (Continued)

Measure	Location	Unadjusted				Adjusted				
		Est.	SE	*t*	*p*-value	Est.	SE	*t*	*β*	*p*-value
	Central mid	−0.085	0.023	−3.638	0.000	−0.089	0.027	−3.355	−0.212	0.001
	Temporal L	−0.065	0.019	−3.434	0.001	−0.088	0.022	−4.049	−0.249	0.000
	Anterior L	−0.068	0.020	−3.341	0.001	−0.082	0.025	−3.318	−0.211	0.001
	Anterior mid	−0.072	0.024	−3.058	0.002	−0.079	0.028	−2.828	−0.182	0.005
	Temporal R					−0.068	0.022	−3.115	−0.197	0.002
Cognitive concerns TBIQOL	Temporal L					−0.006	0.002	−2.840	−0.308	0.005

Regression parameters for the EEG bands and locations with significant effects after alpha correction to control false discovery rate at 5%. For clarity, models with non-significant effects are not included (please see Supplementary material). No effects were observed in the theta or gamma band.
Est, non-standardized regression coefficient estimate; SE, standard error; β, standardized regression coefficient.

cognitive performance. Furthermore, the reduction of beta power has convergent findings in similar populations as detailed above.

4.2. Cognitive function is related to delta and beta activity

A higher level of delta and reduced beta was predicted by poorer fluid cognitive ability. No effect of current cognition or premorbid IQ was observed in alpha or theta. This may be due to the relatively small age distribution of the present sample or the limited nature of the cognitive tests (we did not evaluate full-scale IQ). The lack of theta effects may be due to the choice of fluid cognition as the cognitive domain of interest, which emphasizes processing speed, short-term memory, and executive processing, and very little long-term memory or vigilance demand associated with theta activity (56, 57). The involvement of delta and beta, however, is consonant with fluid cognition demands. Delta and delta–beta coordination are correlated with integrating cognitive functions over large areas of the brain (58), processes, for instance, underlying P300 (59). Delta oscillations have been implicated in response inhibition and balance between internal and external representations (60), while prestimulus delta–beta coordination underlies auditory temporal prediction accuracy (34) and cortical excitability for movement (61), and delta coordinates higher frequency activity to direct attention (62). Taken in the context of the findings of the present study, the delta–beta system underlying fluid cognition is relevant to late chronic mTBI, especially beta, shown similarly in moderate–severe injury by Shah et al. (50).

4.3. Subjective distress associated with delta elevation

Greater distress on all symptom measures was related to higher delta power. This was similar to effects reported in the acute phase of mTBI and other populations with subjective complaints, especially the higher power in low frequencies. Therefore, there appears to be a continuity between the slow wave correlate of symptoms early and much later (years) in recovery from injury. Furthermore, the symptoms continued to predict greater delta activity even after controlling for cognitive function, suggesting the slow oscillations track sensitivity to or expression of perceived difficulties, in addition to the cognitive processes described earlier. This illustrates a deep modulatory role of the delta networks and is interesting in light of the characterization of delta oscillations as critical in motivation, mood, and appetitive states (63), as well as biasing toward internal representations (64).

Finally, while previous studies have reported acute and chronic slowing with mTBI, there was no significant effect of any of the injury variables in the present study. This may be because of the long time since injury (10 years on average in the present study compared with 9 months for Franke et al.). However, the increased slow waves also represented a state of reduced cognition above and beyond the distress. Therefore, there appears to be a true dysfunctional state characterized by increased delta, but it is not related to the injury, at least at long lags. Therefore, there may be a risk of misattribution and bias of positive retrospective mTBI classification when cognitive problems and distress symptoms are emphasized and when the phase is very chronic (2+ years out from injury).

4.4. Evolution of mTBI effects on EEG over time

Previous analyses showed that PTA affected the delta band (8, 10), but this was relatively early after injury, in the subacute phase or on average less than a year after worst blast exposure. However, the present analysis suggests that very chronic impacts are on the alpha–beta bands, a finding consistent with the report of Lewine et al. (13). Together, these findings paint a picture of effects evolving over a very long time period, beyond just the 3 months typically associated with the resolution of symptoms and neuropsychological deficits. The pattern is acute widespread impacts to delta, theta, alpha, and beta. Then, during the subacute-early chronic phase, TBI effects are still observable in delta. Finally, in the very chronic phase, delta effects are primarily attributable to "internalizing symptoms" with subtle effects in alpha–beta for the higher dose (more and more severe) of mTBI. This transition

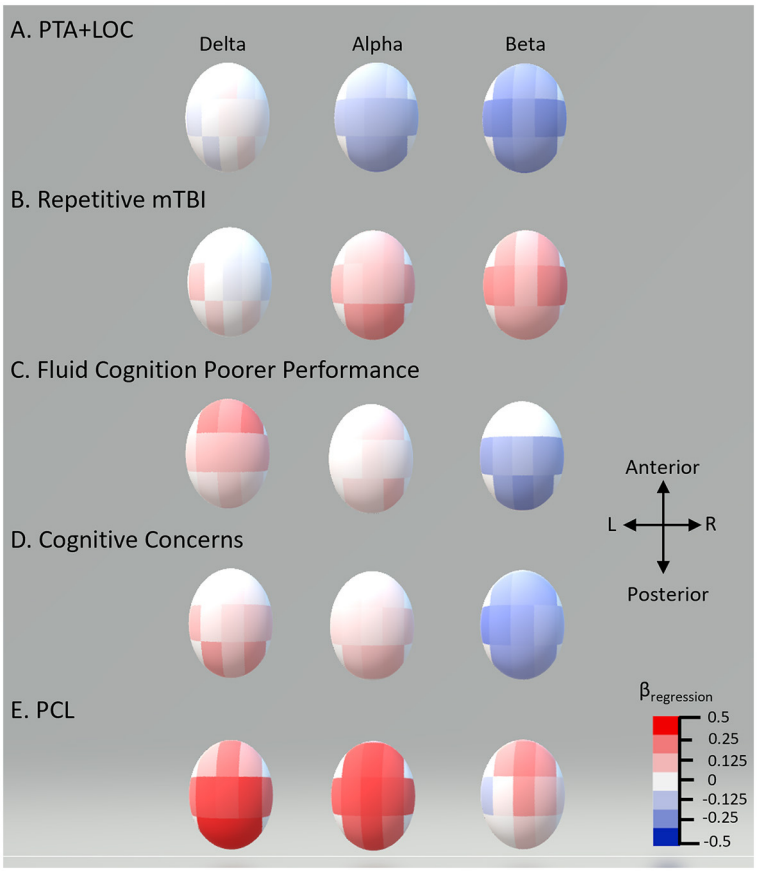

FIGURE 1
Standardized multiple regression coefficients (β) by scalp recording region. Topographic plot of standardized multiple regression coefficients for each of the 11 regions for the EEG bands showing significant differences in multiple regression.

from widespread effects including delta to alpha–beta suggests an evolution of neurophysiological effects of mTBI with PTA/LOC from deep modulatory (delta) to altered attention and sensory filtering (alpha–beta); the injury gets "better" in the sense of less extensive neurophysiological effects but still affects higher order processes. This hypothesized trajectory will continue to be tracked in the longitudinal LIMBIC-CENC analyses.

5. Limitations

The limitations of the present study include, foremostly, an observational design. Because of unmeasured variables and cohort effects in this type of design, one can never truly infer that the injury features are the cause of the chronic EEG change, as unmeasured confounds may exist. A single measure of cognitive function was used, while it was a composite measure and thus captured a large domain, the present results do not extend to non-measured domains. For psychological functioning, symptom measures and no diagnoses were used, likely lowering the specificity of effects and emphasizing the tendency to report distress. Finally, the multiple comparisons threshold choice affects outcomes (e.g., effects of PTA and repetitive TBI in gamma band similar to beta but did not meet the threshold for significance after correction).

6. Conclusion

The simple history of mTBI does not have long-term effects on resting EEG. However, higher levels of mTBI dose and severity have distinct chronic correlates in higher frequency resting EEG. Cognitive complaints may indicate specific problems with the functioning of this network. Different, slower resting oscillations may underlie difficulties with cognitive processing and psychological distress. In conclusion, the present study illustrates the complexity of even resting-state spectra as a measure of brain injury effects, in the varied influences from remote neurological events to subjective psychological states. Thus, because of the varied effects due to different injury variables and psychological injury correlates, studies of EEG of mTBI must account for more than simple injury status. Beta power reduction in particular may be a useful biomarker of chronic effects of more severe injuries involving PTA and loss of consciousness.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and

accession number(s) can be found below: Federal Interagency TBI Repository: https://fitbir.nih.gov/.

Ethics statement

The studies involving humans were approved by the Virginia Commonwealth University/Richmond VA/Walter Reed National Military Medical Center/Minneapolis VA IRBs. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

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Supplementary material

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Sensory functions and their relation to balance metrics: a secondary analysis of the LIMBIC-CENC multicenter cohort

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Introduction: Among patients with traumatic brain injury (TBI), balance problems often persist alongside hearing and vision impairments that lead to poorer outcomes of functional independence. As such, the ability to regain premorbid independent gait may be dictated by the level of sensory acuity or processing decrements that are shown following TBI assessment. This study explores the relationships between standardized sensory acuity and processing outcomes to postural balance and gait speed.

Methods: Secondary analysis was performed on the Long-Term Impact of Military-Relevant Brain Injury Consortium Chronic Effects of Neurotrauma Consortium LIMBIC (CENC) data set. Separate regression analyses were carried out for each of the balance assessments (via Computerized Dynamic Posturography, CDP) and walking speed.

Discussion: TBI frequency was significantly related to the majority of single CDP outcomes (i.e., Conditions 2–6), while various sensory processing outcomes had task-specific influences. Hearing impairments and auditory processing decrements presented with lower CDP scores (CDP Conditions 3,5,6, and 1–3 respectively), whereas greater visual processing scores were associated with better CDP scores for Conditions 2,5, and 6. In sum, patients with TBI had similar scores on static balance tests compared to non-TBI, but when the balance task got more difficult patients with TBI scored worse on the balance tests. Additionally, stronger associations with sensory processing than sensory acuity measures may indicate that patients with TBI have increased fall risk.

KEYWORDS

TBI, balance, sensory functions, auditory, vision

1. Introduction

Patients with traumatic brain injury (TBI) often have chronically persisting symptoms of dizziness, nausea, and postural instability. This includes patients with mild TBI, in whom balance and gait problems can persist for more than 3 months (1–8), especially when caused by blast exposure (e.g., military injury, industrial accidents) (9). Besides balance impairments, blast-related TBI has been associated with a loss of hearing (19%), vision (34%) or both (32%) in a TBI population admitted to a Veterans Affairs (VA) Polytrauma Rehabilitation Center (PRC). When both hearing and vision are impaired, poorer functional independence at discharge has been reported (10). Critically, this is independent of TBI severity. The ability to regain premorbid balance and independent gait may be dictated by the ability to process, interpret, and combine, sensory information. Specifically, gait speed and the ability to maintain balance may be dictated by the perceived sensory information and subsequent sensorimotor integration and motor transformation necessary for successful task execution (11).

Postural control (whether for balance or gait purposes) depends on the integration of information from visual, vestibular, and somatosensory systems (12). In healthy individuals, the weighting of each sensory input adjusts to a decrease or loss in quality from any one input to preserve balance and maintain postural stability (13), and optimize movement efficiency (12). For example, while vision is an important sensory system used to maintain optimal postural stability (14), when visual information is occluded (c.f., closing your eyes) the CNS can adapt the weighting of the visual system, and upregulate the sensitivity of the vestibular and somatosensory inputs to maintain balance (13). However, during more complex (and dynamic) tasks, integration informed by all sensory inputs may be more critical to task success. When walking in cluttered terrain, where multiple obstacles complicate foot-placement (15), visual information can be leveraged in a feed-forward manner to register (1) where the foot needs to be placed safely and (2) ongoing visual monitoring of the foot to safely place the foot.

While few studies have investigated how impaired sensory systems affect the mobility of patients post-TBI, we can gather insights from the known influences to balance [including increased fall risk (16)] and deterioration in gait speed and performance that occur with sensory decline as a function of aging (17, 18). It is well known though that eyesight, hearing, vestibular function (17), and proprioception (18) all decline with age. While evidence indicates that the decline in sensory systems may play a role in the increase of fall risk (16) and deterioration of gait speed, these relationships have not been extensively studied. In the general population, the elderly rely more on their visual system to maintain postural stability, and gait is slower and more variable when the visual system is perturbed (19). Further, visual acuity, contrast sensitivity, and stereo acuity were also associated with greater risk of walking limitations during a 5-year follow-up (20). Finally, impaired hearing is reported to be related to a slower maximal gait speed, self-reported walking difficulties (19), and postural stability (21, 22). This relationship between hearing and gait speed and balance may be explained by the information hearing provides of our surroundings and/or because the vestibular organs share structure and function: they are anatomically closely localized, share fluid-filled bony compartments and blood circulation, are both served by the eighth cranial nerve, and have similar mechanosensory receptor hair cells, which detect sound, head movements, and orientation in space. However, all these findings are in the aging population in general, and it is largely unknown how sensory decline and balance, and mobility impairments are related to central nervous system deficits due to TBI.

Therefore, the aim of this study was to determine relationships amongst balance, gait, and sensory measures in a large cohort study including patients with one or more mild TBIs. It is hypothesized that the quality of gait and balance decline as the number and severity of sensory impairments increase.

2. Methods

2.1. Design

The study utilized an observational design with cross-sectional analyses using hierarchical regression to examine the predictive value of sensory measures of hearing and vision including auditory and visual processing measures on gait and balance.

Methods are described in more detail in van der Veen et al. (23).

2.2. Outcome measures

2.2.1. Sensory-specific balance assessment (via CDP scores)

The computerized dynamic posturography (CDP) protocol on the NeuroCom Smart Balance Master (previously Natus, Inc) was used to assess postural balance. An embedded dual-plate force platform was used to generate equilibrium scores; ranging from 0 (touching a support surface, shifting feet, or falling) to 100 (little or no sway) for six sensory conditions: (1) all sensory inputs available; (2) no visual feedback; (3) distorted visual feedback because visual surround is "center of pressure referenced" (movements are proportional to the anterior–posterior displacement of the COP); (4) distorted somatosensory feedback because supporting platform is "center of pressure referenced"; (5) same as condition 4, but now with eyes closed; and (6) distorted visual and somatosensory feedback because both visual surround and supporting platform are "center of pressure referenced" (Figure 1). Each subject performed three trials for each condition, with an overall Composite CDP score calculated as a weighted average of the 6 scores (i.e., conditions 1 and 2 are weighted 1/3 as much as conditions 3 through 6).

2.2.2. Walking speed

Gait was measured as part of the NIH Toolbox by the 4-meter walk score representing gait speed (24). This test is adapted from the 4-meter walk test in the short physical performance battery, an assessment tool for evaluating lower extremity functioning in older persons. Participants were asked to walk 4 meters at their usual pace twice, both attempts were timed in seconds, with the better trial used for scoring (calculation to walking speed in m/s).

2.3. Sensory tests

2.3.1. Corrected visual acuity

Visual acuity is a measure determining clarity of vision with the subject standing 20 feet from the Snellen Eye Chart and the distance at which the participant can read the line of letters (25). If the

FIGURE 1
Schematic representation of the CDP the various panels represent the different balance assessments; (1) eyes open with fixed surface and surroundings, (2) eyes closed with fixed surface, (3) eyes open with fixed surface and sway-referenced visual surround, (4) eyes open with sway-referenced surface and fixed visual surround, (5) eyes closed with a sway-referenced surface, and (6) eyes open with sway-referenced surface and visual surround.

participant normally wears glasses or contact lenses, the test was performed while wearing glasses or contacts. A left and right visual acuity score was measured and a threshold score for the right eye was met with a visual acuity score of 20/40.

2.3.2. Visual spatial memory

The brief visuospatial memory test-revised (BVMT-R) is a measure of immediate and delayed visual memory (26). It requires the participant to reproduce line figures from memory. The BVMT-R provides twelve scores; three recall performance scores, one for each trial; a delayed recall score; three memory summary scores; three summary learning scores; hits (number of correct 'yes' responses) during the delayed recognition tasks; and a false alarm score (number of incorrect 'yes' responses) during the delayed recognition task.

2.3.3. Auditory processing

The Scan-3 test is comprised of a screening battery of tests to detect auditory processing disorders in adolescents and adults (27). The test evaluates temporal processing with three subtests: gap detection; auditory figure ground; and competing words.

2.3.4. Hearing handicap

The hearing handicap inventory for adults (HHIA) is a well-studied and widely used self-report measure of the respondent's perceived hearing difficulty (28). The 11-item screening version used in this study is composed of two subscales (emotional and situational).

2.4. Data analysis

Participant characteristics were summarized using means and standard deviations or frequencies (see Table 1). Missing data was accounted for using multiple imputation using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp), see percentages in Figure 2. Five imputed datasets were created using a fully condition specification. The estimates were then combined, and standard errors were adjusted to account for the uncertainty due to missingness. Hierarchical regressions were performed using SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp) with TBI classification and covariates of interest grouped in the following 5 steps: (1) the number of TBIs suffered, age, and sex, (2) the separate HHIA items, (3) separate BVMT items, (4) visual acuity, and (5) items of the SCAN3 (see Table 2 for a complete overview of the items entered in the regression). Separate hierarchical regression analyses were carried out for each of the balance assessment outcome measures (i.e., best 4 m walk score, CDP composite, CDP condition 1–6). Sensory measures were removed from the regression equations when collinearity was found (VIF > 10). Statistical significance was determined using a Benjamini-Hochberg correction, where the critical p values were based on the 27 tests per regression and a fall discovery rate of 20%.

3. Results

3.1. Participants

The study includes data from 1550 participants, but only 241 (15.55%) cases were complete (see Figure 2). All participants were included in analyses due to the use of multiple imputation. Of these 1550, 1248 suffered at least one TBI and 281 were participants with no history of TBI (non-TBI). For demographics, see Table 1.

TABLE 1 Participant demographics, mean ± standard deviation, except for sex male, feale.

	TBI		Control		Total	
	Mean	Std	Mean	Std	Mean	Std
Age (mean/std)	39.93	9.57	40.01	10.08	39.95	9.66
Sex (male/female)	1126	140	221	63	1347	
TBI	2.7	1.93	0	0	2.2	2.03
walking speed (m/s)	1.24	0.37	1.2	0.22	1.24	0.35
CDP composite	72.63	13.78	74.7	8.92	73.01	13.09
CDP1	92.43	5.05	92.76	4.06	92.5	7.00
CDP2	88.19	7.44	89.87	3.9	88.5	9.34
CDP3	86.7	9.99	88.88	4.63	87.1	17.12
CDP4	59.14	18.01	76.09	11.7	73.76	19.22
CDP5	58.67	20.03	61.6	14.57	59.59	21.91
CDP6	72.63	22.61	60.57	18.13	59.02	19.09
Visual acuity right	1.00	0.34	1.00	0.34	1.00	0.34
Visual acuity left	1.03	0.33	1.05	0.35	1.03	0.34
Scan-3	0.47	0.50	0.49	0.50	0.47	0.50
HHIA	16.45	8.53	15.21	7.11	16.26	8.33
BVMT-R mean recall	42.52	12.32	42.68	12.10	42.55	12.28
BVMT-R delayed recall	44.18	13.02	45.95	12.73	44.51	12.98
BVMT-R mean learning	51.66	11.74	53.55	10.74	52.01	11.20

3.2. Walking speed

Table 2 presents the complete hierarchical regression results for the 4 m walking speed. Step 2 revealed a negative association between the difficulty with the item "understanding movies" ($p = 0.012$), "problems with hearing" ($p = 0.003$), and walk score. Step 3 indicated an increase in valid items recalled after a delay was associated with slower walking speeds; age ($p = 0.006$) became related to faster walking speeds. Although Step 4 (visual acuity added) increased variance accounted for to 12.0%, none of the visual acuity measures were significant; visual spatial recall memory (BVMT-R delayed recall score, $p = 0.013$) remained positively related to 4 m walk time. Step 5 added audio processing and increased variance accounted for to 14.0%. The ability to distinguish audio target from noise showed a relation with faster walking speeds ($p = 0.001$), indicating the ability to distinguish words from noise was related to longer 4 m walk times. See Table 2 for the complete results.

3.3. CDP composite

Table 3 presents the complete hierarchical regression results for the CDP composite score. Step 1 accounted for 6.2% of the variance of the composite CDP score. All demographic measures were found to be related to balance measured with the CDP combined score. Age, sex, and number of TBI are negatively correlated with the CDP composite score, indicating older people ($p = 0.039$), females ($p = 0.045$), and people with more TBIs suffered ($p < 0.001$) have more balance difficulties. Step 2, revealed an association between self-reported absence of difficulty with hearing ($p = 0.001$) and a better CDP composite score. Step 3 showed visual spatial recall memory (BVMT-R delayed recall score, $p = 0.014$) was positively related to the CDP composite score. A positive relationship was shown between auditory processing [the ability to distinguish audio target from noise ($p = 0.034$) and the ability to repeat both words ($p = 0.020$)] and CDP composite score in step 5. See Table 3 for the individual measures.

3.4. CDP condition 1 eyes open with fixed surface and visual surround

Table 4 represents the complete hierarchical regression results for the CDP condition 1 score. Step 1 accounted for 2.1% of the variance of the CDP condition 1 score. In step 2, an association between increased difficulty understanding new people ($p = 0.025$) and worse CDP condition 1 score was found. In step 5 a relationship was shown between auditory processing (the ability to repeat both words, $p = 0.001$) and CDP condition 1. See Table 4 for the individual measures.

3.5. CDP condition 2 eyes closed with a fixed surface

Table 5 represents the complete hierarchical regression results for the CDP condition 2 score. Both Age ($p = 0.010$) and number of TBI ($p = 0.001$) were shown to be negatively related to CDP condition 2 score in step 1. Step 2, the absence of difficulty hearing ($p = 0.013$) was associated with a better CDP condition 2 score. Step 3 revealed a positive association was shown for the delayed recall score ($p = 0.001$). Step 4 showed visual learning score ($p = 0.008$) has a negative association with the CDP condition 2. Step 5 showed a positive relationship was shown between auditory processing [the ability to repeat both words ($p < 0.001$)] and CDP condition 2 scores. See Table 5 for the individual measures.

3.6. CDP condition 3 eyes open with fixed surface and sway-referenced visual surround

Table 6 represents the complete hierarchical regression results for the CDP condition 3 score. In step 1 number of TBI ($p = 0.001$) was shown to be negatively related to CDP condition 3 scores. Step 2 showed the absence of difficulty hearing ($p = 0.004$) was associated with a better CDP condition 3 score. A positive relationship was shown between auditory processing [the ability to repeat both words

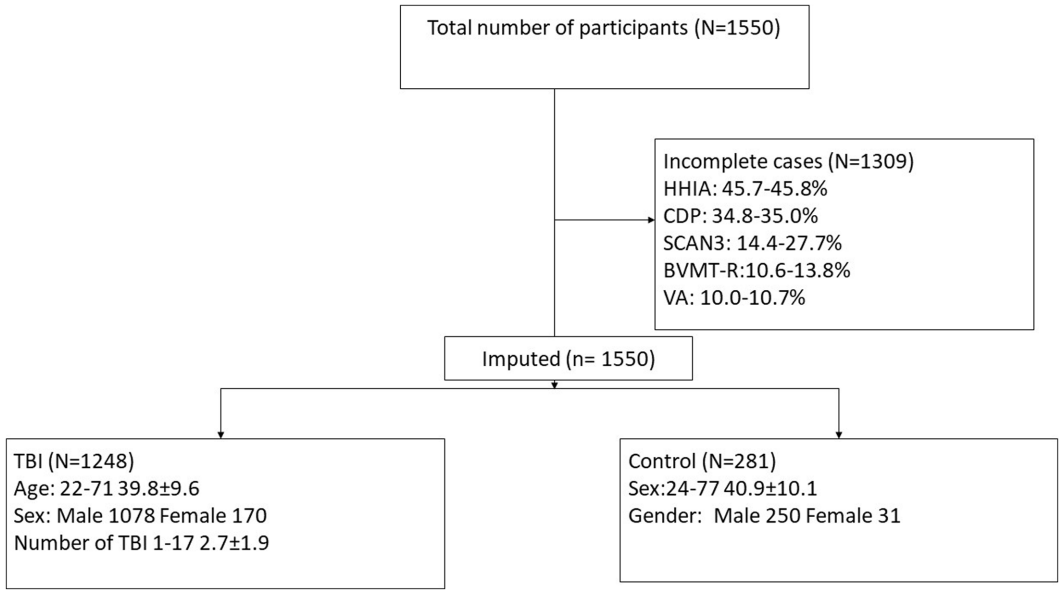

FIGURE 2
Consort diagram demonstrating participant selection for the current study. HHIA, Hearing Handicap Inventory for Adults; CDP, Computerized Dynamic Posturography; SCAN-3, Tests for Auditory Processing Disorders; BVMT-R, Brief Visuospatial Memory Test-Revised; VA, Visual acuity; TBI, traumatic brain injury.

($p = 0.021$) and CDP condition 3 score in step 5]. See Table 6 for the individual measures.

3.7. CDP condition 4 eyes open with sway-referenced surface and fixed visual surround

Table 7 represents the complete hierarchical regression results for the CDP condition 4 score. In step number of TBI ($p = 0.006$) showed a negative relation to CDP condition 4 score. In step 4, visual processing measures showed a positive association with recall score ($p = 0.033$). See Table 7 for the individual measures.

3.8. CDP condition 5 eyes closed with a sway-referenced surface

Table 8 represents the complete hierarchical regression results for the CDP condition 5 score. In step 1 both age ($p = 0.020$) and number of TBI ($p < 0.001$) were shown to be negatively related to CDP condition 5 score. Step 2, showed the absence of difficulty hearing ($p < 0.001$) was associated with a better CDP condition 5 score. In step 4 visual processing measures showed a negative association between recall score ($p = 0.004$). See Table 8 for the individual measures.

3.9. CDP condition 6 eyes open with sway-referenced surface and visual surrounds

Table 9 represents the complete hierarchical regression results for the CDP 6 score. In step 1 both age ($p = 0.021$) and number of TBI ($p = 0.016$) were shown to be negatively related to CDP condition 6 score. In step 2 the absence of difficulty hearing ($p < 0.001$) was associated with better CDP condition 6 score. Step 3 revealed recall score ($p = 0.004$) showed a positive relation. In step 4 visual processing measure showed a negative association with learning score ($p = 0.011$). See Table 9 for the individual measures.

4. Discussion

The goal of this study was to determine the relationships between sensory function and postural balance among current and former combat-exposed service members, with and without a history of mTBI(s). Balance is dependent on the ability to combine and process sensory information, identifying the fidelity of these signals and using this information to adjust the weighting of the sensory information (12). This study reinforces that postural balance is a complex control problem that utilizes multiple sensory systems and requires the ability to successfully process multiple inputs at the executive processing level.

In general, individuals with TBI can reliably maintain postural stability (as evidenced by high CDP scores for Condition 1 in Table 1) and ambulate at similar speeds successfully when sensory input from vision, proprioception, or vestibular systems are unperturbed. However, individuals with TBI have more difficulty when adjustments in the weighting of these sensory inputs are required due to various experimental perturbations; swaying surrounding or base of support, or the occlusion of vision.

The most consistent feature across regression analyses was that sensory disruptions (vision, vestibular, or somatosensory) and subsequent lower balance assessment outcomes (via CDP 2–6 scores) were associated with the number of TBIs reported (29). Additionally, females appear to have more difficulty keeping their balance when proprioception is unreliable (e.g., on a swaying surface) than males.

TABLE 2 Results from the hierarchical regression for best walk score.

WALK score (m/s)	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.021				0.052				0.074				0.130				0.157			
Constant	1.176	0.050	23.325	0.000	1.176	0.069	17.029	0.000	1.161	0.123	9.441	0.000	0.791	0.142	5.573	0.000	0.757	0.148	5.099	0.000
DEMOGAGEYEARS	0.002	0.001	1.661	0.097	0.002	0.001	1.964	0.050	0.003	0.001	2.655	0.008	0.004	0.001	3.372	0.002	0.003	0.001	2.695	0.010
GENDERTYP	−0.008	0.027	−0.291	0.771	−0.005	0.027	−0.195	0.845	−0.010	0.028	−0.370	0.712	−0.006	0.026	−0.244	0.808	−0.024	0.026	−0.934	0.350
TOTAL_TBI	0.002	0.004	0.525	0.600	0.003	0.005	0.680	0.497	0.003	0.005	0.594	0.552	0.000	0.005	0.068	0.946	0.000	0.005	0.064	0.949
HHIASEMBARRASSEDNEWPEOPLE					−0.006	0.005	−1.318	0.191	−0.006	0.005	−1.307	0.194	−0.006	0.004	−1.285	0.201	−0.005	0.004	−1.231	0.221
HHIASFEELFRUSTRATED					0.004	0.011	0.354	0.727	0.004	0.011	0.346	0.734	0.004	0.011	0.341	0.737	0.004	0.011	0.374	0.714
HHIASDIFFICULTYUNDERSTANDING					−0.005	0.010	−0.502	0.617	−0.006	0.011	−0.533	0.597	−0.009	0.010	−0.879	0.384	−0.010	0.010	−1.040	0.303
HHIASFEELHANDICAPPED					−0.003	0.009	−0.373	0.709	−0.002	0.009	−0.179	0.858	0.001	0.009	0.065	0.948	0.000	0.009	−0.026	0.980
HHIASDIFFICULTYVISITING					0.001	0.011	0.080	0.937	0.001	0.011	0.103	0.919	−0.001	0.011	−0.102	0.920	−9.948E-05	0.011	−0.009	0.993
HHIASDIFFICULTYINMOVIES					−0.025	0.011	−2.227	0.039	−0.026	0.012	−2.259	0.039	−0.023	0.011	−2.031	0.061	−0.021	0.010	−2.138	0.043
HHIASARGUMENTSFAMILY					0.005	0.009	0.539	0.598	0.006	0.010	0.597	0.561	0.004	0.010	0.392	0.702	0.004	0.009	0.403	0.693
HHIASDIFFICULTYLISTENINGTV					−0.002	0.009	−0.258	0.798	−0.003	0.009	−0.326	0.746	−0.005	0.009	−0.567	0.573	−0.006	0.008	−0.714	0.477
HHIASHAMPERSPERSONALLIFE					0.006	0.010	0.567	0.575	0.006	0.011	0.560	0.581	0.007	0.011	0.633	0.536	0.006	0.010	0.621	0.541
HHIASDIFFICULTYRESTAURANT					0.003	0.009	0.292	0.771	0.002	0.009	0.192	0.848	0.002	0.008	0.204	0.839	0.003	0.008	0.415	0.678
HHIASPROBLEMWITHHEARING					0.007	0.021	0.356	0.723	0.009	0.021	0.449	0.654	0.004	0.021	0.174	0.862	−0.010	0.022	−0.469	0.641
BVMTRRECALLTSCORE									0.003	0.001	2.292	0.022	0.003	0.001	2.452	0.016	0.003	0.001	2.589	0.011
BVMTRLEARNINGTSCORE									−0.001	0.001	−0.759	0.448	1.079E-05	0.001	0.011	0.991	0.000	0.001	−0.351	0.726
BVMTRDELAYEDRECALLTSCORE									−0.004	0.001	−2.993	0.003	−0.004	0.001	−3.147	0.002	−0.003	0.001	−2.711	0.008
BVMTRHITRAWSCORE									0.008	0.038	0.200	0.842	0.000	0.036	0.006	0.995	−0.001	0.036	−0.025	0.980
BVMTRFALSEALARMRAWSCORE									−0.065	0.041	−1.583	0.114	−0.049	0.041	−1.178	0.239	−0.043	0.040	−1.068	0.286
BVMTRDISCRIMINTATIONRAWSCORE									0.005	0.033	0.156	0.876	0.007	0.032	0.223	0.823	0.011	0.031	0.347	0.729
VA_RT_score													0.056	0.068	0.829	0.430	0.044	0.066	0.669	0.522
VA_RT_inter													0.116	0.120	0.972	0.370	0.109	0.112	0.976	0.367
VA_LT_score													0.151	0.088	1.716	0.137	0.148	0.087	1.692	0.142
VA_LT_inter													0.014	0.194	0.071	0.946	0.004	0.180	0.020	0.985
SCAN3GAPDETECTGRADE																	0.062	0.037	1.665	0.102
SCAN3AUDITFIGURECOMBINEDSCORE																	0.012	0.002	6.340	0.000
SCAN3COMPETEWORDCOMBINEDSCORE																	−0.011	0.002	−5.550	0.000

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TABLE 3 Results from the hierarchical regression for CDP composite.

CDP composite	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.062				0.094				0.118				0.124				0.138			
Constant	79.471	1.925	41.286	0.000	76.658	2.638	29.061	0.000	66.965	3.970	16.869	0.000	62.879	4.383	14.347	0.000	53.958	4.876	11.066	0.000
DEMOGAGEYEARS	−0.074	0.035	−2.123	0.039	−0.065	0.036	−1.796	0.081	−0.040	0.037	−1.086	0.286	−0.030	0.040	−0.737	0.469	−0.001	0.040	−0.013	0.990
GENDERTYP	−1.811	0.901	−2.010	0.045	−2.262	0.870	−2.599	0.009	−2.411	0.863	−2.795	0.005	−2.402	0.858	−2.800	0.005	−2.386	0.854	−2.796	0.005
TOTAL_TBI	−0.654	0.154	−4.243	0.000	−0.488	0.166	−2.933	0.005	−0.525	0.166	−3.160	0.003	−0.545	0.165	−3.297	0.002	−0.558	0.162	−3.444	0.001
HHIASEMBARRASSEDNEWPEOPLE					−0.103	0.201	−0.512	0.618	−0.091	0.203	−0.445	0.665	−0.085	0.200	−0.427	0.678	−0.056	0.204	−0.274	0.789
HHIASFEELFRUSTRATED					0.075	0.356	0.212	0.835	0.104	0.344	0.303	0.765	0.097	0.340	0.285	0.779	0.060	0.332	0.181	0.858
HHIASDIFFICULTYUNDERSTANDING					0.035	0.387	0.091	0.929	0.053	0.373	0.141	0.889	0.004	0.378	0.012	0.991	0.069	0.363	0.189	0.852
HHIASFEELHANDICAPPED					−0.235	0.325	−0.723	0.473	−0.128	0.311	−0.411	0.682	−0.095	0.309	−0.306	0.760	−0.059	0.308	−0.190	0.850
HHIASDIFFICULTYVISITING					−0.090	0.452	−0.198	0.847	−0.122	0.460	−0.265	0.797	−0.152	0.464	−0.327	0.750	−0.168	0.473	−0.356	0.730
HHIASDIFFICULTYINMOVIES					0.094	0.323	0.292	0.772	0.110	0.325	0.337	0.739	0.138	0.319	0.433	0.669	0.153	0.311	0.493	0.625
HHIASARGUMENTSFAMILY					−0.255	0.284	−0.899	0.380	−0.246	0.260	−0.948	0.351	−0.264	0.261	−1.010	0.322	−0.201	0.265	−0.761	0.454
HHIASDIFFICULTYLISTENINGTV					−0.089	0.414	−0.214	0.835	−0.120	0.408	−0.295	0.774	−0.135	0.403	−0.336	0.744	−0.063	0.379	−0.165	0.872
HHIASHAMPERSPERSONALLIFE					−0.381	0.370	−1.030	0.319	−0.281	0.355	−0.792	0.439	−0.265	0.357	−0.744	0.467	−0.233	0.348	−0.671	0.510
HHIASDIFFICULTYRESTAURANT					−0.106	0.318	−0.333	0.741	−0.184	0.333	−0.552	0.586	−0.182	0.351	−0.519	0.610	−0.160	0.346	−0.464	0.648
HHIASPROBLEMWITHHEARING					2.721	0.750	3.627	0.001	2.624	0.755	3.475	0.002	2.517	0.762	3.303	0.003	1.974	0.730	2.703	0.010
BVMTRRECALLTSCORE									0.096	0.039	2.459	0.014	0.098	0.040	2.480	0.014	0.084	0.040	2.115	0.036
BVMTRLEARNINGTSCORE									−0.042	0.028	−1.512	0.131	−0.035	0.028	−1.262	0.207	−0.040	0.028	−1.427	0.153
BVMTRDELAYEDRECALLTSCORE									0.008	0.037	0.224	0.823	0.004	0.037	0.106	0.916	0.004	0.037	0.104	0.917
BVMTRHITRAWSCORE									1.372	1.175	1.167	0.243	1.271	1.192	1.066	0.287	1.186	1.187	0.999	0.318
BVMTRFALSEALARMRAWSCORE									−1.123	1.285	−0.874	0.382	−1.039	1.284	−0.809	0.418	−0.857	1.284	−0.667	0.505
BVMTRDISCRIMINTATIONRAWSCORE									−0.190	1.060	−0.180	0.857	−0.159	1.066	−0.149	0.881	−0.101	1.072	−0.094	0.925
VA_RT_score													0.381	1.377	0.277	0.783	0.453	1.381	0.328	0.744
VA_RT_inter													3.145	2.878	1.093	0.306	2.834	2.852	0.994	0.349
VA_LT_score													0.928	1.572	0.590	0.561	0.656	1.580	0.415	0.682
VA_LT_inter													−0.270	3.366	−0.080	0.938	0.010	3.307	0.003	0.998
SCAN3GAPDETECTGRADE																	−0.371	1.158	−0.321	0.749
SCAN3AUDITFIGURECOMBINEDSCORE																	0.157	0.071	2.205	0.034
SCAN3COMPETEWORDCOMBINEDSCORE																	0.195	0.079	2.471	0.020

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TABLE 4 Results from the hierarchical regression for CDP condition 1, standing balance.

CDP1 standing balance	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.021				0.053				0.083				0.087				0.109			
Constant	93.490	0.782	119.553	0.000	93.469	1.253	74.590	0.000	89.763	1.822	49.272	0.000	92.089	2.282	40.347	0.000	90.893	3.011	30.188	0.000
DEMOGAGEYEARS	−0.015	0.015	−0.987	0.328	−0.017	0.015	−1.096	0.278	−0.009	0.016	−0.561	0.577	−0.006	0.015	−0.404	0.687	0.007	0.015	0.481	0.631
GENDERTYP	−0.210	0.402	−0.522	0.602	−0.247	0.400	−0.616	0.538	−0.291	0.397	−0.732	0.465	−0.318	0.392	−0.813	0.417	−0.150	0.400	−0.374	0.709
TOTAL_TBI	−0.076	0.063	−1.213	0.225	−0.054	0.064	−0.835	0.404	−0.056	0.064	−0.888	0.375	−0.048	0.064	−0.739	0.460	−0.052	0.064	−0.804	0.422
HHIASEMBARRASSEDNEWPEOPLE					0.026	0.071	0.372	0.713	0.034	0.070	0.488	0.629	0.038	0.068	0.558	0.580	0.040	0.071	0.555	0.584
HHIASFEELFRUSTRATED					0.057	0.148	0.385	0.704	0.061	0.146	0.417	0.681	0.052	0.144	0.360	0.723	0.044	0.147	0.302	0.766
HHIASDIFFICULTYUNDERSTANDING					−0.303	0.133	−2.281	0.025	−0.297	0.128	−2.319	0.021	−0.278	0.130	−2.146	0.033	−0.258	0.127	−2.037	0.043
HHIASFEELHANDICAPPED					0.013	0.143	0.094	0.925	0.046	0.141	0.323	0.748	0.057	0.139	0.407	0.685	0.071	0.139	0.509	0.613
HHIASDIFFICULTYVISITING					−0.221	0.166	−1.330	0.199	−0.225	0.169	−1.330	0.201	−0.211	0.168	−1.250	0.228	−0.218	0.169	−1.288	0.216
HHIASDIFFICULTYINMOVIES					0.063	0.153	0.414	0.684	0.062	0.153	0.408	0.688	0.058	0.149	0.386	0.704	0.050	0.160	0.309	0.761
HHIASARGUMENTSFAMILY					0.002	0.108	0.023	0.982	0.013	0.105	0.126	0.900	0.017	0.105	0.160	0.874	0.030	0.107	0.283	0.778
HHIASDIFFICULTYLISTENINGTV					0.078	0.133	0.589	0.560	0.071	0.134	0.532	0.599	0.073	0.133	0.550	0.587	0.099	0.136	0.726	0.475
HHIASHAMPERSPERSONALLIFE					0.053	0.167	0.319	0.755	0.084	0.171	0.493	0.631	0.074	0.168	0.440	0.667	0.088	0.170	0.515	0.616
HHIASDIFFICULTYRESTAURANT					0.066	0.131	0.507	0.614	0.053	0.138	0.384	0.704	0.041	0.141	0.293	0.772	0.036	0.137	0.263	0.794
HHIASPROBLEMWITHHEARING					0.303	0.440	0.687	0.508	0.251	0.443	0.566	0.584	0.281	0.445	0.631	0.543	0.243	0.410	0.592	0.565
BVMTRRECALLTSCORE									0.008	0.019	0.404	0.688	0.009	0.019	0.488	0.627	0.004	0.019	0.231	0.818
BVMTRLEARNINGTSCORE									−0.024	0.014	−1.714	0.091	−0.025	0.014	−1.776	0.081	−0.024	0.015	−1.667	0.103
BVMTRDELAYEDRECALLTSCORE									0.013	0.017	0.722	0.472	0.012	0.018	0.695	0.489	0.008	0.018	0.426	0.671
BVMTRHITRAWSCORE									1.032	1.205	0.857	0.425	1.030	1.209	0.852	0.428	1.076	1.261	0.853	0.429
BVMTRFALSEALARMRAWSCORE									−0.930	1.013	−0.918	0.385	−0.976	1.039	−0.939	0.376	−0.988	1.077	−0.917	0.389
BVMTRDISCRIMINTATIONRAWSCORE									−0.364	1.091	−0.333	0.751	−0.370	1.101	−0.336	0.749	−0.422	1.145	−0.369	0.726
VA_RT_score													−0.131	0.608	−0.215	0.830	−0.059	0.632	−0.094	0.926
VA_RT_inter													−0.791	1.325	−0.597	0.569	−0.791	1.340	−0.590	0.573
VA_LT_score													0.611	0.581	1.052	0.295	0.617	0.571	1.079	0.282
VA_LT_inter													−2.230	2.001	−1.114	0.309	−2.080	1.894	−1.098	0.314
SCAN3GAPDETECTGRADE																	−1.104	0.853	−1.294	0.233
SCAN3AUDITFIGURECOMBINEDSCORE																	−0.048	0.048	−0.992	0.352
SCAN3COMPETEWORDCOMBINEDSCORE																	0.117	0.033	3.551	0.001

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TABLE 5 Results from the hierarchical regression for CDP condition 2, occluded vision.

CDP2 no vision	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.068				0.096				0.122				0.125				0.144			
Constant	91.853	0.980	93.698	0.000	90.872	1.306	69.566	0.000	86.644	2.751	31.494	0.000	85.906	3.316	25.909	0.000	78.958	3.526	22.396	0.000
DEMOGAGEYEARS	−0.050	0.019	−2.611	0.010	−0.046	0.019	−2.383	0.018	−0.044	0.020	−2.156	0.034	−0.039	0.021	−1.901	0.061	−0.018	0.022	−0.799	0.430
GENDERTYP	−0.303	0.563	−0.538	0.592	−0.556	0.555	−1.001	0.318	−0.555	0.538	−1.032	0.303	−0.555	0.540	−1.029	0.304	−0.518	0.535	−0.968	0.334
TOTAL_TBI	−0.458	0.117	−3.911	0.001	−0.369	0.103	−3.589	0.001	−0.359	0.105	−3.423	0.002	−0.364	0.105	−3.465	0.001	−0.369	0.105	−3.521	0.001
HHIASEMBARRASSEDNEWPEOPLE					−0.003	0.098	−0.033	0.974	0.010	0.093	0.107	0.916	0.015	0.090	0.164	0.870	0.033	0.095	0.351	0.728
HHIASFEELFRUSTRATED					−0.064	0.259	−0.248	0.810	−0.061	0.243	−0.249	0.808	−0.066	0.244	−0.270	0.792	−0.101	0.250	−0.403	0.696
HHIASDIFFICULTYUNDERSTANDING					0.004	0.271	0.016	0.988	0.020	0.252	0.080	0.937	0.005	0.254	0.020	0.985	0.072	0.239	0.299	0.769
HHIASFEELHANDICAPPED					−0.111	0.252	−0.440	0.668	−0.084	0.244	−0.344	0.736	−0.073	0.241	−0.302	0.767	−0.048	0.235	−0.205	0.840
HHIASDIFFICULTYVISITING					−0.127	0.228	−0.557	0.584	−0.128	0.227	−0.564	0.580	−0.133	0.230	−0.577	0.571	−0.145	0.238	−0.608	0.552
HHIASDIFFICULTYINMOVIES					0.112	0.205	0.548	0.589	0.130	0.207	0.626	0.539	0.141	0.213	0.665	0.515	0.133	0.189	0.704	0.487
HHIASARGUMENTSFAMILY					−0.187	0.182	−1.024	0.324	−0.176	0.184	−0.957	0.356	−0.184	0.186	−0.989	0.341	−0.146	0.185	−0.788	0.446
HHIASDIFFICULTYLISTENINGTV					0.032	0.255	0.126	0.902	0.032	0.250	0.128	0.901	0.025	0.250	0.102	0.921	0.078	0.230	0.341	0.740
HHIASHAMPERSPERSONALLIFE					−0.063	0.258	−0.246	0.811	−0.020	0.257	−0.079	0.938	−0.016	0.258	−0.063	0.951	0.005	0.254	0.020	0.985
HHIASDIFFICULTYRESTAURANT					−0.224	0.225	−0.995	0.337	−0.228	0.228	−0.997	0.337	−0.226	0.232	−0.973	0.349	−0.223	0.226	−0.984	0.343
HHIASPROBLEMWITHHEARING					1.306	0.480	2.719	0.013	1.207	0.469	2.575	0.017	1.177	0.466	2.525	0.018	0.926	0.467	1.981	0.058
BVMTRRECALLTSCORE									−0.056	0.026	−2.198	0.031	−0.055	0.026	−2.121	0.038	−0.063	0.025	−2.588	0.011
BVMTRLEARNINGTSCORE									−0.049	0.018	−2.685	0.008	−0.047	0.019	−2.516	0.014	−0.048	0.019	−2.530	0.014
BVMTRDELAYEDRECALLTSCORE									0.080	0.024	3.277	0.001	0.078	0.025	3.115	0.003	0.077	0.025	3.099	0.003
BVMTRHITRAWSCORE									1.659	2.083	0.796	0.462	1.624	2.092	0.777	0.473	1.470	2.088	0.704	0.513
BVMTRFALSEALARMRAWSCORE									−1.330	1.666	−0.798	0.453	−1.290	1.672	−0.772	0.468	−1.182	1.691	−0.699	0.510
BVMTRDISCRIMINTATIONRAWSCORE									−0.701	1.931	−0.363	0.732	−0.693	1.925	−0.360	0.734	−0.610	1.932	−0.316	0.765
VA_RT_score													0.425	1.359	0.312	0.763	0.583	1.351	0.431	0.678
VA_RT_inter													0.193	2.052	0.094	0.928	−0.026	2.053	−0.013	0.990
VA_LT_score													0.380	1.202	0.316	0.758	0.142	1.181	0.121	0.906
VA_LT_inter													−0.302	1.527	−0.198	0.845	−0.033	1.458	−0.023	0.982
SCAN3GAPDETECTGRADE																	0.548	0.744	0.737	0.465
SCAN3AUDITFIGURECOMBINEDSCORE																	0.038	0.047	0.816	0.425
SCAN3COMPETEWORDCOMBINEDSCORE																	0.198	0.040	4.889	0.000

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TABLE 6 Results from the hierarchical regression for CDP condition 3, sway referenced vision.

CDP3	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.078				0.109				0.184				0.128				0.138			
Constant	90.616	1.500	60.409	0.000	88.043	2.127	41.383	0.000	86.874	3.614	24.038	0.000	84.624	5.078	16.665	0.000	77.732	5.614	13.845	0.000
DEMOGAGEYEARS	−0.024	0.031	−0.789	0.439	−0.013	0.031	−0.427	0.674	−0.006	0.032	−0.192	0.850	−0.002	0.033	−0.058	0.955	0.016	0.035	0.456	0.655
GENDERTYP	−0.765	0.794	−0.963	0.341	−1.103	0.762	−1.448	0.152	−1.140	0.757	−1.506	0.137	−1.132	0.730	−1.551	0.124	−1.165	0.726	−1.604	0.111
TOTAL_TBI	−0.760	0.120	−6.362	0.000	−0.631	0.123	−5.123	0.000	−0.620	0.123	−5.018	0.000	−0.633	0.122	−5.175	0.000	−0.638	0.122	−5.243	0.000
HHIASEMBARRASSEDNEWPEOPLE					−0.002	0.162	−0.010	0.992	0.011	0.158	0.069	0.946	0.015	0.151	0.099	0.922	0.036	0.153	0.234	0.819
HHIASFEELFRUSTRATED					−0.028	0.226	−0.124	0.902	−0.027	0.220	−0.125	0.901	−0.034	0.222	−0.156	0.877	−0.067	0.228	−0.294	0.770
HHIASDIFFICULTYUNDERSTANDING					0.262	0.298	0.879	0.392	0.262	0.295	0.887	0.388	0.220	0.286	0.771	0.450	0.277	0.281	0.985	0.336
HHIASFEELHANDICAPPED					−0.292	0.243	−1.201	0.234	−0.265	0.248	−1.068	0.290	−0.270	0.244	−1.106	0.272	−0.255	0.242	−1.054	0.295
HHIASDIFFICULTYVISITING					−0.468	0.282	−1.659	0.110	−0.459	0.286	−1.604	0.123	−0.476	0.279	−1.705	0.101	−0.481	0.281	−1.713	0.100
HHIASDIFFICULTYINMOVIES					−0.148	0.261	−0.564	0.578	−0.145	0.261	−0.553	0.586	−0.123	0.270	−0.456	0.654	−0.122	0.264	−0.463	0.648
HHIASARGUMENTSFAMILY					−0.174	0.221	−0.790	0.440	−0.160	0.222	−0.720	0.481	−0.172	0.233	−0.739	0.472	−0.134	0.232	−0.580	0.571
HHIASDIFFICULTYLISTENINGTV					0.250	0.346	0.722	0.490	0.252	0.343	0.735	0.483	0.244	0.343	0.712	0.496	0.296	0.327	0.907	0.388
HHIASHAMPERSPERSONALLIFE					0.092	0.280	0.330	0.745	0.118	0.271	0.433	0.669	0.138	0.274	0.503	0.621	0.156	0.274	0.568	0.577
HHIASDIFFICULTYRESTAURANT					−0.322	0.272	−1.185	0.251	−0.320	0.278	−1.151	0.266	−0.296	0.305	−0.971	0.351	−0.285	0.299	−0.954	0.358
HHIASPROBLEMWITHHEARING					2.142	0.648	3.304	0.004	2.098	0.657	3.196	0.005	2.003	0.638	3.138	0.005	1.689	0.662	2.553	0.020
BVMTRRECALLTSCORE									−0.047	0.031	−1.503	0.134	−0.047	0.031	−1.538	0.125	−0.056	0.031	−1.771	0.078
BVMTRLEARNINGTSCORE									−0.057	0.025	−2.287	0.025	−0.055	0.026	−2.091	0.043	−0.057	0.026	−2.207	0.032
BVMTRDELAYEDRECALLTSCORE									0.038	0.031	1.237	0.218	0.038	0.031	1.231	0.220	0.039	0.031	1.239	0.218
BVMTRHITRAWSCORE									0.915	1.582	0.578	0.578	0.887	1.588	0.559	0.591	0.742	1.608	0.461	0.657
BVMTRFALSEALARMRAWSCORE									−1.895	1.431	−1.324	0.206	−1.809	1.454	−1.244	0.234	−1.671	1.461	−1.144	0.273
BVMTRDISCRIMINTATIONRAWSCORE									−0.177	1.460	−0.121	0.906	−0.188	1.447	−0.130	0.900	−0.096	1.460	−0.066	0.949
VA_RT_score													2.252	1.303	1.729	0.100	2.347	1.343	1.747	0.100
VA_RT_inter													−0.269	3.202	−0.084	0.936	−0.517	3.215	−0.161	0.878
VA_LT_score													−1.114	1.349	−0.826	0.421	−1.355	1.325	−1.022	0.322
VA_LT_inter													1.665	3.324	0.501	0.634	1.896	3.277	0.579	0.583
SCAN3GAPDETECTGRADE																	0.659	0.910	0.725	0.470
SCAN3AUDITFIGURECOMBINEDSCORE																	0.091	0.059	1.552	0.134
SCAN3COMPETEWORDCOMBINEDSCORE																	0.147	0.061	2.435	0.021

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TABLE 7 Results from the hierarchical regression for CDP condition 4, sway references base of support.

CDP4	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.041				0.064				0.091				0.100				0.109			
Constant	78.610	2.707	29.043	0.000	76.141	3.788	20.103	0.000	63.228	6.408	9.867	0.000	55.647	6.700	8.305	0.000	47.700	8.322	5.732	0.000
DEMOGAGEYEARS	−0.016	0.050	−0.321	0.750	−0.013	0.052	−0.243	0.810	0.015	0.055	0.278	0.784	0.019	0.058	0.337	0.740	0.043	0.058	0.741	0.467
GENDERTYP	−2.563	1.350	−1.898	0.061	−2.938	1.293	−2.272	0.024	−3.092	1.278	−2.420	0.016	−3.000	1.295	−2.317	0.022	−3.074	1.337	−2.299	0.024
TOTAL_TBI	−0.597	0.216	−2.766	0.006	−0.464	0.237	−1.959	0.055	−0.525	0.235	−2.237	0.029	−0.551	0.236	−2.340	0.023	−0.568	0.233	−2.440	0.018
HHIASEMBARRASSEDNEWPEOPLE					−0.209	0.271	−0.772	0.454	−0.186	0.269	−0.692	0.501	−0.180	0.264	−0.681	0.507	−0.150	0.277	−0.539	0.600
HHIASFEELFRUSTRATED					0.181	0.452	0.400	0.692	0.199	0.449	0.443	0.661	0.206	0.436	0.472	0.640	0.177	0.427	0.414	0.681
HHIASDIFFICULTYUNDERSTANDING					0.008	0.540	0.015	0.988	0.032	0.530	0.060	0.953	−0.048	0.535	−0.089	0.930	−0.007	0.514	−0.014	0.989
HHIASFEELHANDICAPPED					0.185	0.408	0.455	0.650	0.312	0.401	0.776	0.438	0.326	0.403	0.810	0.418	0.357	0.401	0.890	0.374
HHIASDIFFICULTYVISITING					−0.053	0.635	−0.084	0.935	−0.098	0.656	−0.149	0.885	−0.153	0.648	−0.237	0.818	−0.163	0.659	−0.247	0.810
HHIASDIFFICULTYINMOVIES					0.069	0.543	0.128	0.901	0.112	0.553	0.203	0.843	0.134	0.538	0.249	0.808	0.174	0.530	0.328	0.748
HHIASARGUMENTSFAMILY					−0.236	0.316	−0.747	0.457	−0.250	0.314	−0.797	0.427	−0.264	0.318	−0.831	0.408	−0.203	0.322	−0.630	0.530
HHIASDIFFICULTYLISTENINGTV					−0.034	0.608	−0.057	0.956	−0.079	0.603	−0.132	0.898	−0.095	0.591	−0.161	0.876	−0.030	0.564	−0.054	0.958
HHIASHAMPERSPERSONALLIFE					−0.529	0.498	−1.062	0.302	−0.402	0.477	−0.843	0.408	−0.378	0.486	−0.777	0.446	−0.354	0.475	−0.746	0.464
HHIASDIFFICULTYRESTAURANT					−0.036	0.610	−0.060	0.954	−0.141	0.584	−0.242	0.813	−0.103	0.584	−0.176	0.864	−0.065	0.576	−0.112	0.913
HHIASPROBLEMWITHHEARING					2.225	1.212	1.836	0.086	2.007	1.209	1.660	0.118	1.852	1.250	1.482	0.161	1.176	1.191	0.988	0.337
BVMTRRECALLTSCORE									0.122	0.057	2.147	0.033	0.122	0.058	2.114	0.036	0.108	0.058	1.880	0.062
BVMTRLEARNINGTSCORE									4.402E-05	0.043	0.001	0.999	0.009	0.044	0.210	0.834	0.002	0.043	0.043	0.965
BVMTRDELAYEDRECALLTSCORE									0.037	0.053	0.691	0.490	0.033	0.053	0.613	0.540	0.036	0.053	0.684	0.494
BVMTRHITRAWSCORE									−0.144	2.207	−0.065	0.949	−0.215	2.162	−0.099	0.922	−0.211	2.079	−0.101	0.920
BVMTRFALSEALARMRAWSCORE									0.502	2.382	0.211	0.835	0.643	2.387	0.269	0.790	0.854	2.333	0.366	0.718
BVMTRDISCRIMINTATIONRAWSCORE									1.116	1.854	0.602	0.553	1.151	1.847	0.623	0.539	1.180	1.800	0.655	0.517
VA_RT_score													−0.733	1.936	−0.379	0.706	−0.807	1.968	−0.410	0.683
VA_RT_inter													4.011	4.119	0.974	0.359	3.703	4.052	0.914	0.387
VA_LT_score													0.814	2.149	0.379	0.708	0.591	2.151	0.275	0.786
VA_LT_inter													3.782	4.767	0.793	0.450	3.919	4.763	0.823	0.434
SCAN3GAPDETECTGRADE																	−0.773	1.860	−0.416	0.681
SCAN3AUDITFIGURECOMBINEDSCORE																	0.254	0.119	2.131	0.051
SCAN3COMPETEWORDCOMBINEDSCORE																	0.091	0.108	0.836	0.410
																	1.176	1.191	0.988	0.337

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TABLE 8 Results from the hierarchical regression for CD5, sway references base of support and occluded vision.

CDP 5	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.059				0.091					0.109			0.113				0.122			
Constant	68.654	2.989	22.971	0.000	63.823	3.839	16.624	0.000	48.588	5.733	8.475	0.000	44.918	6.887	6.522	0.000	35.020	7.781	4.501	0.000
DEMOGAGEYEARS	−0.126	0.053	−2.399	0.020	−0.108	0.055	−1.973	0.057	−0.071	0.055	−1.290	0.205	−0.060	0.058	−1.032	0.311	−0.026	0.059	−0.445	0.659
GENDERTYP	−1.727	1.316	−1.313	0.189	−2.412	1.330	−1.813	0.070	−2.639	1.317	−2.005	0.045	−2.639	1.311	−2.013	0.044	−2.603	1.318	−1.974	0.049
TOTAL_TBI	−0.938	0.249	−3.766	0.000	−0.702	0.267	−2.628	0.013	−0.753	0.266	−2.828	0.008	−0.770	0.267	−2.885	0.007	−0.785	0.263	−2.979	0.005
HHIASEMBARRASSEDNEWPEOPLE					−0.259	0.215	−1.207	0.230	−0.243	0.222	−1.093	0.279	−0.238	0.219	−1.087	0.280	−0.206	0.220	−0.938	0.351
HHIASFEELFRUSTRATED					0.275	0.534	0.514	0.614	0.303	0.537	0.564	0.581	0.291	0.528	0.552	0.588	0.251	0.507	0.495	0.626
HHIASDIFFICULTYUNDERSTANDING					0.198	0.509	0.389	0.700	0.194	0.505	0.384	0.703	0.163	0.526	0.309	0.760	0.235	0.511	0.459	0.649
HHIASFEELHANDICAPPED					−0.611	0.480	−1.272	0.209	−0.478	0.464	−1.031	0.305	−0.438	0.469	−0.934	0.353	−0.394	0.464	−0.849	0.398
HHIASDIFFICULTYVISITING					0.347	0.534	0.651	0.521	0.328	0.535	0.613	0.545	0.301	0.533	0.565	0.577	0.280	0.538	0.521	0.607
HHIASDIFFICULTYINMOVIES					−0.030	0.483	−0.062	0.951	−0.054	0.482	−0.111	0.912	−0.034	0.482	−0.070	0.945	−0.020	0.473	−0.043	0.966
HHIASARGUMENTSFAMILY					−0.377	0.406	−0.929	0.363	−0.353	0.380	−0.929	0.359	−0.364	0.381	−0.955	0.346	−0.294	0.381	−0.772	0.445
HHIASDIFFICULTYLISTENINGTV					−0.295	0.501	−0.590	0.563	−0.353	0.500	−0.706	0.489	−0.362	0.496	−0.730	0.474	−0.281	0.465	−0.605	0.550
HHIASHAMPERSPERSONALLIFE					−0.519	0.622	−0.835	0.422	−0.406	0.629	−0.646	0.532	−0.396	0.636	−0.623	0.547	−0.358	0.627	−0.572	0.580
HHIASDIFFICULTYRESTAURANT					−0.205	0.473	−0.433	0.667	−0.289	0.505	−0.572	0.573	−0.304	0.521	−0.584	0.566	−0.284	0.519	−0.547	0.591
HHIASPROBLEMWITHHEARING					4.138	1.036	3.995	0.000	3.948	1.051	3.757	0.000	3.867	1.061	3.645	0.001	3.283	1.065	3.081	0.003
BVMTRRECALLTSCORE									0.162	0.058	2.825	0.005	0.166	0.058	2.853	0.004	0.151	0.058	2.593	0.010
BVMTRLEARNINGTSCORE									−0.003	0.042	−0.070	0.944	0.005	0.043	0.112	0.911	0.001	0.043	0.013	0.989
BVMTRDELAYEDRECALLTSCORE									−0.062	0.060	−1.035	0.302	−0.068	0.060	−1.135	0.258	−0.069	0.060	−1.143	0.255
BVMTRHITRAWSCORE									2.305	2.079	1.109	0.274	2.194	2.137	1.027	0.312	2.091	2.193	0.954	0.349
BVMTRFALSEALARMRAWSCORE									−1.836	2.520	−0.729	0.474	−1.800	2.539	−0.709	0.486	−1.608	2.566	−0.626	0.538
BVMTRDISCRIMINTATIONRAWSCORE									−0.494	1.984	−0.249	0.806	−0.438	2.014	−0.218	0.830	−0.373	2.057	−0.181	0.858
VA_RT_score													−0.947	2.224	−0.426	0.673	−0.847	2.201	−0.385	0.702
VA_RT_inter													4.362	4.303	1.014	0.340	4.028	4.272	0.943	0.372
VA_LT_score													1.761	2.258	0.780	0.441	1.454	2.263	0.642	0.525
VA_LT_inter													−1.552	3.753	−0.414	0.683	−1.223	3.668	−0.333	0.742
SCAN3GAPDETECTGRADE																	−0.441	1.696	−0.260	0.795
SCAN3AUDITFIGURECOMBINEDSCORE																	0.158	0.098	1.606	0.112
SCAN3COMPETEWORDCOMBINEDSCORE																	0.233	0.119	1.962	0.060

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TABLE 9 Results from the hierarchical regression for CDP condition 6, sway references base of support and vision.

CDP 6	Model 1				Model 2				Model 3				Model 4				Model 5			
	B	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*	*B*	Std. error	*t*	*p*
R^2	0.046				0.080				0.113				0.120				0.128			
Constant	68.716	3.077	22.331	0.000	64.929	4.274	15.190	0.000	51.166	7.334	6.977	0.000	46.428	7.624	6.090	0.000	35.666	8.934	3.992	0.000
DEMOGAGEYEARS	−0.126	0.054	−2.332	0.021	−0.118	0.055	−2.127	0.035	−0.072	0.056	−1.289	0.200	−0.057	0.060	−0.952	0.345	−0.015	0.059	−0.260	0.795
GENDERTYP	−2.803	1.512	−1.853	0.064	−3.379	1.501	−2.252	0.025	−3.714	1.475	−2.517	0.012	−3.753	1.461	−2.569	0.010	−3.655	1.458	−2.506	0.012
TOTAL_TBI	−0.678	0.275	−2.461	0.016	−0.456	0.275	−1.656	0.101	−0.532	0.278	−1.914	0.060	−0.552	0.278	−1.984	0.051	−0.572	0.276	−2.073	0.042
HHIASEMBARRASSEDNEWPEOPLE					−0.008	0.450	−0.019	0.986	−0.009	0.455	−0.021	0.984	−0.007	0.456	−0.015	0.989	0.030	0.462	0.065	0.950
HHIASFEELFRUSTRATED					−0.014	0.701	−0.020	0.984	0.066	0.679	0.097	0.924	0.058	0.669	0.086	0.933	0.016	0.669	0.025	0.981
HHIASDIFFICULTYUNDERSTANDING					−0.337	0.611	−0.552	0.587	−0.288	0.585	−0.492	0.626	−0.338	0.599	−0.564	0.578	−0.264	0.588	−0.450	0.657
HHIASFEELHANDICAPPED					−0.519	0.625	−0.830	0.417	−0.301	0.581	−0.518	0.608	−0.224	0.582	−0.384	0.704	−0.165	0.587	−0.281	0.781
HHIASDIFFICULTYVISITING					0.222	0.943	0.236	0.820	0.133	0.948	0.140	0.892	0.094	0.956	0.098	0.924	0.065	0.972	0.067	0.949
HHIASDIFFICULTYINMOVIES					0.337	0.540	0.624	0.537	0.370	0.554	0.667	0.511	0.400	0.548	0.729	0.472	0.422	0.538	0.783	0.440
HHIASARGUMENTSFAMILY					−0.238	0.688	−0.346	0.739	−0.213	0.646	−0.330	0.750	−0.234	0.642	−0.364	0.725	−0.146	0.656	−0.223	0.829
HHIASDIFFICULTYLISTENINGTV					−0.379	0.641	−0.591	0.566	−0.423	0.625	−0.677	0.511	−0.443	0.619	−0.717	0.487	−0.352	0.598	−0.588	0.566
HHIASHAMPERSPERSONALLIFE					−0.699	0.614	−1.140	0.270	−0.538	0.575	−0.935	0.360	−0.529	0.569	−0.929	0.363	−0.478	0.561	−0.852	0.403
HHIASDIFFICULTYRESTAURANT					0.326	0.514	0.635	0.529	0.146	0.549	0.266	0.792	0.112	0.569	0.196	0.846	0.142	0.570	0.249	0.806
HHIASPROBLEMWITHHEARING					3.797	1.030	3.685	0.000	3.809	1.030	3.698	0.000	3.689	1.042	3.540	0.000	2.957	1.056	2.801	0.005
BVMTRRECALLTSCORE									0.224	0.074	3.009	0.004	0.228	0.075	3.034	0.004	0.209	0.076	2.738	0.009
BVMTRLEARNINGTSCORE									−0.128	0.050	−2.574	0.011	−0.117	0.050	−2.368	0.018	−0.123	0.049	−2.498	0.013
BVMTRDELAYEDRECALLTSCORE									−0.022	0.070	−0.313	0.755	−0.029	0.070	−0.416	0.679	−0.031	0.069	−0.452	0.653
BVMTRHITRAWSCORE									0.038	2.396	0.016	0.988	−0.120	2.415	−0.050	0.961	−0.148	2.464	−0.060	0.953
BVMTRFALSEALARMRAWSCORE									1.135	2.703	0.420	0.678	1.141	2.681	0.425	0.674	1.354	2.676	0.506	0.617
BVMTRDISCRIMINTATIONRAWSCORE									1.776	2.187	0.812	0.424	1.830	2.202	0.831	0.414	1.849	2.225	0.831	0.414
VA_RT_score													−0.887	2.959	−0.300	0.768	−0.813	2.970	−0.274	0.788
VA_RT_inter													7.226	2.963	2.438	0.017	6.862	2.877	2.385	0.018
VA_LT_score													1.905	2.593	0.735	0.469	1.606	2.653	0.605	0.551
VA_LT_inter													−3.335	4.860	−0.686	0.506	−2.975	4.811	−0.618	0.548
SCAN3GAPDETECTGRADE																	−1.495	2.141	−0.698	0.489
SCAN3AUDITFIGURECOMBINEDSCORE																	0.197	0.121	1.635	0.111
SCAN3COMPETEWORDCOMBINEDSCORE																	0.262	0.136	1.919	0.067

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Counterintuitively, age shows to be associated with faster walking speed, however as expected, older participants had lower scores on balance assessments (CDP 2, 5 & 6 and the Composite score).

Surprisingly, variance accounted for by the combination of all demographic and sensory acuity/processing items only attributed 10.9 and 14.0% of the total variability in the balance and gait outcomes. While this may seem limited, many factors affect gait and balance not accounted for in these models. In general, more associations were found between the visual and auditory processing measures compared to specific hearing and vision impairments, more in-depth discussion follows below.

Deficits in hearing as assessed by the self-reported hearing difficulties on the hearing handicap questionnaire (HHIA-S) showed associations with measures of balance (CDP, except CDP1) and gait. Participants who indicated to have problems with hearing showed to have slower walking speeds and lower balance scores (CDP composite and CDP2-6). Additionally, 'difficulty understanding movies' showed an association with slower walking speeds. These findings are consistent with previous studies by Viljanen et al. (21) showing that women with poorer hearing have poorer postural control and higher fall risk. Authors have postulated this to be related to the anatomical location of the vestibular system to the auditory system, along with their shared vestibulocochlear nerve, vascular supply, similar mechanosensory receptor hair cells, which detect sound, head movements, and orientation in space, and therefore with balance (21).

Auditory processing (SCAN3) was shown to be associated with gait speed and balance (composite score and CDP 1–3). The ability to better distinguish words from noise (SCAN audio figure score) was associated with faster gait speeds and better CDP composite score, so in general better gait and balance. Additionally, the ability to better repeat word pairs (compete word score) presented to be associated with faster gait speeds and better balance scores while proprioception was not perturbed (i.e., standing surface was stable in CDP1-3). So, when proprioception does not have to be re-weighted, but vision may or may not be perturbed, participants with a better ability to recall word pairs are shown to be better at maintaining balance with all sensory intact (CDP 1), or occluded or perturbed vision (CDP 2 and 3). In previous literature auditory processes have been shown to slow down gait; elderly stop walking when talking (30), and affect foot placement; stroke survivors lag auditory cues for foot falls (31). These findings suggest that the ability to inhibit noise, remember word pairs, and process auditory stimuli benefits gait speed and balance.

Visual acuity (VA) only showed an association with balance when vision and proprioception were sway-referenced, participants with impaired vision on the right had worse balance scores on the CDP6. No associations were found for visual acuity and walking speed, nor the other balance measures. In previous literature relationships of visual acuity among other visual measures and self-reported ability to walk a quarter of a mile or walking up 10 steps (20) were shown in the aging population (70–79). The lack of associations with vision, gait, and balance in this study could be caused by multiple factors. One of these factors may be that other visual functions are more important for balance and gait, like peripheral vision or spatial relations. Secondly, the demographics (age range 22–71) of this cohort did only show impaired vision (20/40 met) of 4.2% in the right eye and 2.7% in the left, where Swenor et al. found 7.4% to have vision impairment when looking with both eyes. Additionally, literature has reported various outcomes on the associations between vision, balance, and gait measures. Many studies have indicated the ability to detect movements (32, 33) or having visual blur (34, 35) affects balance. Visual acuity may not be directly related to gait speed or balance, it has been identified as a risk factor for falls (36–40), however, when adjusting for age these associations were not found (41–48).

Visual processing (BVMT) showed a more complex association with gait speed and balance. The ability to immediately recall a figure was associated with faster gait speed, while a delayed recall was associated with slower gait speed. Doi et al. showed that better visual memory was associated with faster gait speed, especially in participants with mild cognitive impairment (49). This is in agreement with literature showing people slow down (15, 50) and attentional costs increase (51–53) when walking to visual targets, and sway area (an often used balance measure) increases when eyes are closed (54). However, better delayed recall (after a 25-min delay) is associated with slower gait speeds. This association of slower gait speed with delayed memory as increased cortical attention/demand is required to recall, therefore visual processing requires greater attentional resources (55). Better general balance scores (CDP composite) and balance when vision was compromised or occluded and proprioception was compromised (CDP 5 and 6) are associated with better direct visual recall and better balance when vision was occluded (CDP 2) showed associations with delayed recall. Indicating that participants who rely on visuo-spatial memory when visual information is crude may prevent them from indicating what sensory information is reliable and upregulate those systems, affecting their ability to maintain balance. This confirms that visual processing is more important when proprioception is compromised.

4.1. Limitations

A large proportion of the non-TBI participants (53.85%) had relatively low SOT-composite scores (less than 75). In a manufacturer's stated normative data set only 20% of 'normal' individuals had composite scores below 75. The higher proportion in our sample may be due to comorbidities, including chronic pain, PTSD, and sleep apnea in Veterans and Service Members (56), which previous preliminary analyses have linked to lower SOT-composite scores in Veterans and Service Members (9). Given that our sample had all served in the military and was predominantly male, results may not generalize to civilian or female populations and therefore, a similar analysis may be performed with a general public control group in the future. Therefore, relationships between sensory and processing deficits and gait and balance may be underestimated. In the future, similar analysis may be done on a population with greater balance and gait deficits and or when this cohort ages more.

Additionally, a large proportion of the data had to be imputed due to missing values. However, imputing missing values is known to reduce bias and improve efficiency over complete case analysis over excluding missing data (57, 58).

5. Conclusion

In general, individuals with TBI maintained postural stability and ambulation as well as their healthy counterparts, likely showing an

ability to adapt to their sensory impairments (shown in acuity and processing outcomes). However, balance deficits may be unmasked when re-weighting inputs is required due to sensory disruption (e.g., during light adaptation to a dimly lit room), and may have greater consequences with more frequent exposure to TBIs. Our findings reinforce that sensory processing (rather than acuity) is more associated with negative balance and gait outcomes and potential increases in fall risk.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the CENC/LIMBIC data board has to approve data availability. Requests to access these datasets should be directed to Sudeep Karki Sudeep Karki@vcuhealth.org.

Ethics statement

The studies involving humans were approved by Richmond VAMC Research and Development Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SV: conceptualize, analyze, and write a first draft. RP: conceptualize analysis, statistical advice, and proofread. LF: EEG data analysis and proofread. AA, KS, SS, EW, AS, JT, and WW: conceptualize analysis, methods, and proofreading. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Headache among combat-exposed veterans and service members and its relation to mild traumatic brain injury history and other factors: a LIMBIC-CENC study

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Background: Headache (HA) is a common persistent complaint following mild traumatic brain injury (mTBI), but the association with remote mTBI is not well established, and risk factors are understudied.

Objective: Determine the relationship of mTBI history and other factors with HA prevalence and impact among combat-exposed current and former service members (SMs).

Design: Secondary cross-sectional data analysis from the Long-Term Impact of Military-Relevant Brain Injury Consortium—Chronic Effects of Neurotrauma Consortium prospective longitudinal study.

Methods: We examined the association of lifetime mTBI history, demographic, military, medical and psychosocial factors with (1) HA prevalence ("lately, have you experienced headaches?") using logistic regression and (2) HA burden via the Headache Impact Test-6 (HIT-6) using linear regression. Each lifetime mTBI was categorized by mechanism (blast-related or not) and setting (combat deployed or not). Participants with non-credible symptom reporting were excluded, leaving $N = 1{,}685$ of whom 81% had positive mTBI histories.

Results: At a median 10 years since last mTBI, mTBI positive participants had higher HA prevalence (69% overall, 78% if 3 or more mTBIs) and greater HA burden (67% substantial/severe impact) than non-TBI controls (46% prevalence, 54% substantial/severe impact). In covariate-adjusted analysis, HA prevalence was higher with greater number of blast-related mTBIs (OR 1.81; 95% CI 1.48, 2.23), non-blast mTBIs while deployed (OR 1.42; 95% CI 1.14, 1.79), or non-blast

mTBIs when not deployed (OR 1.23; 95% CI 1.02, 1.49). HA impact was only higher with blast-related mTBIs. Female identity, younger age, PTSD symptoms, and subjective sleep quality showed effects in both prevalence and impact models, with the largest mean HIT-6 elevation for PTSD symptoms. Additionally, combat deployment duration and depression symptoms were factors for HA prevalence, and Black race and Hispanic/Latino ethnicity were factors for HA impact. In sensitivity analyses, time since last mTBI and early HA onset were both non-significant.

Conclusion: The prevalence of HA symptoms among formerly combat-deployed veterans and SMs is higher with more lifetime mTBIs regardless of how remote. Blast-related mTBI raises the risk the most and is uniquely associated with elevated HA burden. Other demographic and potentially modifiable risk factors were identified that may inform clinical care.

KEYWORDS

traumatic brain injury, concussion, headache, postconcussive headache, veterans, blast injuries, military medicine, prediction

Introduction

Headache (HA) is an important worldwide health problem, with HA disorders (>5 stereotypical HA episodes per year) ranked as the second leading cause of years lived with disability (1). HA is also a common sequela of traumatic brain injury (TBI) in both civilian (2) and military (3) populations. Although HA can occur after any severity of TBI, the focus of this study is HA among persons with mild TBI (mTBI), which accounts for well over 80% of TBI events.

Prior longitudinal studies show HA is a common persistent complaint following mTBI in both military (4, 5) and civilian (6) populations. HA disorders in patients with mTBI may or may not meet the criteria to be termed "posttraumatic" HA. Specifically, the International Classification of Headache Disorders-3 (ICHD-3) classifies HA after TBI as a secondary HA disorder when the initial HA onset or exacerbation of pre-existing headache begins within 7 days following trauma or injury, or within 7 days after recovering consciousness and/or within 7 days after recovering the ability to sense and report pain (7). Posttraumatic HA is considered to be persistent if it lasts beyond 3 months after injury, which is the commonly accepted timeframe for transition from acute to persistent or chronic HA from any condition, including as a primary disorder. The classification of posttraumatic HA is progressively more challenging to determine as the TBI event becomes more remote (e.g., years later). Acute or persisting posttraumatic HA may resolve over time, but another HA may later emerge for which the TBI may not be a contributing factor. Accordingly, almost all existing research on HA in the very chronic phase of TBI does not attempt to make the distinction between trauma-related HA and HA from other viable sources (8).

Risk factors for having HA in either the acute or chronic phase after TBI are not well understood (8, 9). Intuitively, greater severity of TBI would presume greater risk for HA; however, research has not clearly demonstrated this relation. Some studies paradoxically show greater prevalence of HA after mTBI compared to moderate or severe (mod-sev) TBI (9); however, these studies may be biased with over-representation of patients with mTBI seeking medical care for high symptom levels, including HA, versus the majority who rapidly recover and are not included in these studies. Large studies that have examined the prevalence of HA remotely after mod-sev TBI have not demonstrated an association with TBI severity indices such as posttraumatic amnesia (PTA) duration and HA (2, 3). Given this, there remains significant debate about the extent of any late effect, including HA, that is potentially attributable to a remote TBI alone versus other factors and comorbidities, especially those related to mental health.

Beyond TBI severity, risk factors for HA after TBI have been primarily examined with respect to acute predictors (8). For the chronic phase of TBI, the most frequently cited risk factors include female sex and history of HA disorder prior to TBI, especially migraine type (10), in both patients with mTBI (11) and mod-sev TBI (2, 12). Findings on differences related to age are mixed, with some studies showing younger age as a risk factor (13, 14). Other factors associated with poorer HA outcomes include lower education, learning disabilities, sleep difficulties, lifestyle factors (e.g., alcohol use), self-efficacy, and resilience. In the military population, combat deployment itself was identified as a risk factor for HA disorders, although TBI history was not assessed (15). Another aspect is the relationship between HA symptoms and other active health conditions, particularly mental health. Posttraumatic stress disorder (PTSD) and depression symptoms among military service members (SMs) have been associated with post-deployment HA (15, 16). Studies in the civilian population have also demonstrated an association between PTH and PTSD, anxiety, and depression (9, 10). Despite these and other investigations, a recent systematic review concluded that there are no identified evidence-based risk factors for HA (8) in the chronic phase after TBI and that further studies are warranted.

Thus, there is an evidence gap related to the scope of the HA problem among persons with previous mTBI (s) in both military and civilian populations. Better information is needed regarding HA prevalence and risk factors to inform clinical care, including targeted screening and monitoring strategies and the identification and treatment of modifiable co-morbidities that are associated with

increased HA prevalence. The objectives of this study were to (1) describe the prevalence and impact of HA among combat-exposed current and former SMs with varied mTBI histories (2), assess the unique contribution of mTBI history on their remote (mean >10 years after mTBI) HA prevalence and impact of current headache on daily life activities, and (3) examine the effects of other factors on remote HA prevalence and impact.

Methods

Design

Using a cross-sectional design, this study analyzed LIMBIC-CENC Prospective Longitudinal Study (PLS) enrollment data. Detailed information on methods, including aims, recruitment procedures, eligibility of the LIMBIC-CENC PLS project is available elsewhere (17, 18). In brief, the LIMBIC-CENC PLS is a large multi-center longitudinal, observational study of current and former United States SMs with combat exposure, with both an established cohort (baseline) and ongoing enrollment (prospective, longitudinal) at 11 sites located across the country. The primary objective is to better understand the long-term neurologic effects of combat exposures in general and mTBI in particular, and their interrelationships with other aspects of health. During the baseline evaluation, all participants completed a comprehensive assessment including face-to-face structured interviews, self-reported questionnaires, extensive neuropsychological testing, biometrics, and many other tests not used for the current analyses. For the self-reported questionnaires, most participants completed them in-person in a quiet office space on either paper copies or a web-based application. Research staff only intervened if paper form completion was incomplete, to request the mark any missing response (s). If the participant questioned research staff on interpretation of any item then they were instructed to use their best judgement based on the scripted instructions from the validated instrument. To shorten the time of their in-person visit, some participants chose to complete their self-reported questionnaires at home on the internet or by mailing or bring in paper versions. The LIMBIC-CENC PLS, including creation of a database registry and all secondary analyses, was approved by the local Institutional Review Boards at each enrollment site.

Participants

LIMBIC-CENC PLS participants have variable lifetime mTBI histories, ranging from entirely negative to over 10 prior mTBIs. To be eligible, individuals were required to be 18 years of age or older and have a history of combat exposure. The only exclusions were a history of mod-sev TBI or a major neurological or psychiatric disorder that significantly impaired functioning. Individuals with other common mental health conditions, such as depression or PTSD, were included. All participants provided written consent prior to any study procedures.

For this secondary analysis, all LIMBIC-CENC PLS participants whose enrollment (baseline) assessment data were available at time of dataset extraction were included ($n = 1{,}846$). Because the current study focus was HA in the chronic phase of mTBI, we excluded individuals who had sustained an mTBI within 6 months prior to enrollment ($n = 21$) or missing data ($n = 11$) on the HA outcome measure. We also excluded participants with evidence of noncredible symptom reporting based on failing ($n = 129$) the Mild Brain Injury Atypical Symptom (mBIAS) scale, a validated self-reported measure of symptom reporting credibility in the mTBI population using the developer's recommended cut-point of 8 or higher (19). This left a final analytic sample of 1,685 participants (see Figure 1).

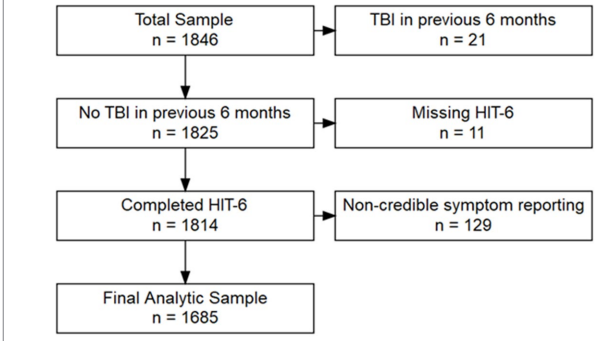

FIGURE 1
Study sample inclusion flow diagram.

Measures

Lifetime mild TBI history

Clinical diagnosis of mTBI was assessed via a multi-step process centered on a structured face-to-face interview. The first step was to identify and catalog every potential concussive events (PCEs) across each participant's lifetime using a modified version of a validated TBI screening interview, the Ohio State University TBI Identification (OSU TBI-ID) (20) to. PCEs were then assessed more thoroughly with a validated structured interview tool, the Virginia Commonwealth University retrospective Concussion Diagnostic Interview (VCU rCDI) (21) which has an algorithm that generates a preliminary TBI diagnosis. The algorithm-generated diagnosis was then reviewed by the site principal investigator, checked against available medical records, and further reviewed by a centralized quality assurance process that included an expert committee to determine a final clinical diagnosis according to VA/DoD definition of mTBI (22). This diagnosis also adheres to the American Congress of Rehabilitation Medicine criteria for definition of mTBI (23). Based on the VCU rCDI interview information, each positive mTBI was categorized by environmental context: sustained during a combat deployment (combat mTBI) versus other time of life (non-combat mTBI), mechanism (blast-related versus blunt-only), and presence of early onset HA after TBI (within 2 weeks). We also examined time since last mTBI for the current analyses.

Headache point prevalence and impact (primary outcomes)

The Headache Impact Test (HIT-6) is a validated 6-item self-reported questionnaire of HA burden on daily functioning during the past 4 weeks (24). Total scores for impact range from 36 to 72, and levels can be interpreted as little or no impact (49 or less), some impact (50–55), substantial impact (56–59), and severe

impact (60–78). The HIT-6 does include one item (item #1) that directly queries pain intensity ("when you have headache, how often is your pain severe?") We also included a stem question "lately, have you experienced headaches?" that was used as a point prevalence estimate. If participants asked how "lately" was defined, they were instructed to use their own judgement.

Basic demographics

Age and self-identity of gender, race, and ethnicity were collected at baseline by Behavioral Risk Factor Surveillance System (BRFSS) a self-reported questionnaire developed the Centers for Disease Control and Prevention (25).

Military exposures

Total months combat-deployed was calculated by summing the duration of every military combat deployment ascertained by military records. Combat intensity was measured by Section D of the Deployment Risk and Resiliency Inventory, Version 2 (DRRI-2), a self-reported questionnaire of military combat exposures (26). During the LIMBIC-CENC PCE/TBI structured interview, participants were also queried on the number of controlled blast exposures they were exposed to during lifetime.

Psychosocial factors

The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5) is a 20-item self-report questionnaire measure of post-traumatic stress disorder (PTSD) symptoms including re-experiencing, avoidance and numbing, hyperarousal, and negative cognitions and mood (27) over the past month. Higher scores reflect greater symptom severity. The Patient Health Questionnaire (PHQ-9) assessed self-reported depression symptoms over the past 2 weeks (28). Scores range from 0 (none) to 27 (severe). Alcohol use (no alcohol use, non-hazardous use, versus hazardous use) was determined from the Alcohol Use Disorder Identification Test (AUDIT-C), a self-reported questionnaire (29). Post-deployment social support was assessed with the Deployment Risk and Resiliency Inventory, Version 2 (DRRI-2) Section O (DRRI-2-O), a 10-item self-reported questionnaire on the extent to which family, friends, coworkers, employers, and community provide emotional sustenance and instrumental assistance (26). Finally, self-efficacy was ascertained by the general self-efficacy (GSE) scale, a self-reported questionnaire with a higher total score indicating greater self-efficacy (30).

Medical comorbidities

Using the forementioned BRFSS self-reported questionnaire, we collected self-reported hypertension, hyperlipidemia, diabetes, stroke, and other neurological disorders. Subjective sleep quality over the past month was evaluated with the Pittsburgh Sleep Quality Index (PSQI), (31), another self-reported questionnaire. Sleep apnea symptoms were assessed via a modified version of the STOP-BANG self-reported questionnaire, with high risk classified by scores greater than or equal to three (32). Obesity categories were created by directly measuring height and weight to then calculate body mass index (BMI).

Statistical methods

The relationship between the HA prevalence outcome (lately, have you experienced headache?) stratified by groups based on number of historical lifetime mTBIs (none, 1–2 mTBI, and 3+ mTBIs) was first assessed using Pearson's chi-squared test. For those subjects who disclosed experiencing HA lately, HIT-6 total score, HIT-6 impact categories, and HIT-6 item #1 were summarized using mean (standard deviation, SD) or counts and percentages. These variables were compared across mTBI history groups using the Kruskal–Wallis rank sum test for HIT-6 total score because of the ordered nature of the history groups and Pearson's chi-squared test for HIT-6 total score impact categories and HIT-6 item #1 responses.

Pairwise chi-squared tests were used to examine all possible paired comparisons between mTBI groups and HIT-6 stem question as well as HIT-6 impact categories. Dunn's test was used for pairwise comparisons between mTBI groups and HIT-6 total score. All *post hoc* analyses used Bonferroni's correction to account for inflated type I error from multiple testing. Clinical and demographic characteristics were then reported using mean (SD) and median (interquartile range, IQR) for continuous variables and counts and percentages for categorical variables. These variables were stratified by whether they endorsed experiencing HA lately and compared across groups using the Wilcoxon rank sum test for continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables.

We analyzed the prevalence outcome (experiencing HA lately) using univariable and multivariable logistic regression because it is a binary (yes/no) variable. Among the subjects who endorsed experiencing HA lately, linear regression was used with for the HA impact outcome (HIT-6 total score) because it is a continuous variable. For all models, assumptions such as linearity, normality, etc. were assessed to verify that the model was appropriate to use. Variables that were selected to be included in the models were either primary or secondary variables of interest—blast and mTBI related variables—or covariates selected using a combination of clinical judgment and those that were significantly different between headache groups in bivariate analysis at the 0.05 level. For consistency, we used the same variables for the separate logistic and linear regressions. For cumulative number of lifetime mTBIs, we used three variables: number of blast-related mTBIs, number of blunt combat mTBIs, and number of blunt non-combat mTBIs. This was done to include mTBI context and mechanism together without overlap and because only 1% of blast-related mTBIs occurred outside of deployment during a military training accident. Continuous variables included were scaled in order to compare the 75th percentile to the 25th percentile in both models. Beta coefficients and odds ratios (OR) were reported with 95% confidence intervals (CI) and corresponding *p*-values.

Additionally, variables relevant only to TBI positive participants (early HA after TBI; time since last TBI) were examined in separate sensitivity analysis excluding the TBI negative group.

All analyses were performed using R version 4.2.1. Statistical significance was assessed at the 0.05 level and all tests were two-tailed.

Results

In our final sample of 1,685 combat-exposed current and former SMs, 19% had an entirely negative lifetime mTBI history, 47% had sustained 1–2 mTBIs, and 34% had 3 or more. Rates of positive history across the mTBI mechanism/setting categories were 64% for combat mTBI (s), 65% for non-combat mTBI (s), and 38% for Blast-related mTBI (s).

TABLE 1 Headache (HA) prevalence (experienced HA lately) stratified by # lifetime mTBIs.

	No TBI	1–2 mTBIs	3+ mTBIs	Total	*p*-value[a]
HA lately					**<0.001**
No	173 (54%)	292 (37%)	126 (22%)	591 (35%)	
Yes	148 (46%)	504 (63%)	442 (78%)	1,094 (65%)	
Total	321 (100%)	796 (100%)	568 (100%)	1,685 (100%)	

[a]Pearson's chi-squared test; *p*-values bolded if <0.05.

TABLE 2 Headache (HA) impact stratified by # lifetime mTBIs.

Characteristic	All, *N* = 1,094	No TBI, *N* = 148	1–2 mTBIs, *N* = 504	3+ mTBIs, *N* = 442	*p*-value[a]
HIT-6 total score, mean (SD)	58.7 (8.8)	56.3 (9.4)	59.1 (8.9)	58.9 (8.4)	**0.005**
HIT-6 impact categories, *n* (%)					**0.010**
Little/none	167 (15%)	37 (25%)	73 (14%)	57 (13%)	
Some	212 (19%)	30 (20%)	100 (20%)	82 (19%)	
Substantial	163 (15%)	19 (13%)	68 (13%)	76 (17%)	
Severe	551 (50%)	61 (41%)	263 (52%)	227 (51%)	
Headache severe pain, *n* (%)					**0.009**
Never	22 (2.0%)	9 (6.1%)	7 (1.4%)	6 (1.4%)	
Rarely	226 (21%)	35 (24%)	103 (20%)	88 (20%)	
Sometimes	450 (41%)	55 (37%)	198 (39%)	197 (45%)	
Very often	321 (29%)	37 (25%)	163 (32%)	121 (27%)	
Always	74 (6.8%)	11 (7.5%)	33 (6.5%)	30 (6.8%)	

[a]Kruskal–Wallis rank sum test for HIT-6 total score; Pearson's chi-squared test for HIT-6 and severe pain frequency categories; *p*-value bolded if <0.05.

TABLE 3 Post-hoc comparisons of HIT-6 headache severity categories by # lifetime mTBIs.

Dimension	Value	Never	Rarely	Sometimes	Very often	Always
No TBI	Residuals	3.813652	1.0080197	−0.9946525	−1.201409	0.3696650
No TBI	*p*-values	**0.002054**	1.00	1.00	1.00	1.00
1–2 mTBIs	Residuals	−1.358659	−0.1816307	−1.1715848	1.995985	−0.2711308
1–2 mTBIs	*p*-values	1.00	1.00	1.00	0.689033	1.00
3+ mTBIs	Residuals	−1.271198	−0.5162789	1.8814657	−1.192143	0.0184043
3+ mTBIs	*p*-values	1.00	1.00	0.8986290	1.00	1.00

p-value bolded if <0.05.

HA prevalence and impact across mTBI history groups (0, 1–2, 3+)

Within our entire sample, the point prevalence of endorsing yes to "lately, have you experienced headache?" was 65% at time of enrollment. In general HA was significantly more prevalent and more impactful with higher number of lifetime mTBIs. Specifically, HA prevalence was 46% for those with no prior TBI, 63% for 1–2 lifetime mTBIs, and 78% for 3+ lifetime mTBIs (see Table 1).

Among the participants endorsing HA lately, the HIT-6 total scores, the impact level categories, and HIT-6 item #1 responses also all differed by the number of lifetime mTBI groups (see Table 2). For all three measures, the 3-group difference was driven by lower symptoms for the negative TBI group compared to the two positive mTBI groups, with no difference between the 1–2 mTBI and 3+ mTBIs groups in post-hoc pairwise comparisons. For example, the rate of severe HA pain sometimes, often or always was 70% for the no TBI group compared to 79% for those with 1–2 or 3+ lifetime mTBIs (see Table 3 for HIT-6 item #1 post-hoc testing; the other post-hoc testing data are available in Supplementary Tables S1, S2).

Sample characteristics and bivariate relationships to prevalence of HA lately

Characteristics of the cohort to be examined as covariates are displayed in Table 4 for categorical variables and Table 5 for continuous variables, with the overall sample in the left-hand column and stratified by HA "lately" negative and positive groups in the right-hand columns. Unadjusted bivariate relationships with HA lately prevalence were assessed between each characteristic with differences at $p < 0.05$

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TABLE 4 Categorical covariates stratified by absence/presence of headache (HA).

Characteristic	Overall		Experienced HA lately		*p*-value[b]
	N = 1,685[a]	*N* missing	No, *N* = 591[a]	Yes, *N* = 1,094[a]	
Gender		1			**<0.001**
Male	1,467 (87%)		548 (93%)	919 (84%)	
Female	217 (13%)		43 (7.3%)	174 (16%)	
Race		11			0.5
White	1,230 (73%)		442 (75%)	788 (72%)	
Black or African American	311 (19%)		99 (17%)	212 (19%)	
American Indian or Alaska Native	16 (1.0%)		4 (0.7%)	12 (1.1%)	
Asian	26 (1.6%)		7 (1.2%)	19 (1.7%)	
Other	91 (5.4%)		34 (5.8%)	57 (5.2%)	
Ethnicity		20			**0.006**
Not Hispanic or Latino	1,383 (83%)		507 (87%)	876 (81%)	
Hispanic or Latino	282 (17%)		79 (13%)	203 (19%)	
Blast TBI	615 (36%)	0	118 (20%)	497 (45%)	**<0.001**
Non-blast TBI	1,203 (71%)	0	386 (65%)	817 (75%)	**<0.001**
Deploy TBI	900 (53%)	0	202 (34%)	698 (64%)	**<0.001**
Non-deploy TBI	1,098 (65%)	0	358 (61%)	740 (68%)	**0.004**
Early HA after TBI[c]	388 (28%)	0	89 (21%)	299 (32%)	**<0.001**
Controlled blast exposures		0			**0.025**
None	470 (28%)		179 (30%)	291 (27%)	
Minimal (1–9)	424 (25%)		159 (27%)	265 (24%)	
Light (10–29)			273 (16%)	100 (17%)	
Moderate (30–98)	230 (14%)		73 (12%)	157 (14%)	
Heavy (99+)	288 (17%)		80 (14%)	208 (19%)	
Alcohol use (AUDIT-C)		6			**0.018**
None	304 (18%)		91 (15%)	213 (20%)	
Moderate	789 (47%)		268 (46%)	521 (48%)	
Risky	586 (35%)		229 (39%)	357 (33%)	
PCL-5/PTSD		8			**<0.001**
No PTSD (≤35)	1,176 (70%)		500 (85%)	676 (62%)	
Possible PTSD (36–49)	291 (17%)		60 (10%)	231 (21%)	
Highly probable PTSD (≥50)	210 (13%)		28 (4.8%)	182 (17%)	
PHQ-9/depression		18			**<0.001**
No depression (0–4)	602 (36%)		335 (57%)	267 (25%)	
Mild depression (5–9)	486 (29%)		146 (25%)	340 (31%)	
Moderate depression (10–15)	386 (23%)		85 (14%)	301 (28%)	
Moderate/severe depression (≥16)	193 (12%)		21 (3.6%)	172 (16%)	
BMI category		12			0.074
<20	18 (1.1%)		5 (0.9%)	13 (1.2%)	
>29	882 (53%)		289 (49%)	593 (55%)	
20–29	773 (46%)		293 (50%)	480 (44%)	
HTN	588 (35%)	0	188 (32%)	400 (37%)	0.069
Stroke	8 (0.5%)	0	2 (0.3%)	6 (0.5%)	0.8
Neuro disorder	72 (4.3%)	0	24 (4.1%)	48 (4.4%)	>0.9
Diabetes	91 (5.4%)	0	32 (5.4%)	59 (5.4%)	>0.9
OSA high risk (STOP-BANG)	315 (19%)	23	82 (14%)	233 (22%)	**<0.001**

[a]*n* (%).

[b]Pearson's chi-squared test; Fisher's exact test; *p*-value bolded if <0.05.

[c]*N* = 1,364 with positive mTBI histories.

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TABLE 5 Continuous covariates stratified by absence/presence of Headache (HA).

Characteristic	Overall		Experienced HA lately		*p*-value[a]
	N = 1,685	*N* missing	No, *N* = 591	Yes, *N* = 1,094	
Age (years)		0			**0.042**
Mean (SD)	41 (10)		42 (11)	40 (9)	
Median (IQR)	39 (33, 48)	0	40 (32, 51)	39 (33, 47)	
Num of lifetime mTBIs					**<0.001**
Mean (SD)	2.16 (1.97)		1.59 (1.69)	2.47 (2.05)	
Median (IQR)	2.00 (1.00, 3.00)		1.00 (0.00, 2.00)	2.00 (1.00, 3.00)	
Time since last TBI (years)[b]		0			**<0.001**
Mean (SD)	12 (9)		14 (11)	11 (8)	
Median (IQR)	10 (6, 14)		11 (7, 18)	9 (5, 13)	
Num of non-blast TBIs overall		0			**<0.001**
Mean (SD)	1.62 (1.66)		1.33 (1.48)	1.78 (1.73)	
Median (IQR)	1.00 (0.00, 2.00)		1.00 (0.00, 2.00)	1.00 (0.00, 3.00)	
Num non-blast TBIs when deployed		0			**<0.001**
Mean (SD)	0.36 (0.64)		0.23 (0.50)	0.43 (0.69)	
Median (IQR)	0.00 (0.00, 1.00)		0.00 (0.00, 0.00)	0.00 (0.00, 1.00)	
Num non-blast TBIs not deployed		0			**<0.001**
Mean (SD)	1.27 (1.42)		1.11 (1.31)	1.36 (1.46)	
Median (IQR)	1.00 (0.00, 2.00)		1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	
Num of months combat deployed		34			**<0.001**
Mean (SD)	20 (13)		18 (12)	21 (13)	
Median (IQR)	15 (11, 26)		14 (10, 24)	17 (12, 28)	
Combat intensity (DRRI-2)		3			**<0.001**
Mean (SD)	37 (15)		33 (13)	39 (15)	
Median (IQR)	34 (24, 48)		30 (22, 40)	37 (26, 50)	
Num of controlled blasts		0			**0.002**
Mean (SD)	28 (37)		23 (34)	30 (38)	
Median (IQR)	7 (0, 45)		5 (0, 30)	8 (0, 50)	
Depression (PHQ9)		18			**<0.001**
Mean (SD)	7.7 (5.9)		5.0 (4.9)	9.2 (5.9)	
Median (IQR)	7.0 (3.0, 11.0)		4.0 (1.0, 8.0)	8.5 (5.0, 13.0)	
PTSD (PCL5)		8			**<0.001**
Mean (SD)	25 (19)		17 (16)	30 (18)	
Median (IQR)	23 (9, 39)		12 (3, 25)	28 (15, 44)	
Sleep quality (PSQI)		28			**<0.001**
Mean (SD)	10.2 (4.8)		7.9 (4.5)	11.4 (4.4)	
Median (IQR)	10.0 (7.0, 14.0)		8.0 (4.0, 11.0)	12.0 (8.0, 15.0)	
Social support (DRRI-2)		2			**<0.001**
Mean (SD)	39 (8)		40 (8)	38 (8)	
Median (IQR)	40 (34, 45)		42 (36, 47)	39 (33, 44)	
Self-efficacy (GSE)		3			**<0.001**
Mean (SD)	32.1 (4.8)		33.3 (4.5)	31.4 (4.9)	
Median (IQR)	32.0 (29.0, 36.0)		34.0 (30.0, 37.0)	31.0 (28.0, 35.0)	

[a]Wilcoxon rank sum test; *p*-value bolded if <0.05.

[b]Time since last mTBI only applies to participants with positive mTBI histories (*N* = 1,364).

bolded. The type and number of every type of lifetime mTBI was different between groups, as was time since last TBI, early HA after TBI, gender, ethnicity, age, number of controlled blast exposures, combat intensity, combat deployment time, alcohol use, obstructive sleep apnea risk level, symptomatology of depression, PTSD, and sleep quality, as well as social support and self-efficacy.

Main multivariable regression analyses

Results of the main logistic regression for Experiencing HA Lately (at the time of enrollment) are displayed in Table 6 showing odds ratios (OR), confidence interval (CI) and *p*-values. For TBI history, the number of lifetime mTBIs of every type was significant, including blast-related (OR = 1.81), blunt during combat-deployment (OR = 1.42), and blunt outside of deployment (OR = 1.23). Other significant factors included identifying as female (OR = 3.57), age (0.76), total months combat-deployed (OR = 1.22), and symptoms of depression on PHQ-9 (OR = 1.56), PTSD on PCL-5 (OR = 1.54), and disturbed sleep quality on PSQI (OR = 1.77).

Results of the linear regression for HA impact measured by HIT-6 total score among participants experiencing HA lately are displayed in Table 7. For TBI history, only blast-related mTBIs were significant (Beta 0.6). Blunt-only mTBIs did not reach significance, regardless of contextual type (combat or non-combat). Other factors found significant in the HIT-6 linear regression that were also significant in the HA prevalence logistic regression were female identity (Beta 3.5), younger age (Beta −0.98), PTSD symptoms (Beta 4.9), and reduced sleep quality (Beta 1.4). Demographic characteristics that were significant in the HIT-6 score linear regression model but not the preceding HA prevalence model were Black racial identity (Beta 2.4) and Hispanic/Latino ethnic identity (Beta 2.0) as compared with White/non-Hispanic racial/ethnic identity. Additionally, risky alcohol use was associated with lower HIT-6 total scores (Beta −2.3) compared to non-drinkers. Overall, Multiple R^2 for the model was 0.350, indicating the model accounted for 35% the variance in HIT-6 total score.

Multivariable regression sensitivity analyses for mTBI-positive participants only

When excluding the TBI negative participants, time since last mTBI was not significant ($p > 0.05$) in either the logistic regression prevalence or linear regression HA impact models, nor was HA onset within 2 weeks of mTBI (full sensitivity analysis results are available in Supplementary Tables S3, S4).

Discussion

This study provides valuable empirical data on the prevalence, risk factors and impact of HA among previously combat-deployed SMs and veterans. The overall sample ($n = 1,685$), which included 19% with negative TBI histories, had a HA point prevalence (i.e., HA lately) of 65%. Even though mTBI (s) were mostly very remote, with a median 10 years since last mTBI, a greater number of mTBIs was associated with higher HA prevalence, reaching 78% for participants with 3 or more mTBIs (see Table 1). Additionally, a greater number of lifetime mTBIs was associated with more impactful HA when HA was endorsed (see Table 2). For example, 67% showed substantial or severe impact on HIT-6 when mTBI history was positive in contrast to 54% when negative.

A unique aspect of our study was to examine current HA burden in relation to military-relevant subtypes of mTBI history including mechanism (blast-related or not) and setting (combat-deployed or not). This was done while also adjusting for and examining many other potential HA contributors including demographic, military, medical, and psychological factors. Thus, our findings provide additional insights into how HA impact may vary by mechanism and setting that are unique to SMs and veterans and that are independent of PTSD, depression, sleep quality and self-efficacy. The covariate-adjusted logistic regression model for HA prevalence (see Table 6) showed higher prevalence with a greater number of any subtype of mTBI (see Table 6), with the nominally highest OR for blast-related mechanism (OR 1.81; 95% CI 1.48, 2.23). Broadly, these findings provide strong empirical evidence that lifetime mTBI history is an independent risk factor for chronic HA symptoms. They are also consistent with Hoge et al. (33) who showed that HA was the main symptom linked to combat mTBI history at an earlier timepoint after adjusting for similar factors including PTSD. Prior work examining less rigorous ICD coding among combat veterans has also demonstrated an increased risk of HA diagnosis codes with respect to mTBI history codes when adjusting for psychiatric condition codes.

In our covariate adjusted models for HA impact (see Table 7), the most striking finding was greater impact for blast-related mTBI but not for blunt-only mTBI. On average, the HIT-6 total score was 0.6 points higher for each additional blast mTBI. In contrast, blunt-only mTBIs were not associated with higher HIT-6 scores in our adjusted analyses, in either deployed or non-deployed setting. This finding, together with the nominally higher odds for HA prevalence after blast mTBI (see Table 6), suggests that veterans and SMs with blast-related mTBI may have unique susceptibility to chronic HA problems. Animal model research has identified vascular pathology and inflammatory changes unique to blast-TBI, and if translatable to humans may contribute to the poorer HA outcomes after blast-related mTBI. Our finding of greater HA impact for blast-related mTBI has some parallel with a prior study in the warrior strong cohort study ($n = 1,074$) showing that soldiers with posttraumatic HA ($n = 198$) had greater headache complexity ($p < 0.001$) compared to non-concussed soldiers ($n = 647$) (34), but they did not specifically examine blast mechanism. It is also worth noting again that we observed elevated risk at very remote time points and even after adjusting for concurrent symptom measures including PTSD, depression, sleep quality and self-efficacy.

Surprisingly, our sensitivity analysis (see Supplementary Tables S3, S4) restricted to mTBI positive participants showed that neither the self-report of early onset HA after mTBI (within 2 weeks) nor time since last mTBI was associated with either outcome, HA prevalence or HA impact, when adjusting for other covariates. The non-association with early onset HA suggests that the HA in our sample on average does not meet the definition of PTHA *per se*, however our study design which lacked acute data could not directly examine this question. The lack of change over time must be interpreted with the caveat that we only included participants who were greater than 6 months since their last mTBI, so all were already in the "chronic" stage. This non-association does suggest

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TABLE 6 Multivariable logistic regression—experience headaches lately yes/no.

Characteristic	OR[a]	95% CI[b]	*p*-value[c]
Num of blast TBIs (combat and noncombat)	1.81	1.48, 2.23	**<0.001**
Num of combat/nonblast TBIs	1.42	1.14, 1.79	**0.002**
Num of noncombat/nonblast TBIs	1.23	1.02, 1.49	**0.034**
Num of months combat deployed	1.22	1.04, 1.44	**0.018**
Combat intensity (DRRI-2 combat total)	1.10	0.84, 1.43	0.5
Controlled blast exposures			
None	—	—	
Minimal (1–9)	1.06	0.76, 1.47	0.7
Light (10–29)	0.98	0.67, 1.43	>0.9
Moderate (30–98)	1.20	0.79, 1.83	0.4
Heavy (99+)	1.09	0.72, 1.65	0.7
Age	0.76	0.62, 0.94	**0.010**
Gender			
Male	—	—	
Female	3.57	2.37, 5.48	**<0.001**
Race			
White	—	—	
Black or African American	0.94	0.68, 1.30	0.7
American Indian or Alaska Native	2.39	0.58, 16.4	0.3
Asian	2.62	1.06, 7.21	**0.046**
Other	0.53	0.30, 0.95	**0.031**
Ethnicity			
Not Hispanic or Latino	—	—	
Hispanic or Latino	1.33	0.93, 1.92	0.12
Alcohol use (AUDIT-C)			
None	—	—	
Moderate	1.27	0.89, 1.81	0.2
Risky	0.87	0.60, 1.25	0.4
HTN			
No	—	—	
Yes	1.19	0.91, 1.56	0.2
BMI categories			
20–29	—	—	
<20	1.00	0.31, 3.63	>0.9
>29	1.04	0.80, 1.35	0.8
OSA high risk (STOP-BANG)	1.13	0.80, 1.61	0.5
Depression (PHQ-9 total score)	1.56	1.13, 2.15	**0.007**
PTSD (PCL-5 total)	1.54	1.07, 2.23	**0.020**
Sleep quality disturbance (PSQI total score)	1.77	1.39, 2.26	**<0.001**
Social support (DRRI-2 social total)	1.15	0.95, 1.40	0.2
Self-efficacy (GSE total score)	1.07	0.86, 1.34	0.5

[a]OR, odds ratio (expressed as 75th versus 25th percentile for continuous variables).
[b]CI, confidence interval.
[c]*p*-value bolded if <0.05.

that post-acute HA in this population does not fade over time, and that there is a potential unmet care need.

Regarding other covariates, our study indicates that combat deployment duration itself is a unique risk factor for later HA prevalence (see Table 6), suggesting a contribution to a general physiologic and/or psychologic stress exposure that chronically increases HA risk. This finding has also been demonstrated in prior research (15), and may help explain why the OR for HA prevalence in our study was higher if the blunt-only mTBI was sustained during deployment compared to some other time of life. A potential explanation for these findings is that the additional stressors of combat deployment interfere with early recovery from mTBI, increasing the odds of late effects such as HA disorders.

Our large sample, which included 217 females (13%), enabled us to examine their relative risk for HA, a previously understudied research question in the military population due to insufficient numbers of females in most prior HA studies. Our results show that female sex had the nominally highest OR (3.57, 2.37, 5.48) for experiencing HA lately (see Table 6), and had a strong association with higher HA impact (Beta 3.5; 2.1, 4.8; see Table 7). These findings are consistent with the literature from the general population indicates that females are not only at higher risk for experiencing general pain (35), but are also at higher risk for HA, especially migraine-type (36). Given the high rate of migraine type HA that has been demonstrated after TBI (3, 6, 9, 37), a potential mechanistic explanation for the risk elevation for female individuals in our study is related to unmasking a genetic predisposition (38) and/or hormonally-mediated increases in calcitonin gene-related peptide levels (39). Younger age was found to be associated with both HA prevalence and HA impact in our study (see Tables 6, 7), and this is also similar to studies of HA in the general population. In our study, Black racial identity and Hispanic/Latino ethnicity were uniquely associated with higher HA impact compared to White/non-Hispanic participants (see Table 7). These demographic findings suggest that individuals representing marginalized or historically excluded groups (individuals identifying as female, Black, or Hispanic/Latino) may benefit from treatment programs that use targeted outreach strategies, address access barriers, and include appropriate patient education materials.

Symptom measures examined as covariates including depression, PTSD, and sleep quality, were significantly associated with prevalence of experiencing HA lately (see Table 6). PTSD and sleep quality were also associated with HA impact (see Table 7), with higher PTSD symptom endorsement (75th versus 25th percentile on PCL-5) showing the nominally strongest relationship to HIT-6 of any covariate (Beta 4.9; 3.6, 6.2). Thus, combat-exposed military personnel with PTSD are at greatest risk for having their HA contribute to severe negative life impact. Given the concurrent data collection for all of these symptom measures, the pathway of these relationship cannot be determined. However, a bidirectional relationship seems most plausible, as has been demonstrated between migraine and depression in the general population (40). Additionally, sleep quality is likely to both impact and be impacted by HA presence and severity of HA impact, as individuals may engage in compensatory behaviors (e.g., napping) in response to HA-related sleep disturbances, which are detrimental to nighttime sleep quality, and ultimately lower headache threshold (41).

These symptom measure covariate findings demonstrate how HA could complicate and interact with other aspects of outcome in this population. These also represent modifiable targets for treatment. Treatment implications include the potential benefit of cognitive behavioral therapy for HA in this population. The findings also support a holistic approach to caring for persons with chronic HA after TBI that addresses all potential modifiable factors, including medical-based management of headache and mood disorders along with psycho-behavioral management. Future longitudinal analysis could provide further insights into treatment by elucidating the directional pathways of these associations.

A seemingly paradoxical finding in our study was a reduced HA impact for alcohol use at a risky level verses abstinence (see Table 7). This is consistent with a systematic review showing that people with migraine HA consume less alcohol than peers (42). While it is possible that alcohol use is a protective factor, it may be that alcohol use patterns are measuring one or more latent trait variables that may better explain this association. Support for this comes from prior research on alcohol often showing an asymmetrical U-shaped relationship with a variety of health outcomes in the general population. For HA in particular, data identifying alcohol as a trigger for migraine is limited (42), with a recent large study showing no association (43).

For other exposures or medical factors, covariates with no significance in either model included hypertension, hyperlipidemia, obstructive sleep apnea risk level, body mass index, combat intensity, and number of controlled blast exposures. Psychosocial variables with negative findings in both models included social support and general self-efficacy.

Study strengths

Study strengths included our large sample ($n = 1{,}685$) of individuals with military combat exposure drawn from the LIMBIC-CENC multicenter cohort with rigorously determined lifetime mTBI histories and a large breadth of data available from their comprehensive assessments. The sample was also diverse racially (19% Black identity) and ethnically (17% Hispanic or Latino identify). The inclusion of non-TBI comparators and incorporation of sociodemographic and symptom measures allowed us to better determine the unique contribution of their prior mild TBIs on current HA burden. The inclusion of military-relevant mTBI classification also allowed us to parse out the effects of blast-related mechanism and combat-deployed setting. By demonstrating TBI and other risk factors for HA prevalence and HA impact in this population and showing the association with psychological functioning, our study also highlights an opportunity to advance clinical care and patient outcomes.

Study limitations

A limitation of this study was the use of self-report questionnaires for most of the measures including mental health comorbidities and the HA outcome. Other study limitations with respect to the HA outcome included a lack of information on pre-morbid HA, a previously shown predictor of HA after TBI (2),

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TABLE 7 Multivariable linear regression for HIT-6 total score (multiple R^2 = 0.350).

Characteristic	Beta[a]	95% CI[b]	*p*-value[c]
Num of blast TBIs (combat and noncombat)	0.60	0.05, 1.1	**0.033**
Num of combat/nonblast TBIs	0.38	−0.32, 1.1	0.3
Num of noncombat/nonblast TBIs	−0.07	−0.73, 0.59	0.8
Num of months combat deployed	−0.02	−0.60, 0.56	>0.9
Combat intensity (DRRI-2 combat total)	0.38	−0.56, 1.3	0.4
Controlled blast exposures			
None	—	—	
Minimal (1–9)	−1.0	−2.3, 0.30	0.13
Light (10–29)	−0.29	−1.8, 1.2	0.7
Moderate (30–98)	−0.73	−2.3, 0.83	0.4
Heavy (99+)	−0.74	−2.2, 0.77	0.3
Age (years)	−0.98	−1.8, −0.13	**0.023**
Gender			
Male	—	—	
Female	3.5	2.1, 4.8	**<0.001**
Race			
White	—	—	
Black or African American	2.4	1.1, 3.6	**<0.001**
American Indian or Alaska Native	2.5	−1.7, 6.6	0.2
Asian	−1.0	−4.5, 2.4	0.6
Other	2.4	0.27, 4.5	**0.027**
Ethnicity			
Not Hispanic or Latino	—	—	
Hispanic or Latino	2.0	0.80, 3.3	**0.001**
Alcohol use (AUDIT-C)			
None	—	—	
Moderate	−0.54	−1.8, 0.71	0.4
Risky	−2.3	−3.6, −0.91	**0.001**
HTN			
No	—	—	
Yes	0.53	−0.45, 1.5	0.3
BMI categories			
20–29	—	—	
<20	0.57	−3.6, 4.8	0.8
>29	−0.29	−1.3, 0.70	0.6
OSA high risk (STOP-BANG)	0.68	−0.54, 1.9	0.3
Depression (PHQ-9 total score)	0.66	−0.39, 1.7	0.2
PTSD (PCL-5 total)	4.9	3.6, 6.2	**<0.001**
Sleep quality disturbance (PSQI total score)	1.4	0.46, 2.3	**0.003**
Social support (DRRI-2 social total)	0.26	−0.44, 0.96	0.5
Self-efficacy (GSE total score)	−0.70	−1.5, 0.08	0.079

[a]Beta expressed as 75th versus 25th percentile for continuous variables.
[b]CI, confidence interval.
[c]*p*-value bolded if <0.05.

and on premorbid migraine and psychological health with both previously shown predictors of persistent PTHA (10). We also lacked that data differentiating continued HA persistence versus *de novo* onset long after mTBI. We did collect and include HA symptoms within 2 weeks of mTBI as a covariate, which had no significant effect t in either the HA prevalence or the HA impact regression model. Thus, the HA prevalence associations with remote combat and non-combat mTBIs and HA impact association with combat mTBIs we found suggest a risk elevation that does not fit criteria for the current diagnostic term of posttraumatic HA as per The International Classification of Headache Disorders (ICHD) (7): HA onset (or worsening of premorbid HA) "within 7 days following trauma or injury, or within 7 days after recovering consciousness and/or within 7 days after recovering the ability to sense and report pain" (8). Regardless, we cannot determine if the HA reported may have persisted since injury or developed at some period of time after injury in relation to other factors or co-occurring health conditions. Our assessment of headache did not include data on specific quality, location, duration, and additional features (e.g., photophobia, nausea) of headaches that would allow further investigation between differences in headache type (e.g., tension-type, migraine-type, cervicogenic, mixed). Further, prior research has shown medication overuse is associated with persistence of PTHA (10) and some participants may had HA resolution with proper treatment, but we did not examine the potential mediating effect of medications and other treatments received. Lastly, although we used a validated structured interview method with layers of quality assurance, the retrospective identification of historical mTBI is prone to recall bias. More recent mild TBI diagnosis criteria guidelines include the use of blood biomarkers (44), an emerging area of research which so far is only validated for acute head CT decision making with respect to complicated mild TBI with associated intracerebral hemorrhage (45).

Implications for future research

Future research is needed to better understand the relationships we found between HA and these other symptom measures and to study effective treatments and behavioral interventions for HA after mTBI. Future research is also recommended to examine in greater depth factors that may be contributing to the increased HA susceptibility among female SM and veterans. Longitudinal research could offer more insights on causal or directional pathways, especially for the psychologic factors. Our finding of worse HA burden after blast-related mTBI suggests that individuals with blast-related mTBI may need a different type of clinical care pathway and/or treatments compared to blunt-only mTBI, with further research needed including studies examining the mechanism underlying this association. Potential mechanisms may include damage to head and neck tissues resulting in neurogenic inflammation, hyperexcitability of peripheral nociceptors, chronic allodynia/hyperalgesia, damage to spinothalamic/thalamocortical pathways, damage to or dysfunction of pain-inhibition pathways, and/or vascular contributors, including dysregulation of pericranial, intracranial and dural arteries (46).

Conclusion

Experiencing recent HA is extremely common among formerly combat-exposed military personnel and is associated with substantial to severe negative impact on life quality. We demonstrated that remote mTBI history is associated with elevated odds of HA and a higher degree of HA impact, especially for mTBIs that were blast-related. This was shown in both bivariate analyses and multivariable regression adjusting for numerous sociodemographic, health, and symptom measures – including PTSD. These findings highlight the ramifications of mTBI in the military population, and will inform clinical screening, education, and monitoring strategies. Clinical strategies to provide early or targeted intervention should also incorporate the other risk factors we identified among our covariates including female sex, Black racial identity, Hispanic/Latino ethnicity, and younger age. Modifiable treatment targets we identified include PTSD, depression, and sleep quality.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System. https://fitbir.nih.gov/.

Ethics statement

The studies involving humans were approved by Local IRB at every participating site as well as US Department of Defense HRPO. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

WW: conceptualization, methodology, investigation, data interpretation, and writing, reviewing and editing. SC: conceptualization, data interpretation, and writing, reviewing and editing. KE: statistical methods, data curation, data analysis, data interpretation, and writing, reviewing and editing. EW, AM, MC, and MP: methodology and writing, reviewing and editing. CA: data analysis, data interpretation, and reviewing and editing. SW: reviewing and editing. KK: conceptualization, methodology, data interpretation, and writing, reviewing and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Supplementary material

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Subcortical functional connectivity and its association with walking performance following deployment related mild TBI

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Introduction: The relation between traumatic brain injury (TBI), its acute and chronic symptoms, and the potential for remote neurodegenerative disease is a priority for military research. Structural and functional connectivity (FC) of the basal ganglia, involved in motor tasks such as walking, are altered in some samples of Service Members and Veterans with TBI, but any behavioral implications are unclear and could further depend on the context in which the TBI occurred.

Methods: In this study, FC from caudate and pallidum seeds was measured in Service Members and Veterans with a history of mild TBI that occurred during combat deployment, Service Members and Veterans whose mild TBI occurred outside of deployment, and Service Members and Veterans who had no lifetime history of TBI.

Results: FC patterns differed for the two contextual types of mild TBI. Service Members and Veterans with deployment-related mild TBI demonstrated increased

FC between the right caudate and lateral occipital regions relative to both the non-deployment mild TBI and TBI-negative groups. When evaluating the association between FC from the caudate and gait, the non-deployment mild TBI group showed a significant positive relationship between walking time and FC with the frontal pole, implicated in navigational planning, whereas the deployment-related mild TBI group trended towards a greater negative association between walking time and FC within the occipital lobes, associated with visuo-spatial processing during navigation.

Discussion: These findings have implications for elucidating subtle motor disruption in Service Members and Veterans with deployment-related mild TBI. Possible implications for future walking performance are discussed.

KEYWORDS

basal ganglia, movement disorders, globus pallidus, functional connectivity, traumatic brain injury (TBI), service members and veterans, deployment (military), subcortical

Introduction

Since 2000, more than 450,000 Service Members have been diagnosed with traumatic brain injury (TBI), approximately 80% of which are mild in severity (1). Although a full recovery is expected, mild TBI symptoms that persist beyond the weeks and months after injury have been attributed to injury, particularly in the context of pre- or post-morbid psychiatric illness and possibly repetitive head injury (2). These symptoms (e.g., headache, memory symptoms, irritability) are also reported to persist in Veterans with mild TBI (3) who have posttraumatic stress disorder (PTSD), depression, substance use disorder, anxiety, and/ bipolar disorder which are all frequent mental health comorbidities that overlap in individuals with TBI history (4).

Recent work has investigated differences in outcomes by the context in which Service Members and Veterans (SMVs) acquire a mild TBI, specifically between SMVs who suffer a mild TBI while deployed to a combat zone (deployment TBI) and those whose injury occurred in a non-combat (non-deployment TBI) situation (5). There are a number of factors unique to a combat deployment environment that may underlie differences in outcomes, including the emotional impact, physical stress (e.g., sleep deprivation, dehydration), frequency of injuries, timing between injuries, and mechanism of injury (e.g., blunt force trauma versus blast) (6). Mild TBI acquired in a deployment environment has been associated with decrements in cognition (7), lower health-related quality of life (8, 9), and greater symptom report (8, 9). Any physiological changes unique to blast TBI may in part underlie these differences. Although they are not well characterized, greater damage to hippocampal neurons and periventricular parenchyma rather than diffuse axonal injury have been suggested (10). Recent work has also demonstrated differences in the functional connectomes of Veterans with deployment-related versus non-deployment mild TBI that may explain some differences in behavioral outcomes (11).

Veterans with repetitive blast exposure and blunt force mild TBI are reported to have significantly greater balance symptoms and higher scores on the motor scale of the Unified Parkinson's Disease Rating Scale (UPDRS) than Veterans without blast or blunt force TBI (12), and 26.9% of Veterans with TBI due to blast report balance and coordination symptoms, compared to 4.5% of healthy control Veterans (13), suggesting there might be subtle challenges in motor activity associated with balance that negatively impact gait speed. Gait is supported, in part, by the basal ganglia, subcortical structures which include the caudate (which with the putamen and nucleus accumbens form the striatum), and the globus pallidus. Alterations in functional and structural connectivity for subcortical structures involved in motor activity such as walking have also been reported in patients with TBI (14–19).

The association between TBI and neurodegenerative disease (e.g., Parkinson's disease) has long been a focus of the Department of Veterans Affairs (VA) and Department of Defense (DoD). Newsome et al. (15) discussed the potential relationship between altered subcortical FC and movement disorders in Veterans with deployment TBI, but did not present FC data related to motor performance. In the current study, we evaluate the relationship between FC and a measure of walking ability, gait speed, in three groups of SMVs, those who experienced mild TBI during deployment (Deployment TBI), those who experienced mild TBI outside of deployment (Non-deployment TBI), and those with entirely negative TBI history. The NIH Toolbox 4-meter walk test was included in the study because slower gait speed, beyond effects of age, is a marker of cognitive decline (20), greater risk of dementia (21–23), increased brain beta-amyloid (24), and higher risk of disability in older adults (25). We hypothesized that (1) SMVs with Deployment mild TBI would demonstrate altered FC between the basal ganglia (the caudate and globus pallidus) and occipital lobes relative to the Non-deployment mild TBI and TBI negative groups and, (2) greater FC alteration would be associated with slower walking speed.

Methods

Design and participants

Participants were 155 combat-exposed SMVs who were consecutively enrolled in the Long-Term Impact of

Military-Relevant Brain Injury Consortium/Chronic Effects of Neurotrauma Consortium (LIMBIC/CENC) Prospective Longitudinal Study (PLS) at a single site. Participants were determined to have sustained mild TBI(s) either (1) during deployment (Deployment TBI group; $n = 59$), or (2) only outside of (i.e., prior to or following) deployment (Non-deployed TBI group; $n = 61$). A third group with a negative lifetime TBI history (TBI negative group; $n = 35$), was compared to the Deployment and Non-deployment mild TBI groups. After removal of data due to scanner artifact ($n = 11$) and excessive movement (defined as ≥50% volumes with framewise displacement greater than 0.5 mm or 3 standard deviations from the mean; $n = 28$), the final sample size was 116: Deployment TBI ($n = 45$), Non-deployment TBI ($n = 45$), and TBI negative ($n = 26$). The proportion of participants removed due to motion was highly similar across groups: 19% (Deployment TBI), 16% (Non-deployment TBI), and 20% (TBI negative). All study activities were approved by and conducted in accordance with all relevant Institutional Review Boards and other regulatory committees required by the VA and DoD. All participants provided signed informed consent prior to undergoing any study activities. Table 1 summarizes the demographic and clinical features of the groups.

Procedures

Behavioral measures

Behavioral measures were collected as part of the larger LIMBIC-CENC PLS battery. The PTSD Checklist for The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (PCL-5) is a 20-item self-report measure of four clusters of PTSD (intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity) (26). Higher scores indicate greater symptom severity. In Veterans, the PCL-5 has excellent internal consistency (Cronbach's $\alpha = 0.96$) and test–retest reliability ($r = 0.84$) (27).

TABLE 1 Sample Characteristics ($N = 116$).

	Deployment TBI ($n = 45$)		Non-Deployment TBI ($n = 45$)		Unexposed ($n = 26$)		p
	M (SD) or n (%)	range	M (SD) or n (%)	range	M (SD) or n (%)	range	
Age	44.29 (8.23)	30–69	43.33 (9.99)	28–61	44.96 (11.09)	25–68	0.774
Sex							0.360
Male	40 (88.89%)	—	36 (80.00%)	—	20 (76.92%)	—	
Female	5 (11.11%)	—	9 (20.00%)	—	6 (27.08%)	—	
Race							0.513
White	23 (51.11%)	—	30 (66.67%)	—	15 (57.69%)	—	
Black	20 (44.44%)	—	12 (26.67%)	—	10 (38.46%)	—	
Other	2 (4.44%)	—	3 (6.66%)	—	1 (3.85%)	—	
Ethnicity							0.520
Hispanic	2 (4.44%)	—	3 (6.67%)	—	2 (7.69%)	—	
Non-Hispanic	42 (93.33%)	—	41 (91.11%)	—	24 (92.31%)	—	
Unsure	1 (2.22%)		1 (2.22%)		0 (0.00%)	—	
Education							0.599
High School Graduate	1 (2.22%)	—	6 (13.33%)	—	4 (15.38%)	—	
Some College	21 (46.67%)	—	14 (31.11%)	—	10 (38.46%)	—	
Bachelor's Degree	15 (33.33%)	—	15 (33.33%)	—	9 (34.62%)	—	
Master's Degree	8 (17.78%)	—	9 (20.00%)	—	3 (11.54%)	—	
Professional Degree	0 (0.00%)	—	1 (2.22%)	—	0 (0.00%)	—	
TBI frequency	2.62 (1.51)	1–7	2.36 (1.46)	1–7	—	—	0.409
with PTA	1.20 (1.28)	0–6	1.07 (1.23)	0–6	—	—	0.624
with LOC	1.33 (1.28)	0–6	0.51 (0.73)	0–3	—	—	<0.001
Years since most recent TBI	12.41 (9.84)	0.32–43.66	15.13 (11.04)	0.90–45.24	—	—	0.221
PCL-5 Total Score	25.62 (20.34)	1–66	19.27 (15.39)	0–57	3.35 (2.88)	0–11	<0.001
PHQ-9 Total Score	7.57 (6.16)	0–23	6.45 (6.04)	0–21	13.42 (11.69)	0–41	<0.001
Gait Speed Score	1.28 (0.23)	0.62–1.80	1.29 (0.19)	0.88–1.75	1.28 (0.20)	1.10–1.85	0.969

LOC = Loss of Consciousness, TBI = traumatic brain injury, PCL-5 = Posttraumatic Stress Disorder (PTSD) Checklist for DSM-5, PHQ-9 = Patient Health Questionnaire-9, PTA = Posttraumatic Amnesia, SD = Standard Deviation. Group comparison p-values were calculated with ANOVA, t-tests, and chi-square as appropriate for data type.

The 9-Item Patient Health Questionnaire (PHQ-9) (28) is a self-report measure of depression. Higher numbers indicate greater severity. Internal (Cronbach's $\alpha = 0.89$) and test–retest reliability (Cronbach's $\alpha = 0.83$) are excellent.

Gait speed is an important aspect of motor performance and was measured with the NIH Toolbox 4-meter walk test (29). Normative values are available for the test. The intraclass correlation coefficients are considered fair (0.41–0.46) (29). Participants are asked to walk 4 meters at their usual pace, and the time in seconds is measured during each of two trials, with the shortest time used for analysis. A score of meters per second is calculated by dividing 4 by the number of seconds. Higher numbers indicate slower speeds. As a point of reference, the mean gait speed score of a community-dwelling sample of males aged 30–49 years is 1.21; for females 30–49 years, the mean gait score is 1.15 (29).

Functional connectivity

During the resting state acquisition, the MRI technologist instructed each participant to lie still with eyes open and fixated on a marker at the top of the bore and comfortably within their line of sight. MRI technologists spoke with subjects immediately before and after the resting state sequence to provide instructions and to ascertain wakefulness and recorded the information on a form. None of the participants included in the analysis were determined to have fallen asleep during the imaging session.

Image data acquisition

Whole brain imaging was performed using a 32-channel head coil on a Philips 3 T Ingenia system (Philips, Best, Netherlands) at the Collaborative Advanced Research Imaging facility (CARI), Wright Center for Clinical and Translational Research, Virginia Commonwealth University. Regular quality assurance (QA) testing that included QA monitoring of EPI stability (30) as well as geometric accuracy (31) was performed throughout the course of the study, and no issues were detected. BOLD T2*-weighted echo-planar images (EPI) were acquired as 200 volumes with 48 contiguous axial slices of 3.3 millimeter (mm) thickness, 212-mm field of view (FOV), 64×64 matrix, repetition time (TR) of 3,000 ms, echo time (TE) of 30 ms, and an 80-degree flip angle. A set of three dimensional (3D) high-resolution T1-weighted images were also acquired in 170 sagittal slices of 1.2 mm thickness (no gap) with 240 mm FOV, 256×256 matrix, TR of 6.78 ms, TE of 3.16 ms, and a 9.0-degree flip angle.

Statistical analysis

Demographic and behavioral data

Characteristics of the sample are summarized in means, standard deviations, and ranges for continuous variables and counts and percentages for categorical variables. Chi-square tests were performed for categorical comparisons, t-tests for comparisons with two groups, and ANOVA for three groups.

Functional connectivity image processing and analysis

The Functional Connectivity Toolbox (Conn) (32) within Statistical Parametric Mapping (SPM) SPM8 (Wellcome Department of Cognitive Neurology, University College, London, UK) implemented in Matlab (Mathworks Inc. Sherborn MA, USA) was used to process and analyze data. Functional images of each participant were realigned, co-registered with each participant's high resolution anatomical image, normalized to the Montreal Neurological Institute (MNI) template, and smoothed using a 6 mm Full Width - Half Maximum (FWHM) Gaussian filter. Anatomical landmarks in the normalized high resolution anatomical and functional data were visually checked and compared against the MNI template for each participant. Each participant's anatomical image was segmented into gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) masks. Physiological noise was addressed by using average activity within the WM and CSF masks as covariates. Realignment parameters and their first-order derivatives were also covaried. To repair artifact due to frame-by-frame head movement, outlier time points were defined as exceeding 0.5 mm or three standard deviations from the mean image intensity of the complete resting state run, and outliers were included as regressors in the first level general linear model along with motion parameters and their first-order derivatives. Data were band-pass filtered between 0.008 and 0.09 Hz, the default frequency range in the SPM Conn toolbox. The high-pass value was selected to approximate both SPM's default value (0.0078 Hz) and a two-minute value suggested as a standard (0.0083 Hz) (33). The low-pass value approximates the frequently reported 0.08 Hz and 0.10 Hz values and SPM's hemodynamic response function cutoff frequency of 0.091 Hz. FC was measured with single seeds in the left and right caudate and left and right pallidum anatomically defined in the FSL-Harvard Atlas.

A general linear model was used to estimate the correlation between the seeds and the whole brain on a voxel-wise level for individual participants in a first level analysis. Pearson correlation coefficients were then transformed into z-scores using Fisher's method. Group (second level) whole-brain voxel-wise random effects analyses were conducted using the general linear model, in which t-tests were calculated for planned comparisons between the two TBI groups and for each TBI group compared to the TBI negative control group. Analysis of covariance (ANCOVA) with age and total scores on the PHQ-9 and PCL-5 as covariates was then performed to investigate whole brain voxel-wise differences in FC between TBI groups and for each TBI group compared to the TBI Negative group. We first performed simple regressions of age and PHQ-9 and PCL-5 total scores onto the FC of each seed from each group. If results were not significant, the variable was not entered into an ANCOVA. Each covariate was entered separately after verifying the homogeneity of slopes assumption for each seed on a voxel-wise basis.

Regression analysis was conducted for the mean-centered gait speed scores of each subject onto the z-scores representing FC within each group. The regression slopes were then compared between the two TBI groups. The TBI negative group was not included in the comparison between regression slopes because gait speed scores were available for only a subset ($n = 16$) of these subjects.

In SPM, a cluster of voxels is defined as a set of voxels that survives a cluster-defining voxel (height) threshold and which occur spatially contiguous with each other. In this study, the cluster-defining height threshold was set at $p < 0.001$, uncorrected, recommended for control of inflated cluster extent (34). Significance at the cluster level of inference was defined by a corrected cluster threshold of $p < 0.05$, after False

Discovery Rate (FDR) correction for multiple comparisons across the whole brain. Further Bonferroni correction was made for the number of seeds, groups, and tails, or directions, (criterion $p = 0.05/[4 \text{ seeds} \times 3 \text{ groups} \times 2 \text{ directions}] = p = 0.002$).

Results

Symptom and demographic measures

See Table 1. Most group comparisons were nonsignificant, including gait scores, which did not differ among the three groups. The TBI negative group reported significantly lower PCL-5 and PHQ-9 scores than either TBI group, and the Deployment TBI group reported more TBIs with loss of consciousness (LOC) than the Non-deployment group.

Functional connectivity group differences

Results for all FC between-group differences are reported in Table 2. Analyses including covariates are reported in the Supplemental Information (SI; Supplementary Table 1).

Deployment vs. non-deployment TBI

Deployment > Non-deployment TBI

Compared to the Non-deployment TBI group, the Deployment TBI group demonstrated greater FC between the right caudate seed and one cluster in the right superior lateral occipital cortex and angular gyrus (FDR and Bonferroni-corrected cluster threshold $p < 0.000049$, FDR corrected, beta = 0.11, 90% CI [0.08, 0.14]), which remained significant when covarying PHQ-9 and PCL-5 total scores (see Figure 1, Table 2, and Supplementary Table 1). No other seeds were significant.

Non-deployment > Deployment TBI

The Non-deployment TBI group did not have any FC that was significantly greater than the Deployment TBI group.

Deployment TBI vs. TBI negative

Deployment TBI > TBI negative

Compared to the TBI negative group, the Deployment TBI group demonstrated greater FC between the left caudate seed and

TABLE 2 Between Group Analyses Evaluating Left and Right Caudate and Globus Pallidus Seeds.

Group comparison	Cluster-level *p* value (corrected)[a]	Cluster size (k)[b]	Most significant coordinates[c]			Location
			x	y	z	
Deployed > Nondeployed						
a. Left caudate seed	<0.000049	555	64	−50	34	R superior lateral occipital cortex, angular gyrus
b. Right caudate seed	*ns*					
c. Left globus pallidus	*ns*					
d. Right globus pallidus	*ns*					
Nondeployed > Deployed	*NS*					
Deployed > Unexposed						
a. Left caudate seed	< 0.000033	570	−42	−76	38	R superior lateral occipital cortex, angular gyrus
	< 0.000033	562	4	−52	20	Precuneus, PCC
b. Right caudate seed	*ns*					
c. Left globus pallidus	*ns*					
d. Right globus pallidus	*ns*					
Unexposed > Deployed						
a. Left caudate seed	*ns*					
b. Right caudate seed	*ns*					
c. Left globus pallidus	*ns*					
d. Right globus pallidus	<0.00484*	253	−4	−6	46	Bilateral precentral gyri, juxtapositional cortices (formerly SMA), ACC
Nondeployed > Unexposed	*NS*					
Unexposed > Nondeployed	*NS*					

[a]Probability at the cluster level of significance after random field theory family-wise error correction over the whole brain search volume. Cluster probability also survives Bonferroni correction for number of seeds, groups, and tests, (criterion $p = 0.05/[4 \text{ seeds} \times 3 \text{ groups} \times 2 \text{ types of test}] = p = 0.002$).

[b]Number of voxels within a cluster.

[c]Negative values along the x-axis are defined to be in the subject's left hemisphere.

*Marginal significance.

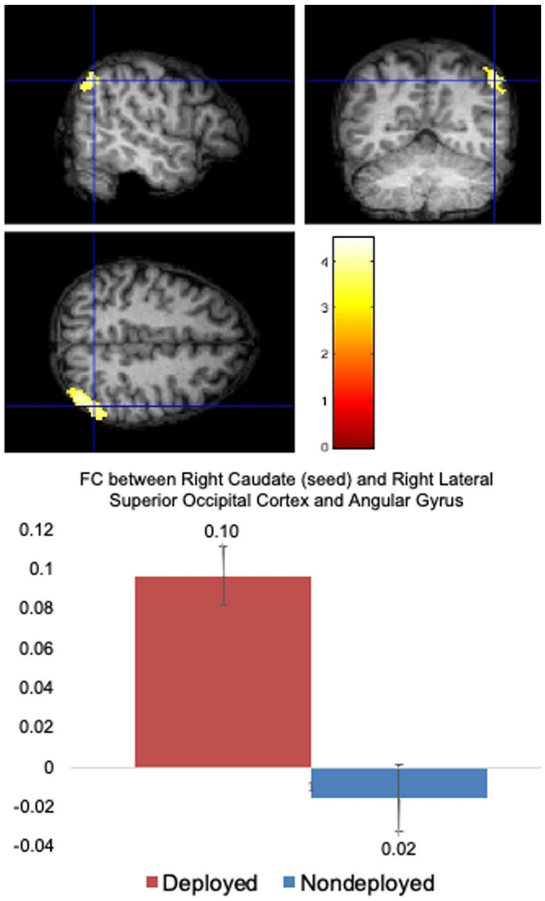


FIGURE 1
Deployed > Non-deployed. The Deployed mTBI group demonstrated significantly greater FC between right caudate (seed) and right lateral superior occipital cortex and angular gyrus than the Nondeployed group. Right side of brain is on the right side of the screen. Color in bar reflects *t*-value. Columns in the bar chart depict means and standard errors.

one cluster in the right superior lateral occipital cortex and angular gyrus (cluster threshold $p < 0.000033$, FDR corrected, beta = 0.15, 90% CI [0.01, 0.19]), and one cluster in precuneus and posterior cingulate cortex (PCC; cluster threshold $p < 0.000033$, FDR corrected, beta = 0.14, 90% CI [0.08, 0.19]), which remained significant when covarying PHQ-9 and PCL-5 total scores (see Table 2 and Supplementary Table 1).

TBI negative > Deployment TBI

The TBI negative group showed greater FC between the right pallidum seed and a cluster in bilateral precentral gyri, juxtapositional cortices (formerly supplementary motor cortex), and anterior cingulate gyrus that approached significance (cluster threshold $p < 0.004084$, FDR corrected, beta = 0.12, 90% CI [0.07, 0.17]) and met significance when covarying PHQ-9 and PCL-5 total scores (see Table 2 and Supplementary Table 1). No other seeds were significant.

Non-deployment TBI vs. TBI negative

No seeds were significant.

Functional connectivity regressions of gait speed scores onto FC

The TBI negative group was examined separately due to smaller sample size to better understand regions associated with walking performance in the absence of mild TBI history.

TBI negative

See Table 3. Positive correlation was nonsignificant for the TBI negative group. However, this group demonstrated a significant negative correlation between gait scores and FC between the left caudate and precuneus (cluster threshold $p = 0.001073$ FDR corrected, beta = −0.65, 90% CI [−0.85, −0.48]), which was also significant after covarying PHQ-9 total scores, but only trending after covarying PCL5 total scores. Covarying PHQ-9 total scores revealed an additional significant cluster in the left temporal pole, anterior inferior temporal gyrus, and anterior temporal fusiform gyrus, which was marginally significant after covarying PCL-5 total scores. No other seeds were significant.

Deployment vs. non-deployment TBI

Deployment > Non-deployment

The Deployment TBI group demonstrated greater negative correlations between gait scores and left caudate FC that did not survive the Bonferroni correction for multiple seeds, groups, and tails ($p < 0.002$), with two clusters involving the right occipital fusiform gyrus, lingual gyrus, and cerebellum VI, a lobule of the posterior lobe (Cluster 1, cluster threshold $p = 0.005$, FDR corrected, beta = 0.57, 90% CI [0.38, 0.77]), and the right superior lateral occipital cortex and occipital pole, and bilateral cuneus (Cluster 2, cluster threshold $p = 0.008$, FDR corrected, beta = 0.60, 90% CI [0.37 0.88]). Examining regressions of each group separately confirmed the negative regressions between walk scores and the two clusters in the left caudate-occipital FC in the Deployment TBI group and no significant clusters in the Non-deployment TBI group. Covarying for PCL-5 and PHQ-9 total scores revealed similar clusters that were marginal in significance, $ps \leq 0.010$ (see Figure 2 and Table 3). No other seeds were significant.

Non-deployment > Deployment TBI

The Non-deployment mild TBI group demonstrated a greater positive association than the Deployed group between gait scores and FC between the right caudate and right frontal pole (cluster threshold $p = 0.001$ FDR corrected, beta = 0.64, 90% CI [0.43, 0.85]), which was also significant or approached significance after covarying PCL-5 and PHQ-9 total scores (cluster threshold $p = 0.002$, and $p = 0.003$, FDR corrected, respectively; see Figure 2 and Table 3).

Discussion

We investigated the effect of mild TBI acquired during military combat deployment on subcortical brain structures associated with movement. SMVs who sustained mild TBI during deployment showed increased FC between the right caudate seed and superior lateral occipital cortex and angular gyrus compared to SMVs with non-deployment mild TBI, and SMVs who are TBI negative,

TABLE 3 Regression analyses relating walk time onto the functional connectivity of caudate and globus pallidus seeds.

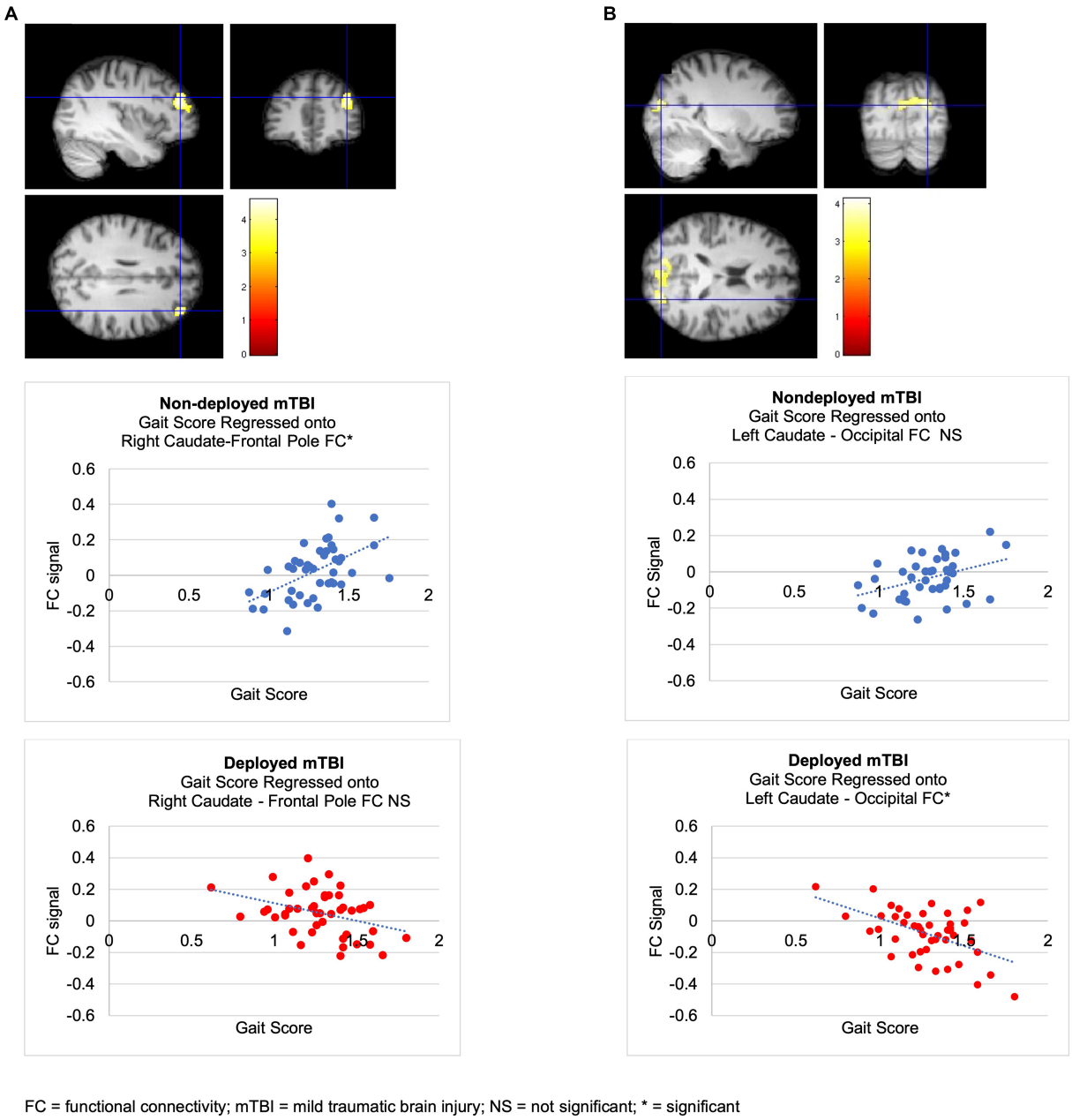
	Cluster-level *p* value (corrected)[a]	Cluster size (k)[b]	Most significant coordinates[c]			Location
			x	y	z	
Unexposed only						
a. Left caudate						
Positive Regression	*ns*					
Negative Regression	<0.001073	199	6	−54	40	Precuneus
b. Right caudate	*ns*					
c. Left globus pallidus	*ns*					
d. Right globus pallidus	*ns*					
Deployed > Nondeployed						
a. Left caudate	*ns*					
b. Right caudate						
Positive Regression	*ns*					
Negative Regression	<0.0000001	1720	−10	−48	8	Precuneus, Posterior Cingulate Gyrus, Bilateral Lingual Gyrus
	<0.000193	404	58	−4	−28	R Middle Temporal Gyrus, Right Temporal Pole, R Inferior Temporal Gyrus
	<0.000321	357	50	−66	24	R Superior Lateral Occipital Cortex
c. Left globus pallidus	*ns*					
d. Right globus pallidus	*ns*					
Nondeployed > Deployed						
a. Left caudate	*ns*					
b. Right caudate						
Positive regression	<0.001	585	38	42	26	Frontal Pole (middle frontal gyrus)
Negative Regression	*ns*					
c. Left globus pallidus	*ns*					
d. Right globus pallidus	*ns*					

[a]Probability at the cluster level of significance after random field theory family-wise error correction over the whole brain search volume. Cluster probability also survives Bonferroni correction for number of seeds, groups, and tests, (criterion $p = 0.05/[4 \text{ seeds} \times 3 \text{ groups} \times 2 \text{ types of test}] = p = 0.002$).
[b]Number of voxels within a cluster.
[c]Negative values along the x-axis are defined to be in the subject's left hemisphere.

suggesting some robustness to the pattern of subcortico-occipital FC specific to combat deployed SMVs with mild TBI. We also observed that altered FC was related to a gait measure. The Non-deployment mild TBI group demonstrated a greater positive association when walk scores were regressed onto FC between the right caudate seed and the right frontal pole than did the Deployment TBI group. Conversely, compared to the Non-deployment group, the Deployment TBI group demonstrated a marginally significant greater negative association between left caudate and occipital regions also including the superior lateral occipital cortex, as well as the lingual gyrus, occipital fusiform gyrus, cerebellum VI, cuneus, and occipital pole. They showed the same pattern when compared to the TBI negative comparison group. FC between the caudate and occipital lobes appears to occur when TBI is acquired during combat deployment and is related to the speed with which combat SMVs with mild TBI history walk.

The regions identified through regression analysis in the Deployment TBI group compared to the TBI negative group and were associated with gait speed are similar to those previously reported (15) (occipital fusiform gyrus, lingual gyrus, cerebellum VI, cuneus, and occipital pole), suggesting that the previous results might have been linked with gait speed. However, there are some differences between the two studies. In Newsome et al. (15), the globus pallidus, rather than the caudate, was significantly correlated with occipital regions. Additionally, the altered FC between the globus pallidus and occipital lobes was an increased anti-correlation rather than the increased positive FC found in this analysis (i.e., above zero in the graph in Figure 1). The proximity of the globus pallidus to the caudate, the imprecise nature of blast impacts, different post-injury intervals [i.e., 5.46 years (15) versus 12.41 years in the current study], and different comparison groups might contribute to differences.

Why would the occipital cortex demonstrate increased FC with the basal ganglia? Occipital cortex and basal ganglia have been reported to be anatomically connected and show co-activation during task and resting state fMRI (rsfMRI) (35–38). In a diffusion study mapping the basal ganglia connectome, lateral occipital cortex was shown to have weak connectivity with globus pallidus and



FC = functional connectivity; mTBI = mild traumatic brain injury; NS = not significant; * = significant

FIGURE 2
Regressions of walk scores onto caudate FC in mTBI groups. **(A)** Non-deployed > Deployed. The Non-deployed mTBI group demonstrated a significantly greater positive relation between walk scores and FC between the right caudate (seed) and right frontal pole than the Deployed mTBI group. Examining regressions of each group separately confirmed that the significant multiple regression with group was due to a positive regression between walk scores and right caudate-right FP FC in the Non-deployed group and revealed no significant clusters in the Deployed group. **(B)** Deployed > Non-deployed. The Deployed mTBI group demonstrated trends toward a greater negative relation between walk scores and FC between the left caudate and two occipital clusters (*ps* = 0.005107 and 0.007525). Examining regressions of each group separately confirmed the negative regressions between walk scores and left caudate-occipital FC in the Deployed group and revealed no significant clusters in the Nondeployed group.

striatum, albeit the putamen (35). In a follow-up study investigating topographical organization as part of the Human Connectome Project, connectivity was found between the globus pallidus and occipital and other lobes (36). In a meta-analysis on human navigation, right caudate was implicated in navigation when objects in a room were understood in relation to a walker's position (egocentric), but not when a walker's position was not linked to objects in a room (allocentric) (37). Both types of navigation involve mental imagery and were linked to activation in fusiform and lingual gyri, precuneus, cuneus, and middle frontal gyrus (37), regions observed in the current study. Intriguingly, FC between basal ganglia and occipital lobes was increased in patients with a movement disorder, essential tremor. The patients demonstrated increased FC between extrastriate cortex (which includes lingual gyrus, cuneus, and superior occipital gyrus) and basal ganglia (globus pallidus, caudate, putamen) compared to healthy controls

(38). The authors attributed the increased FC to enhanced visual feedback (i.e., seeing the tremor themselves) compared to the healthy controls.

Although our participants with Deployment TBI were not given visual feedback, they may have relied more than the other groups on visual information while navigating the room. In a meta-analysis of mapping brain regions to cognitive tasks, the superior lateral occipital cortex was linked to visuospatial tasks and other tasks involving viewing motion (39). The angular gyrus, identified along with the superior lateral occipital cortex to demonstrate increased FC in the Deployment TBI group, has been implicated in identification of one's location in space and time (40).

Overall gait speed means and variances of the three groups were similar, while the relationships between the gait speed scores and FC differed, suggesting that gait itself is not impaired, but the regions each group relied on for gait may be linked to the environment in which the injury occurred. Possibly the extra-FC is required to yield the same results (i.e., support gait) as in non-deployed individuals. In Veterans with mTBI, group differences in functional brain imaging have been reported when there were no group differences in performance of a task (41). Additionally, areas that are responsible for performing a task in healthy people and show altered FC in TBI patients may or may not demonstrate reliability over time. If the altered FC pattern is not available at a later time point, it may not be sufficient for supporting ongoing task performance.

Speculatively, the FC of the Deployment TBI group may reflect individuals' utilizing visuospatial cues in their environment more than the Non-deployment mild TBI or TBI negative groups did. It is also possible that regions for visuospatial processing adapt to provide other types of processing related to walking. Non-deployment TBI, on the other hand, revealed a positive relation between gait speed and FC between right caudate and right frontal pole (i.e., middle frontal gyrus/dorsolateral prefrontal cortex). In a meta-analysis, this region has been implicated specifically in planning while navigating (37). Individuals with non-deployment TBI may rely more on planning when walking is slowed, whereas individuals with deployment TBI may rely more on visuospatial processing, which becomes less accessible for slower gaits given the negative regression between FC and gait speed scores. If this pattern replicates in larger samples, to better understand gate mechanisms, an intriguing follow-up line of inquiry would investigate any pattern in regions the SMVs at the upper end of the range (the slower walkers) recruit and the cognitive processes they employ to potentially guide future rehabilitation in gait-cognition coupling.

In the between-group comparisons, the TBI negative group, compared to the Deployment TBI group, demonstrated greater FC between the caudate and juxtapositional cortex (formerly supplementary motor area [SMA]) than the TBI negative group. When evaluating the association between FC and walking scores, the TBI negative group demonstrated a positive association with the precuneus. The SMA is directly involved in walking and is connected to the caudate and putamen via the frontostriatal tract (42). It is possible that this tract is disrupted in Veterans with deployment TBI, potentially causing them to rely more on other tract(s) to ensure a connection between the caudate and occipital lobes.

The TBI negative group also demonstrated a significant negative association between walk scores and FC between the caudate and precuneus, suggesting that the precuneus plays an important role in walking, particularly faster gait, for SMVs without TBI. The precuneus is anatomically and functionally connected to the caudate (43, 44), and shares FC with the motor and supplementary motor cortices in healthy adults (44), supporting its role in walking.

The pattern of increased FC seen in both TBI groups resembles the hyperconnectivity and hyperactivation often seen in individuals with TBI and has been attributed to additional regions compensating for impaired ones. Hyper-FC often occurs in regions that are recruited in healthy participants as well as other regions. In the analysis evaluating walking scores, the TBI negative group demonstrated greater FC in the precuneus, also known to be involved in walking in healthy non-SMVs. The precuneus showed increased FC in the Deployment TBI group in addition to neighboring and other posterior regions. Many brain regions can be classified with subcomponent regions, and it is possible that parts of the regions providing the compensation are themselves compromised. In that scenario, other regions are recruited because one is not sufficient. Many of the regions noted in our study as having increased FC in the Deployment TBI group are also reported as having altered glucose metabolism in Veterans with mild TBI (12), suggesting they may not be fully functioning.

Compensatory reliance on brain regions not typically associated with gait could precede potential walking difficulties after mild TBI if the altered FC is not reliable or able to provide the neural support necessary for healthy gait, a topic of a potential longitudinal study for future research.

Strengths of the study include the following: (1) Use of study participants at a single site using the same scanner, which eliminated noise that can be incompletely controlled for when using multiple sites and scanners; (2) Inclusion of three groups of SMVs allowing us to compare two types of TBI context to each other and to controls; (3) Requirement that control subjects (TBI-negative group) also have a history of combat deployments. It is often not possible to recruit control subjects with backgrounds similar to the patient population; (4) Use of validated interview methods (rather than self-report) to determine lifetime mTBI histories in all subjects by using validated structured interviews followed by local site review by the principal investigator, as well as vetting to confirm a computer algorithm diagnosis of mTBI for every potential concussive event and a centralized expert committee that adjudicates any remaining uncertain mTBI diagnoses; (5) finally, another strength is that by comparing gait speed, or other aspects of walking, with basal ganglia connectivity, we may be able to define novel endophenotypes that, with further study, may guide clinical care. There are also several limitations in this study. Bonferroni correction was calculated for the number of seeds, groups, and tails, but not for the number of tests (t-tests and ANCOVAs). A follow-up study with increased sample sizes will be more equipped to handle the conservative nature of Bonferroni correction. The PCL-5 and PHQ-9 have some overlap in the symptoms they measure and might have led to some degree of redundancy in the results of the ANCOVAs; however, results of between-group tests with and without covariates were similar, suggesting that both measures might not have significant effects on the results. The PCL-5 does not provide as detailed an assessment of PTSD symptoms and their clinical effect as the Clinician Administered PTSD Scale (CAPS-5) (45). FC from the putamen, a prominent brain region in the basal ganglia was not measured; however current seeds were based on the results of Newsome et al. (15). FC was not measured during the performance of an imagined walking test in the scanner; brain regions involved in walking imagery tasks have been shown to

closely parallel those involved in actual walking in healthy adults, and a walking imagery task is feasible in patients with severe TBI (46). Lastly, the TBI groups were closely matched, except the Deployed group had significantly more TBIs with loss of consciousness (LOC) than the Non-deployed group. LOC in Veterans has been known to be related to altered WM in the brainstem (47). Interestingly, however, subjects with severe TBI who also had disorders of consciousness acutely demonstrated altered default mode network (DMN) functional connectivity while they were comatose, but 6 months later during recovery, their DMN patterns were "indistinguishable" from those of healthy adults (48). While this finding strongly suggests that LOC does not alter the DMN, other FC networks were not tested.

Mild TBI in Veterans has been linked to dementia (49), Parkinson's disease (PD) (50), and progressive neurodegeneration as measured by retinal thickness (51). Slowing in gait speed is associated with risk of dementia and PD in non-SMVs. Although overall gait scores did not differ between groups in the present study, increased FC was associated with faster gait, suggesting that hyper-FC may assist in faster gait. It is possible that people with slower gait were not as adept at functionally connecting the caudate and occipital areas. Alternatively, it is possible that improvements in gait speed scores could be linked to reductions in hyper-FC. In addition to further study of features of walking other than gait speed, such as balance and coordination, patients with hyper-FC might benefit from treadmill therapy to strengthen connections. Treadmill therapy, i.e., a six-week intervention of increasing pace on a treadmill as tolerated, combined with a virtual reality cognitive component, is associated with increased gait speed, improved balance and reduction of FC from the striatum in PD patients (52), and may be useful in Veterans with mild TBI as preventative or early treatment. Further, aberrant FC may precede aberration in behavior. To better understand if deployment-related TBI uniquely impacts FC-gait coupling, future longitudinal studies may test for shifts in compensatory patterns over time in TBI of different etiologies and relate them to performance to potentially provide predictive biomarkers for changes in gait. Furthermore, future rehabilitation clinical trials may benefit by using these novel biomarkers for patient stratification, reducing noise in a complex patient population.

Conclusion

When investigating two etiological settings for mild TBI, we found that SMVs who incurred mild TBI during combat deployment demonstrated increased FC between the basal ganglia and occipital lobes compared to SMVs whose mild TBI occurred outside of deployment and to SMVs who did not have mild TBI. The superior lateral occipital cortex was implicated in the Deployment TBI group both in the between group comparisons and in a negative regression of walking scores onto FC, suggesting a reliance in the Deployment mild TBI group on areas involved in navigation that becomes less available when walking speed is slower. The Non-deployment TBI group demonstrated a positive relationship between walk scores and FC between the caudate and frontal pole, involved in planning during navigation. Findings have implications for elucidating subtle motor disruption in two types of mTBI in SMVs; despite intact walking performance, changes in FC occur, which could have implications for future walking performance.

Data availability statement

Data will be made available to researchers after they have submitted a proposal to the LIMBIC CENC Consortium, it has been approved, and all necessary data sharing agreements have been executed. For further information kindly refer to the LIMBIC-CENC webpage, https://www.limbic-cenc.org/for-tbi-researchers/data-requests-public/.

Ethics statement

The studies involving humans were approved by Richmond Institute for Veterans Research (formerly known as McGuire Research Institute, Inc.). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MN: Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. SM: Writing – original draft, Writing – review & editing. ND: Writing – review & editing. ED: Writing – review & editing. MD: Data curation, Writing – review & editing. CE: Writing – review & editing. CH: Writing – review & editing. GJ: Writing – review & editing. QL: Data curation, Formal Analysis, Writing – review & editing. KK: Writing – review & editing. AM: Writing – review & editing. JR: Writing – review & editing. RS: Writing – review & editing. JS: Writing – review & editing, Formal Analysis, Methodology. BT: Writing – review & editing, Data curation. JW: Writing – review & editing. DT: Writing – review & editing. WW: Funding acquisition, Project administration, Writing – review & editing. EW: Writing – review & editing, Funding acquisition, Project administration, Resources.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1276437/full#supplementary-material

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Frontotemporal disorders: the expansive panoply of syndromes and spectrum of etiologies

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Background: Frontotemporal lobe disorders (FTD) are amongst the most common brain neurodegenerative disorders. Their relatively covert, frequently subtle presentations and diverse etiologies, pose major challenges in diagnosis and treatments. Recent studies have yielded insights that the etiology in the majority are due to environmental and sporadic causes, rather than genetic in origin.

Aims: To retrospectively examine the cognitive and behavioral impairments in the veteran population to garner the range of differing syndrome presentations and etiological subcategories with a specific focus on frontotemporal lobe disorders.

Methodology: The design is a retrospective, observational registry, case series with the collection of epidemiological, clinical, cognitive, laboratory and radiological data on people with cognitive and behavioral disorders. Inclusion criteria for entry were veterans evaluated exclusively at Orlando VA Healthcare System, neurology section, receiving a diagnosis of FTD by standard criteria, during the observation period dated from July 2016 to March 2021. Frontotemporal disorders (FTD) were delineated into five clinical 5 subtypes. Demographic, cardiovascular risk factors, cognitive, behavioral neurological, neuroimaging data and presumed etiological categories, were collected for those with a diagnosis of frontotemporal disorder.

Results: Of the 200 patients with FTD, further cognitive, behavioral neurological evaluation with standardized, metric testing was possible in 105 patients. Analysis of the etiological groups revealed significantly different younger age of the traumatic brain injury (TBI) and Gulf War Illness (GWI) veterans who also had higher Montreal Cognitive Assessment (MOCA) scores. The TBI group also had significantly more abnormalities of hypometabolism, noted on the PET brain scans. Behavioral neurological testing was notable for the findings that once a frontotemporal disorder had been diagnosed, the four different etiological groups consistently had abnormal FRSBE scores for the 3 principal frontal presentations of (i) abulia/apathy, (ii) disinhibition, and (iii) executive dysfunction as well as abnormal Frontal Behavioral Inventory (FBI) scores with no significant difference amongst the etiological groups. The most common sub-syndromes associated with frontotemporal syndromes were the Geschwind-Gastaut syndrome (GGS), Klüver-Bucy syndrome (KBS), involuntary emotional expression disorder (IEED), cerebellar cognitive affective syndrome (CCA), traumatic encephalopathy syndrome (TES) and prosopagnosia. Comparisons with the three principal frontal lobe syndrome clusters (abulia, disinhibition, executive dysfunction) revealed a significant association with abnormal disinhibition FRSBE T-scores with the GGS. The regression analysis supported the potential

contribution of disinhibition behavior that related to this complex, relatively common behavioral syndrome in this series. The less common subsyndromes in particular, were notable, as they constituted the initial overriding, presenting symptoms and syndromes characterized into 16 separate conditions.

Conclusion: By deconstructing FTD into the multiple sub-syndromes and differing etiologies, this study may provide foundational insights, enabling a more targeted precision medicine approach for future studies, both in treating the sub-syndromes as well as the underlying etiological process.

KEYWORDS

frontotemporal lobe disorders (FTD), etiological categories, veterans, cardiovascular risk factors, behavioral neurological evaluation

Background

Our understanding of neurodegenerative disease and dementia has evolved rapidly in the last few decades. As recently as the 1970s and 1980's all dementia was generally considered to be Alzheimer's disease (AD) (1). Frontotemporal lobe disorders (FTD) are now amongst the most common neurodegenerative disorders, after an approximate 130-year diagnostic hiatus, due largely to the under recognition of Pick's disease, first described in 1896 (2). The most important reason appears to have been that Pick bodies are found in only 20% of FTD. The pathology in frontotemporal lobe dementia is now known to be due to several associated pathologies such as TDP-43 (A, B, C), tau, FUS (3) and less commonly Pick bodies. In addition to the behavioral and primary progressive aphasia subtypes (semantic aphasia, non-fluent aphasia), cortico-basal degeneration, progressive supranuclear palsy and amyotrophic lateral sclerosis are other recognized clinical variants. In a recent wide-ranging retrospective cohort study, the Frontotemporal Dementia Incidence European Research Study (FRONTIERS) in 9 European countries concluded that the annual incidence rate of 2.36 cases per 100,000 person-years appears more common than formerly appreciated and should be considered irrespective of age (4). In contrast to the frontotemporal dementias, recent studies have yielded insights that the majority may be due to environmental and sporadic causes, rather than being genetic in origin and presenting with mild to moderate behavioral impairment termed frontotemporal disorders or syndromes, rather than dementia (5, 6).

From a diagnostic point of view, much depends on what clinical population is being studied. Cognitive and behavioral neurological disorders are common in the Veteran population as sequelae of traumatic brain injury, post-traumatic stress disorders and neurotoxicological exposure, often presenting as frontotemporal syndromes (7–9). Their relatively covert and frequently subtle presentations and diverse etiologies, pose major challenges in diagnosis and treatments. Yet, these conditions often afflict the most plastic areas of the brain providing potential opportunities for successful interventions. Many, widely differing pathophysiological entities for frontotemporal syndromes have been reported. These include traumatic brain injury (10), vascular causes (11), neurotoxicological syndromes such as Gulf War Illness (primarily a synaptopathy, associated with acute phase lipids, Agent Orange exposure) (9, 12), autoimmune disorders (13), cerebral mechanical aberrations such as sagging brain syndromes (14), infectious causes, including Whipple's disease (15) and traumatic encephalopathy/chronic traumatic encephalopathy spectrum (16), in addition to the group of frontotemporal lobe dementias. Furthermore, milder forms of FTD with little deterioration over time, such as the mild frontotemporal phenocopy variant have been reported (3). Some of these frontotemporal syndromes may stabilize for decades and even improve, in contradistinction to the traditional dementias such as Alzheimer dementia (AD). Hence timeous and precise diagnosis may allow precision treatment strategies to be implemented.

Mild cognitive impairment occurs years to decades prior to AD and importantly, from a clinical perspective, 30% may have a remediable underlying cause and improve with appropriate treatment (17, 18). Mild behavioral impairment, with recent validated scales, is now also being recognized with similar opportunities for intervention (19). Metabolic syndromes which tend to target the more posterior association areas and the default mode network, often result in the Alzheimer's spectrum of cognitive dysfunction. The more anterior association cortices of the frontal and anterior temporal lobes are more prone to trauma, toxins and stressors of various kinds, target primarily the salience network and present primarily with an array of behavioral neurological syndromes (20).

Aims

To retrospectively examine the cognitive and behavioral impairments in the veteran population to garner the range of differing syndrome presentations and etiological subcategories with a specific focus on frontotemporal lobe disorders (FTD).

Methodology

The study design was a retrospective observation case series with analysis of veterans with cognitive and behavioral disorders. FTD were specifically documented, which were encountered exclusively at the Orlando VA Healthcare System (OVAMC), neurology service, Orlando, Florida. The data collection comprised of demographic, epidemiological, clinical, cognitive neurological, behavioral neurological, laboratory and neuroradiological data. The inclusion criteria constituted veterans evaluated exclusively at the OVAMC

neurology section, receiving a diagnosis of FTD by standard criteria, during the observation period dated from July 2016 to March 2021. Exclusion criteria consisted of veterans with cognitive and behavioral syndromes not amenable for further analysis, due to significant behavioral obstacles, multiple comorbid medical or psychiatric conditions or unwilling to undergo further testing. The high number of antipsychotic medications in this exclusion group typically masqueraded with frequent and significant frontal lobe syndromes (abulia, dysexecutive syndrome) as recognized side effects of this class of medications. After syndrome analysis, further exclusions included AD, Lewy Body dementia (LBD), vascular dementia, and mixed dementia syndromes. The studies involving humans were approved by Orlando VA Institutional Research Board Approval IRBNET ID: 1256151-4 and a finalized the approval date on April 11, 2020.

In addition to standard neurological evaluation, a comprehensive screening cognitive and behavioral neurological tool with pre-defined syndromes, according to standard definitions, published elsewhere, was used to guide initial diagnosis (21). Whenever possible the following cognitive and behavioral neurological tests were administered (Figure 1). These included a general cognitive screening test, the MOCA 5-min version (22), a behavioral neurological FTD screening test, the Daphne 6 and 40 (23) and activities of Daily Living using the Katz Disability Scale (24). In addition, specific frontal behavioral tests, the FRSBE (25), Frontal Behavioral Inventory (26) and specific anterior temporal lobe tests and other cognitive syndrome evaluations were used. These included the Boston Naming Test (27), the Bear-Fedio Inventory (BFI) (modified) (28), a Human Klüver Bucy Syndrome Inventory (KBS) (29, 30), a Geschwind-Gastaut inventory (GGS) (31), a delusional misidentification syndrome inventory (DMIS) (32), an involuntary emotional expression disorder (IEED) inventory (33) and a cerebellar cognitive affective syndromes (CCA) inventory (34) (Figure 1). In brief the Human Klüver Bucy syndrome required evidence of any 3 components of (i) visual agnosia, (ii) loss of anger, fear responses with placidity or flattened affect, (iii) altered sexual activity or orientation, (iv) hyperorality or bulimia and hypermetamorphosis (compulsion to manipulate objects in the immediate environment, akin to utilization behavior). The Geschwind-Gastaut syndrome diagnosis was made if any 3 of the following were present; a personality syndrome comprising of: (i) circumstantiality (excessive verbal output, loquacious, hypergraphia, interpersonal viscosity) (ii) Intensified mental life (deepening of emotions, hypermoralism, nascent metaphysical interests, hyper-philosophical), (iii) hyper-religiosity (multiple conversions, deep religious beliefs, mystical states), (iv) altered sexuality (hyposexuality, hyper-sexualism, gender dysphoria, transvestism). DMIS diagnosis was made if a person incorrectly identifies or duplicates persons, places, objects, or even events which may be learned by self-report or substantiated from family members or friends. Many different DMIS have been reported but only 3 types were recorded, including: (i) Capgras syndrome; the belief by the person that a familiar individual or even the person themselves had been replaced by an imposter (hypo-identification), (ii) Fregoli's syndrome; the belief that an individual familiar to the person is actually impersonating and is presenting themselves as a stranger (hyper-identification) and (iii) intermetamorphosis; two people, both familiar to the person, have interchanged identities with one another. For IEED, item number 6 of FRSBE test was used and was graded on a 5-point Likert scale and if ≥ 3 was used as positive diagnosis. This delineated a syndrome characterized by spontaneous outbursts of crying, laughing or both, occurring contextually inappropriately. Cerebellar cognitive affective syndromes (CCA) were diagnosed if there was a relevant cerebellar lesion such as stroke or neoplasm with co-occurring onset of cognitive, behavioral or emotional impairment. Traumatic encephalopathy syndrome was diagnosed according to the criteria proposed by the National Comorbidity Survey Replication with at least one of the core criteria and two of the 9 supportive criteria required for diagnosis (35).

Neuroimaging was performed in all patients, including multimodality MRI imaging sequences (GE 3 Tesla) MRI (T1, T2), fluid attenuation inversion recovery (FLAIR) and diffusion weighted imaging (DWI). CT brain scans were a surrogate if MRI contra-indicated and PET brain (FDG, metabolic) scans were performed in selected patients.

Laboratory testing included routine cognitive impairment and dementia related tests. Genetic testing (*C9orf72*, *GRN*, and *MAPT*) was not recommended if there was no family history of frontotemporal dementia. In addition, other factors were considered including the cost factor, patient preference, lack of utility and lack of genetic counseling management if positive.

FTD clinical subtypes were classified into the standard behavioral variant, semantic aphasia, non-fluent aphasia, cortico-basal degeneration variant, progressive supranuclear palsy variant, FTD and amyotrophic sclerosis variant in accordance with currently accepted classification (36). Etiological entities were based on clinical history, cognitive, behavioral, laboratory and imaging analyses and categorized as:

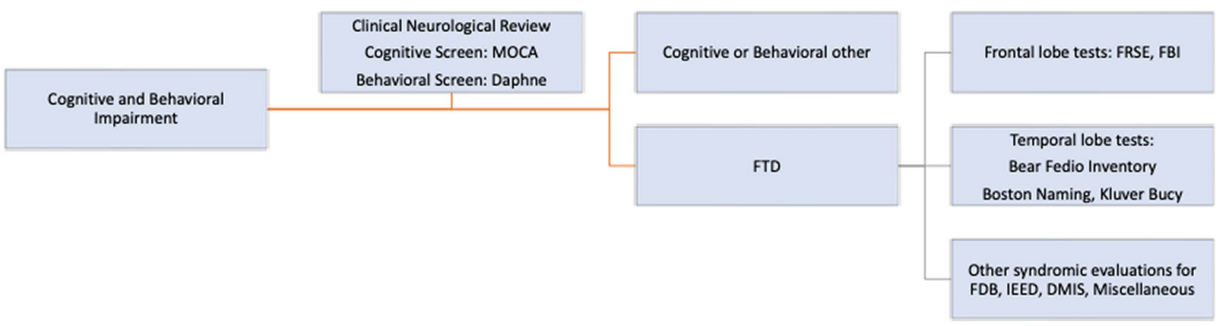

FIGURE 1
Cognitive and behavioral neurological assessment.

1. Traumatic Brain Injury: Centers for Disease Control and ICD-10 criteria for mild and moderate TBI (37).
2. Frontotemporal lobe degenerations and dementias: Daphne Screening test, FBI test (if the score is ≥27).
3. Vascular Cognitive Disorder and dementia: AHA/ASA criteria (38).
4. Neurotoxicological: Gulf War Illness (GWI), Agent Orange, Camp Lejeune toxin exposure. For GWI Illness: Kansas, Haley or Institute of Medicine criteria (9, 39). In brief, there needed to be least 3 of the 6 symptom domains positive (chronic fatigue, cognitive disorders/headache/mood disorder, dyssomnia, somatic pain, gastrointestinal symptoms, typically chronic diarrhea, respiratory symptoms and skin rashes) for a GWI diagnosis to be made in the context of having been deployed in the 1991 Desert Storm conflict. For Agent Orange and Camp Lejeune toxin exposure, appropriate historical time frame and geographic association was used.
5. Alzheimer's dementia: NIH Makhann criteria (40) with specific attention to subtype variants of frontal Alzheimer's, amnestic, visuospatial, logopenic progressive aphasia and posterior cortical atrophy syndrome (Benson's syndrome).
6. Lewy Body dementia: McKeith criteria (41).

The overall clinical and investigative approach in the study was the delineation of FTD into 3 principal categories, namely by FTD clinical variants, by etiological subtypes, and by a number of common and less common subsyndromes.

Statistical analyses

Baseline, demographic, cardiovascular risk factors, cognitive, behavioral data, neuroimaging and presumed etiological categories, were compared between groups. Analysis of variance (ANOVA) and chi-square tests (for categorical variables) were used to examine whether the means between our groups (TBI, vascular, GWI, and other) were statistically different. In addition, a multivariate linear regression analysis was used to examine factors associated with FRSBE scores. A significance level of p-values below 0.05 was chosen. Statistical analysis was performed using Stata Version 16 MP (StataCorp, College Station, TX, USA) for data management and data analysis. Dispersion and position indices were depicted by interquartile ranges (25th, 50th, 75th).

Results

Of the 200 patients with FTD, there were 190 men and 10 women with a mean age of 59.6 years (range 27–90 years) and mean education years of 13.8 (range 8–20 years). Screening cognitive testing with the MOCA tool and frontotemporal behavioral screening with the Daphne test was possible in all patients. This yielded an overall frequency of the generally accepted FTD clinical subtypes in this population, as noted in Figure 2.

Further behavioral neurological analysis with standardized further metric behavioral neurological evaluation was possible in only 105 of the 200 patients. This was primarily due to inability to perform the tests, lack of follow up, missing data, significant comorbidities or medication related effects hindering reliable testing. Analysis of the etiological groups (Figure 3) revealed significantly different younger age of the TBI and GWI veterans who also had higher MOCA scores, the latter which were overall borderline normal. Both the TBI and GWI groups had significantly different higher MOCA scores compared to the "older" vascular group (Figure 4). The TBI group also had significantly more abnormalities of hypometabolism, noted on the PET brain scans. Table 1 summarizes the means, standard deviations, and p-values from the statistical tests performed for the four different groups. Analysis of the behavioral neurological testing was notable for the findings that once frontotemporal disorder had been diagnosed by

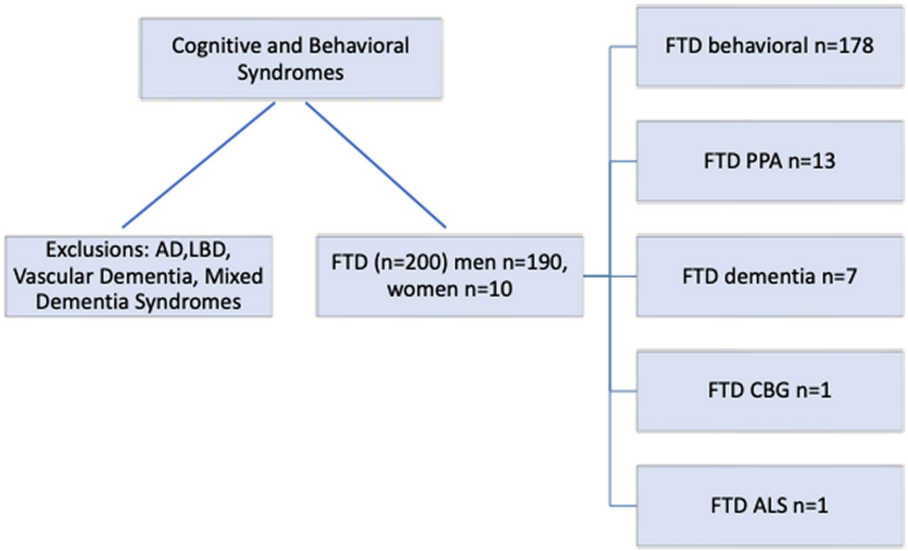

FIGURE 2
Frontotemporal disorders (FTD) cascade and variants. AD, Alzheimer's Disease; LBD, Lewy Body Dementia; FTS, Frontotemporal Syndrome; CTE, Chronic Traumatic Encephalopathy.

the Daphne (or Rascovsky) criteria (42), the four different etiological groups consistently had abnormal FRSBE scores for the 3 principal frontal presentations of (i) abulia/apathy, (ii) disinhibition, and (iii) executive dysfunction as well as abnormal FBI scores. Importantly there was no significant difference amongst the etiological groups (Table 1). This may be regarded as a significant finding underscoring the diagnostic accuracy of the initial FTD diagnosis all of which had similar deficits in the three principal frontal behavioral deficits, namely abulia/apathy, disinhibition and executive dysfunction.

The most common subsyndromes associated with frontotemporal syndromes are depicted in Figure 5. Within this group, GGS was by far the most frequently delineated syndrome. Other relatively common syndromes included KBS, IEED, CCA, TES/CTE and prosopagnosia. Comparisons with the three principal frontal lobe syndrome clusters (abulia, disinhibition, executive dysfunction) revealed a significant association of abnormal disinhibition FRSBE T-scores with the GGS. The regression analysis supported the potential contribution of disinhibition behavior that related to this complex, relatively common behavioral syndrome in this series (Table 2). Linear regression models examining factors associated with FRSBE scores are presented in Table 2. Only patients with GGS had higher FRSBE-D and FRSBE-T scores. The other factors in our models did not have a statistically significant association with FRSBE scores.

Less common subsyndromes entities are depicted in Table 3. These syndromes, in particular, were notable, as they constituted the initial overriding, presenting symptoms and syndromes characterized into 16 separate conditions. They were conveniently subsumed under the 3 principal frontal syndromes of abulia, disinhibition and executive dysfunction and in addition the presumptive category of diaschisis related syndromes.

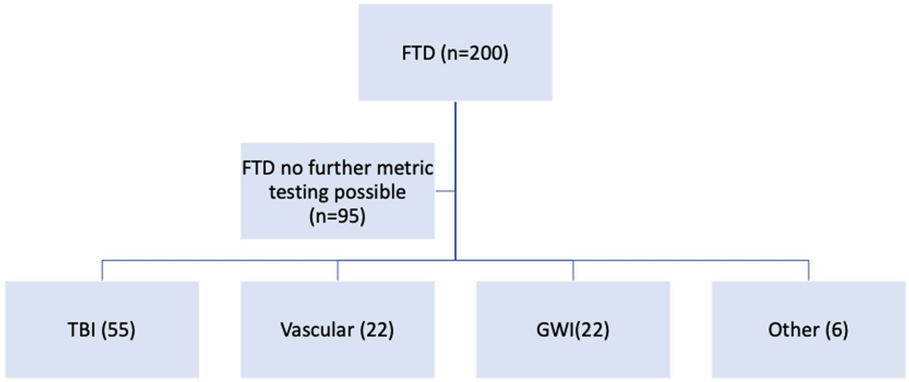

FIGURE 3
FTD syndrome metric analysis and etiological categories (n = 105).

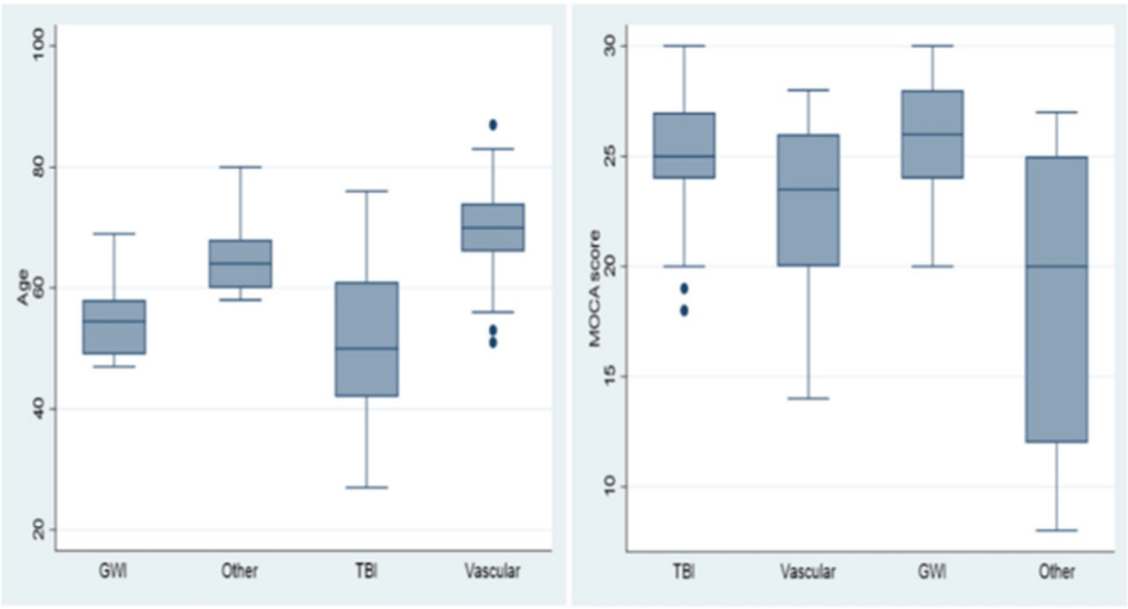

FIGURE 4
Age and MOCA scores, box and whisker plots. Age and MOCA scores differed significantly in the TBI and GWI groups.

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TABLE 1 Comparison among different sub types of FTD.

Item	Subtype				*p*-value
	TBI	Vascular	GWI	Other	
No. of cases	*N* = 55	*N* = 22	*N* = 22	*N* = 6	
Age, years	51 (12.86)	69.5 (9.19)	54.59 (6.37)	65.67 (7.87)	<0.001
Gender, n (%)					0.101
Female	4 (7.27)	1 (4.55)	1 (4.55)	2 (33.33)	
Male	51 (92.73)	21 (95.45)	21 (95.45)	4 (66.67)	
Education, years	13.98 (2.21)	13.5 (2.26)	14.59 (2.17)	14.17 (2.71)	0.451
MOCA score	25.24 (2.65)	23.23 (3.56)	25.45 (3.31)	18.67 (7.47)	<0.001
FBI score	38.77 (11)	40 (11.84)	38.24 (11.1)	45.83 (9.11)	0.485
FRSBE_A	84.5 (20.68)	87.43 (16.99)	88.21 (18.46)	102.8 (22.99)	0.256
FRSBE_D	76.6 (19.51)	81.9 (23.31)	82.21 (18.28)	84.6 (20.67)	0.589
FRSBE_E	84.65 (13.81)	89.33 (17.97)	84.42 (14.14)	100 (19.03)	0.132
FRSBE_T	88.44 (16.71)	90.62 (28.11)	91.21 (15.16)	104.8 (21.05)	0.374
Bear_Fedio score	3.64 (4.62)	2.59 (4.7)	4.64 (4.39)	0.83 (2.04)	0.222
GGS, n (%)					0.080
No	28 (50.91)	16 (72.73)	9 (40.91)	5 (83.33)	
Yes	27 (49.09)	6 (27.27)	13 (59.09)	1 (16.67)	
KBS					<0.001
No	50 (90.9)	22 (100)	21 (95.5)	2 (33.33)	
Yes	5 (9.1)	0 (0)	1 (4.5)	4 (66.67)	
MRI brain scan					0.390
Normal	8 (14.5)	1 (4.5)	4 (18.18)	0 (0)	
Abnormal	47 (85.5)	21 (95.5)	18 (81.82)	6 (100)	
PET scan					0.147
Normal	34 (61.8)	8 (36.36)	13 (59.1)	2 (33.33)	
Abnormal	21 (38.2)	14 (63.64)	9 (40.9)	4 (6.67)	

All values are mean (SD) or otherwise count number (%) as indicated. ANOVA was performed for continuous variables and Pearson Chi-square test was conducted for categorical variables.

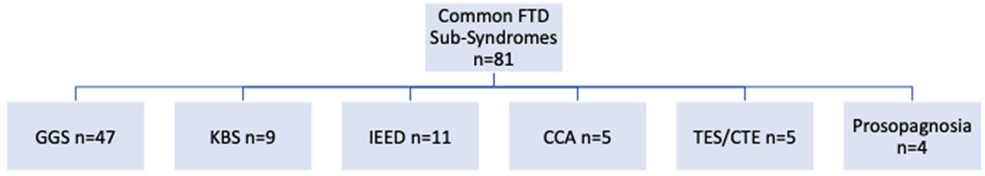

FIGURE 5
FTD clinically diagnosed sub-syndromes.

Discussion

The main findings of this retrospective analysis from the dedicated OVAMC cognitive neurological clinic included the frequency of FTD and the extensive array of behavioral neurological syndromes and sub-syndromes, embraced under the umbrella of FTD. Importantly, these presented mostly in the context of relatively milder cognitive impairment with the mean MOCA score in the TBI of 25.24 (SD 2.65) and GWI 25.45 (SD3.31), where 26 or greater is regarded as the normal range. In many tertiary medical centers, the MMSE and MOCA are screening tests that triage people with cognitive complaints depending on their scores into further investigations or no investigation at all. In this veteran population, the majority of people with TBI, had FTD, rarely in the dementia category because of relatively preserved basic ADLs and IADLs. Although frontotemporal syndromes may conjure up the more commonly known frontotemporal dementias, this study demonstrates that many of mild to moderate behavioral syndromes, in particular post TBI, post cerebrovascular and post neurotoxicological

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TABLE 2 Linear regression model of the factors associated with FRSBE scores (n = 93).

	FRSBE-A score	FRSBE-D score	FRSBE-E score	FRSBE-T score
Patient gender				
Male	Reference	Reference	Reference	Reference
Female	2.56	0.46	−0.72	−0.19
	(−14.4–19.5)	(−16.5–17.4)	(−14.1–12.6)	(−17.3–17.0)
Education (years)	−1.67	−0.62	0.10	−0.77
	(−2.44–1.20)	(−2.44–1.20)	(−1.33–1.53)	(−2.60–1.07)
Age of patient	−0.14	0.28	0.20	0.13
	(−0.48–0.19)	(−0.05–0.62)	(−0.06–0.47)	(−0.20–0.47)
Geschwind-Gastaut	13.51	22.02**	9.50	17.62*
Syndrome diagnosis	(−2.64–29.66)	(5.87–38.17)	(−3.22–22.22)	(1.32–33.93)
Kluver body	11.62	4.15	5.20	8.96
Syndrome diagnosis	(−6.66–29.90)	(−14.13–22.43)	(−9.19–19.6)	(−9.50–27.42)
Bear fedio score	−1.47	−1.45	−1.03	−1.49
	(−3.29–0.35)	(−3.27–0.37)	(−2.46–0.40)	(−3.33–0.35)

95% confidence intervals are reported in parentheses. **$p < 0.01$, *$p < 0.05$.

insults presented with frontotemporal disorders or syndromes and not dementias.

Several additional pertinent findings included the significantly different younger age of the TBI and GWI veterans who also had higher MOCA scores that were overall borderline normal. The MOCA score, the most commonly used cognitive screening study worldwide, being borderline normal in the TBI and GWI groups is important as many members in these groups would have missed being evaluated further in view of the normal MOCA scores, a relatively common practice. The study also presents a remarkable validation of the notable and extensive behavioral neurological repertoire of Andrew Kertesz's "Banana Lady" exposition (43), wherein he tabulated 17 different frontal network syndromes and based the frontal behavioral inventory test on these findings. Herein we noted a veritable number of 16 differing frontal network syndromes aside from those evaluated by the Frontal Behavioral Inventory evaluation (n = 24). The more common sub-syndromes within the realm of FTD, delineated in this study, included GGS, KBS, DMIS, IEED and prosopagnosia. With regard to GGS, there was a trend toward a greater association with the TBI and GWI categories. At the time of writing, GGS have been reported in association with FTD in only two single case reports (44, 45). However, the remarkable frequency we detected in our retrospective series is noteworthy and warrants further attention as such syndromes are not only important for the person and family to understand, but have potential treatment and management options available. It may also be an important example of cerebral diaschisis with at times increased brain function and even superior or superlative brain functions developing particularly after TBI. Knowing more precise sub-syndromes and their etiologies enables the first step needed to deliver a precision medicine intervention.

From a pathophysiological point of view, the syndromes may be understood, with regards to the perspective of:

1. Anatomical – the particular frontotemporal lesions predilection consequent to TBI.
2. White matter fiber tract level disruption from the anterior temporal lobe to the inferior frontal lobe, the uncinate fasciculus.

TABLE 3 Initial presenting syndromes of less common FTD subsyndromes.

Disinhibitory syndromes	
• Field dependent behavior (imitation behavior, utilization behavior)	3
• Hypersexuality including, gender dysphoria	3
• Extreme happiness and jocularity	2
• Hyperorality: eating about one gallon of ice cream per day	1
• Lost fear of alligators as presentation (as part of Klüver Bucy Syndrome)	1
• Hyperekplexia/startle reflex, new onset	1
Diaschisis related	
• New artistic abilities (art or music)	3
• Pan artistic ability (music, illustrative art, poetry, culinary, performing arts, oratorship, philosophy)	1
• Stand-up comedian, increased literary skills, music skills, hypersexuality	1
• Architectural brilliance	1
• Hypervisual illusory spread syndrome	1
• Continuous spontaneous sudden onset hyper-narration, post right middle cerebral artery stroke	1
• Profound hypergraphia with compilation of 2 books of arbitrary notes, comments, presented	1
• Excessive reading of the King James Bible (1,200 pages), 7 times at time of first visit	1
• Profound new interest in astrophysics, loquacity and hypergraphia	1
Abulia related	
• Diogenes syndrome (senile squalor syndrome)	1

3. Network level impairment: salience network.
4. Diaschisis, including subtypes of diaschisis at rest, functional, connectional and connectomal.

The particular predilection of inferior frontal and anterior temporal lobe injury post TBI is worth emphasis as depicted by neuropathological data (Figure 6) (46). This important pathological data has also been confirmed in the neurosurgical literature. Contusion indices in non-missile head injury ($n = 151$) revealed mean contusion indices (MCI) much more commonly in the frontal (MCI 5.7) and temporal lobes (MCI 5.4) as opposed to the sylvian fissure (MCI 2.7), occipital lobe (MCI1.2), parietal lobe (MCI 0.7) and cerebellum (MCI 0.9) (47).

With regards to GGS, the most common FTD sub-syndrome identified, the underlying abnormality may include: impairment of the anatomical circuit malfunction (uncinate fasciculus), a larger network dysfunction impacting the salience network, or secondary to a right hemisphere lesion, with diaschisis phenomena rendering the syndrome of GGS. The abnormal disinhibition FRSBE T-score association was interesting in that this might be a potential mechanism of diaschisis impacting the complex left temporal lobe cognitive and behavioral processes. An overarching insight premise relates to the extensive array of syndromes that are best explained by the brain network theory of remote injury (von Monokow) in both hodological and hodotopical effects of under-activation and overactivation (48). Brain network science (small world, rich club hubs) and the various hodological effects after lesions with clinically apparent diaschisis syndromes (at rest, functional, connectional) demand that the entire brain be evaluated no matter where the lesion topography (49). These can be accomplished by using metabolic positron emission tomography (PET) and resting state brain network imaging. Using such neuroimaging approaches this may further facilitate more precise diagnoses with more uniform subgroup identification. Furthermore, targeted treatments are then more likely to be successful as the specific brain area or network has been identified. The uncinate fasciculus matures the latest (during the 3rd and 4th decades) of all white matter fiber tracts (50). One may surmise that similar to other tertiary cortical circuitry this major tract may be the most vulnerable of all, to a panoply of neurological insults such as TBI, vascular and neurotoxicological injury. As it links the two of the most significant higher cortical function brain centers (frontal, temporal), the presentation of syndromes such as GGS would not be surprising. Furthermore, the study also illustrates, that, far from only focusing on neurological deficits, neurological hyperfunction in its myriad forms is equally informative and important for treatment prospects. Karl Deisseroth, one of the inventors of optogenetics notably proclaimed that the most accurate and insightful ways of deciphering the human brain is through language and the clinical interview, more so than sophisticated current neuroimaging modalities (51). At the present time, scored questionnaires such as the FRSBE, FBI and BFI are key tools that assist in deciphering these syndromes.

The salience network is a pivotal psychiatric network, linked to the to p-factor (psychopathology factor). The salience network is thought to play an important role, acting as a switch to deploy other major cerebral networks. Hence, lesions that affect this network, as an orchestrator influencing other networks, would have a disproportionate and at the same time may serve as a potential therapeutic target for neuromodulation devices, for example (52).

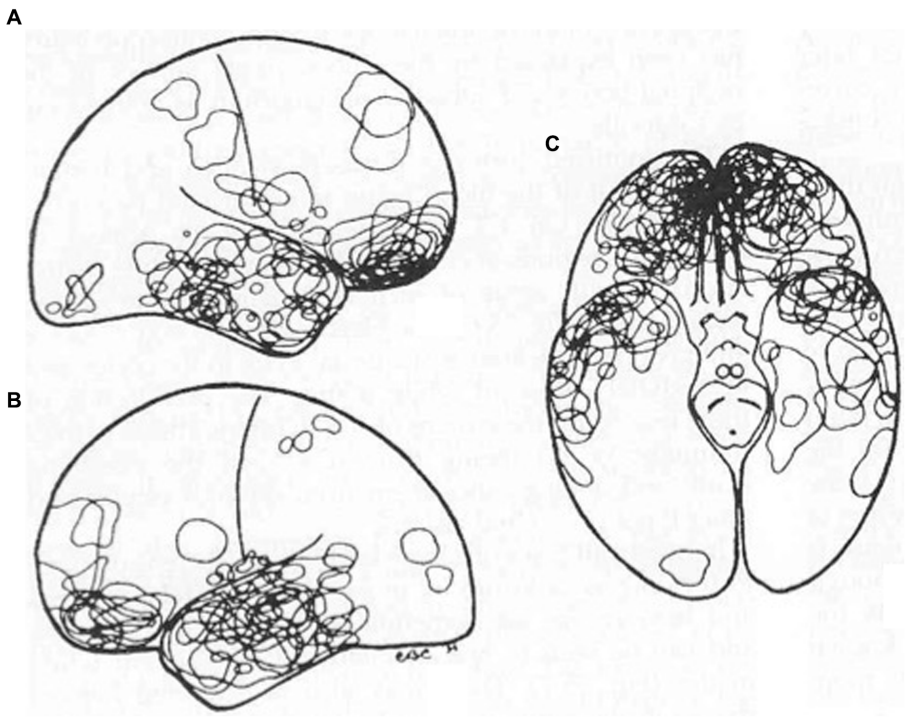

FIGURE 6
TBI: Fronto-temporal injury predilection distribution of contusions in 40 consecutive autopsy cases. Reproduced from Courville, Pathology of the central nervous system, Part 4 (46).

Behavioral and cognitive disorders are especially prone to failure in the constant stimulation and complicated nature that is part of the information age. This requires sustained attention, effective executive function and insightful reasoning for optimal decision-making, appropriate impulse control and inhibition of responses (53). The extensive networks and highly evolved cells, such as pyramidal, spindle and fork cells, that are characteristic of the association cortices, in particular, are targeted. No effective treatments currently exist, and the pharmaceutical industry has recently de-emphasized research in these areas. The reasons include the complexity, the uniquely significant primate association as opposed to the traditional rodent models, that have minimal association cortices. As FTD syndromes originate in the most plastic areas of the brain, these may also hold the promise of providing opportunities for future successful interventions (54). Recent wars have highlighted two signature syndromes that afflict a significant number of deployed personnel. Both affect brain regions with syndromes that are difficult to diagnose and treat. Mild and moderate traumatic brain injury (mTBI) and GWI fall within the domain of FTD (7, 39, 55). These constitute a panoply of disorders, where the presentation is predominantly behavioral, more so than with cognitive impairments. Decoding these syndromes and their causes, are pivotal to potentially effective treatments.

How to make sense of this extensive panoply of syndrome? Frontotemporal syndromes can be viewed as a generic syndrome that encompasses and at times overlaps with several other neurological and neuropsychiatric conditions. Almost all can be subserved under the three principles frontal syndromes of abulia, disinhibition and executive dysfunction in various combinations (Figure 7). Importantly, FTD commonly co-occur with several others, both neurological and neuropsychiatric syndrome. The study also allows additional insights into these FTD syndrome complexes. For example, suicide rates were reported to be 56% higher in Veterans with TBI when compared to veterans without TBI. Suicide rates in US military veterans increased greater than 10-fold from 2006 to 2020 with presumed associations being more frequent mental health conditions, substance abuse, and firearm related violence gun violence (56). This study provides, perhaps an even more likely possibility. The predilection of TBI for the frontotemporal/uncinate fasciculus/salience network components harbor inhibitory circuitry, impulse control, as well as emotional regulation. A very plausible explanatory factor may related to the dysregulation of this important control circuitry which might explain the propensity for suicidal incidents.

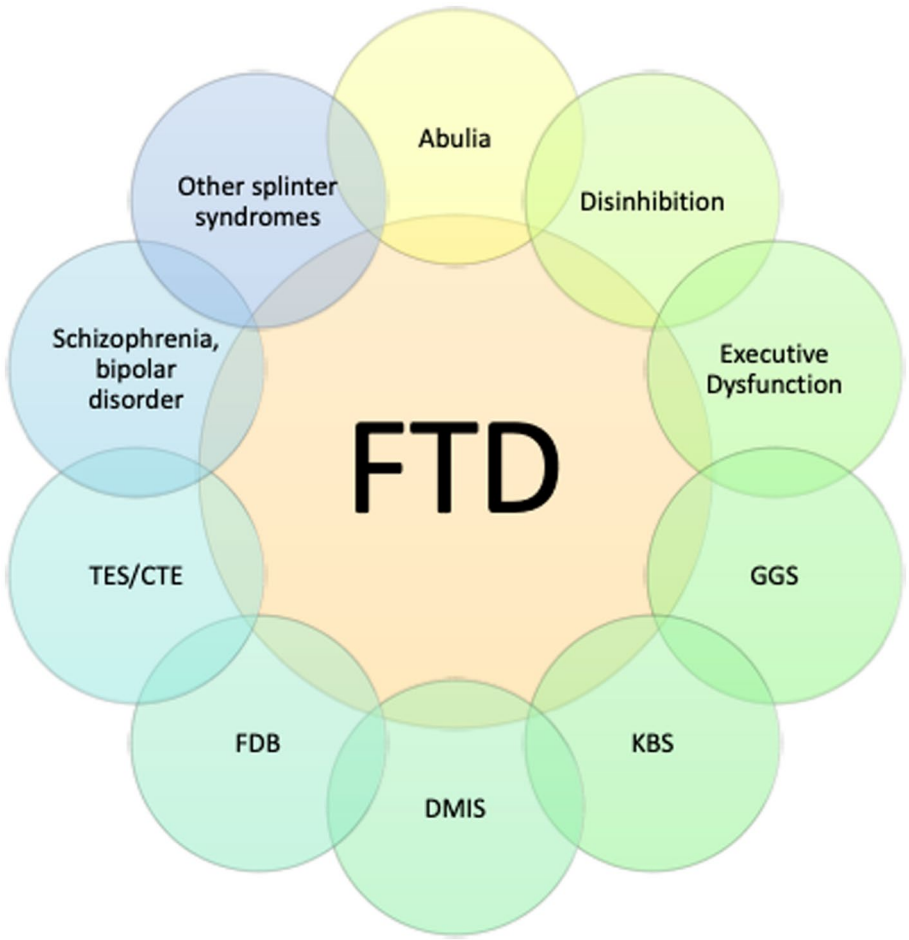

FIGURE 7
Frontotemporal disorders as a generic disorder encompassing many other associated syndromes. GGS - Geschwind-Gastaut syndrome, KBS - Klüver-Bucy syndrome, DMIS - delusional misidentification syndrome, FDB - field dependent behavior (imitation and utilization behavior), TES/CTE - traumatic encephalopathy/chronic encephalopathy syndrome.

Potential limitations and strengths of the review

The most important shortcoming of this study includes the lack of comparison group. Data collection was often incomplete and there was susceptibility to selection and measurement bias. Another limitation pertains to the imprecise assessment of both PTSD and migraine in this population and this data could not be reliably included. Migraine PTSD/depression/anxiety were commonly encountered in this population group. Although these syndromes were ubiquitous syndromes in the FTD population as a whole, more careful delineation amongst the subgroups were however not possible because of a wide variety of heterogeneous assessment scales. Reports from civilian TBI populations are known to be associated with PTSD in almost half the patients (57). The small number of women represented ($n = 10$) although all had the same comprehensive evaluations, does not allow further analysis of gender specific differences and is likely due to the predominance of combat related veterans in this analysis.

Scientific analysis may be regarded as having two basic approaches; the traditional hypothesis driven approach or one that uses a data driven approach. The former has a specific prediction based on a proposed hypothesis and is based on intuition. The data driven approach uses extensive data accrued which enables detection of specific patterns allowing a much more veritable hypothesis formulation. A major advantage of a case series, such as the present one, is that it can be regarded as a screening tool for the most plausible hypotheses that merit further investigation. Hence the strengths of this case series include; high external validity, a wide range of patients sample, the study was inexpensive, short in duration and no interference in the treatment process. A case series has specific advantages in generating new hypotheses and treatment efficacy and the external validity of a case series frequently exceeds that of a randomized controlled trial.

Future recommendations: a precision medicine approach to cognitive and dementia care syndrome, etiology, and co-pathology

Increasingly a precision medicine approach is being heralded both from a syndrome and pathological treatment point of view. Recognizing multiple neuropathological entities in people with dementia improves understanding of diagnosis, prognosis, and expected outcomes from therapies (58). Rapidly accruing evidence is emerging for the efficacy of realm of lifestyle/behavioral interventions in most chronic neurological disease including cognitive impairment, Alzheimer's disease, Parkinsons and more recently frontotemporal dementias (59–61). In addition, a surge of recent neuromodulatory device-based interventions such as magnetic and electrical brain stimulation devices, have shown promise for conditions such as Alzheimer's, depression, schizophrenia and PTSD for example (62–65). However, a precision medicine type approach is first required to decipher the most likely underlying etiology, whether vascular compromise, biochemical deficiencies or neurotoxicological factors and eliminate these as a first step, if possible. For this reason, one of the objectives of this analysis was to pave the way for the establishment of a registry of people with FTD with deconstructing the FTD syndromes, similar to what Stephen Stahl, amongst others, have long proposed in neuropsychiatric disease (66). Once biochemical, toxins, infections and inflammatory abnormalities have been corrected wherever possible, the lifestyle/behavioral interventions can be initiated and monitored for success. The earliest neurobiological defect of cognitive disorders may well be at the neurovascular level with both clinical and neuroimaging studies supporting impaired cerebrovascular reactivity impairment as the first sign of compromise (67). This underscores the essential role of physical exercise which induces both generalized cardiovascular and cerebrovascular health as well as neurotrophic factors that lead to neurogenesis and augment brain circuitry (68). Physical exercise has particularly potent brain protective effects and has been shown to reduce the incidence of dementia by up to 50%. Healthy diet adherence, such as the various categories of keto type low carbohydrate, MIND diet and Mediterranean-type diet have consistently shown reduction in cardiovascular disease, cancer and dementia (69). Working memory may be regarded as the core frontal lobe function central to all other processes including attention, memory, executive function and inhibition, that improve with cognitive exercises that have been developed, such as Brain HQ and Cogmed computerized programs. Once optimization of lifestyle/behavioral factors has been attained, augmentation of the brain's plasticity with neuromodulation (t-DCS, TMS, noninvasive vagal stimulation) devices may be implemented in an intervention group and a control group in groups of similar etiology, with greater chance of success. This has recently been confirmed in a pivotal study specifically for frontotemporal degenerations. FTD neurophysiological oscillatory signatures of gamma and theta to alpha wave coupling have been identified, opening the way for both pharmacological targets and neuromodulation interventions (70).

Frontotemporal syndromes, emanating from TBI and GWI pathophysiological processes, occur in the most sensitive and yet most plastic areas of the brain, with the frontal and anterior temporal lobes being preferentially vulnerable to degeneration during a person's lifespan. However, the emerging concepts that the cerebral networks are impacted, as opposed to only focal lesions, are in support of lifestyle and vascular health promotion that can modify this aging process (71). The brain has tremendous neuroplasticity capability, having 4 x the plasticity of muscles, for example (72). An important recent study in FTD amelioration with physical exercise, emphasizes the efficacy and critical role of physical exercise (59). The accompanying editorial entitled that "diagnosis is not destiny" underscored the pivotal impact of physical exercise in people with FTD despite having potentially disadvantageous genotypes (73).

Conclusion

By deconstructing FTD into the multiple subsyndromes and differing etiologies, this study may provide foundational insights, enabling a more targeted precision medicine approach for future studies, both in treating the sub-syndromes as well as the underlying etiological process.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by VHA Institutional Research Board Approval IRBNET ID: 1256151-4. Approval date: 04/11/2020. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because retrospective analysis of existing data.

Author contributions

MH: Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Writing – original draft. FR: Data curation, Investigation, Writing – review & editing. LB: Investigation, Writing – review & editing. CK: Formal analysis, Software, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Mild traumatic brain injury, PTSD symptom severity, and behavioral dyscontrol: a LIMBIC-CENC study

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Background: Behavioral dyscontrol occurs commonly in the general population and in United States service members and Veterans (SM/V). This condition merits special attention in SM/V, particularly in the aftermath of deployments. Military deployments frequently give rise to posttraumatic stress disorder (PTSD) and deployment-related mild TBI traumatic brain injury (TBI), potentially leading to manifestations of behavioral dyscontrol.

Objective: Examine associations among PTSD symptom severity, deployment-related mild traumatic brain injury, and behavioral dyscontrol among SM/V.

Design: Secondary cross-sectional data analysis from the Long-Term Impact of Military-Relevant Brain Injury Consortium – Chronic Effects of Neurotrauma Consortium prospective longitudinal study among SM/V ($N = 1{,}808$).

Methods: Univariable and multivariable linear regression models assessed the association and interaction effects between PTSD symptom severity, as assessed by the PTSD Checklist for the Diagnostic and Statistical Manual, 5th edition (PCL-5), and deployment-related mild TBI on behavioral dyscontrol, adjusting for demographics, pain, social support, resilience, and general self-efficacy.

Results: Among the 1,808 individuals in our sample, PTSD symptom severity ($B = 0.23$, 95% CI: 0.22, 0.25, $p < 0.001$) and deployment-related mild TBI ($B = 3.27$, 95% CI: 2.63, 3.90, $p < 0.001$) were significantly associated with behavioral

dyscontrol in univariable analysis. Interaction effects were significant between PTSD symptom severity and deployment mild TBI ($B = -0.03$, 95% CI: −0.06, −0.01, $p = 0.029$) in multivariable analysis, indicating that the effect of mild TBI on behavioral dyscontrol is no longer significant among those with a PCL-5 score > 22.96.

Conclusion: Results indicated an association between PTSD symptom severity, deployment-related mild TBI, and behavioral dyscontrol among SM/V. Notably, the effect of deployment-related mild TBI was pronounced for individuals with lower PTSD symptom severity. Higher social support scores were associated with lower dyscontrol, emphasizing the potential for social support to be a protective factor. General self-efficacy was also associated with reduced behavioral dyscontrol.

KEYWORDS

dysregulation, concussion, military members, transition introduction, TBI – traumatic brain injury

Introduction

Behavioral dyscontrol is a challenging clinical problem that cuts across traditional diagnostic boundaries. Wotzel and Arciniegas provide an overview of the literature that encompasses a range of terms describing behavioral dyscontrol following injury, which include emotional lability, irritability, anger, aggression, and challenges in self-regulation (1). These various symptoms denoting behavioral dyscontrol present clinically challenging sequelae that frequently impede rehabilitation efforts, disrupt social support networks and compromise optimal recovery (1, 2). The absence of a standardized or universally accepted definition and the limitations in delineating mental and behavioral presentations following TBI contribute to the complexity of behavioral dyscontrol (1). Although a multitude of factors can influence the development and severity of behavioral dyscontrol, posttraumatic stress disorder (PTSD) and traumatic brain injury (TBI) have been identified as important contributors (2, 3). Veterans who have served in combat deployments are at risk of experiencing TBI and developing PTSD, which also increases their risk for behavioral dyscontrol (4). Understanding potential links among PTSD, deployment mild TBI, and behavioral dyscontrol can inform post-deployment healthcare delivery for Service members and Veterans (SM/Vs).

Deployment-related mild TBI can disrupt neural pathways crucial for impulse control (2). Due to heterogeneity in injury, mild TBI may manifest in various behavioral dyscontrol symptoms, including explosive outbursts, verbal and physical aggression, impaired judgment and planning abilities, and limited self-awareness (1, 2, 5). Similarly, some Veterans with PTSD report experiencing challenges with self-regulation, which may also be associated with symptoms of behavioral dyscontrol such as agitation and explosive behavior (1, 2, 5).

The present analysis aimed to investigate the associations between history of deployment-related mild TBI, PTSD symptoms, and behavioral dyscontrol in a cohort of combat SM/Vs. Given that prior work identified poorer outcomes for SM/Vs with TBI and high PTSD symptom severity, we hypothesized that behavioral dyscontrol would be highest among those with deployment-related mild TBI and high PTSD symptom severity (6–8).

Methods

Design

This cross-sectional study utilized data from the baseline visit of the longitudinal, multi-center Prospective Longitudinal Study (PLS) conducted by the Long-term Impact of Military-relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) (9). The primary objective of the PLS is to assess the effects of mild TBI (s) and other comorbidities on neurological and psychological outcomes among combat-exposed SM/Vs (10). During the baseline visit, participants completed a comprehensive assessment, which included structured interviews, questionnaires, neuropsychological testing, and biometric measurements (11).

Participants

The PLS is conducted across 11 recruitment sites. Enrollment is ongoing, with over 2,000 SM/Vs enrolled. Participants were recruited primarily through targeted mailings. Eligible individuals included SM/Vs who had deployed to a combat zone, were at least 18 years of age, and had no history of moderate to severe TBI or major neurological or psychiatric illnesses resulting in a significant long-term decrease in functional status (e.g., schizophrenia, spinal cord injury) (9). Common comorbidities, including PTSD and depression, were permitted. The study obtained approval from the regional Institutional Review Boards of the participating facilities, and written consent was obtained from all participants before any procedures were conducted. The available sample size for the presented analyses at the time of database extraction was $N = 2{,}069$. Participants were excluded from these analyses for missing data on key measures ($n = 118$) and for noncredible symptom-reporting profiles on the mild

Brain Injury Atypical Symptoms (mBIAS) questionnaire (10) ($n = 143$). These exclusions left a final analytic sample size of $N = 1{,}808$. Within this cohort, 278 experienced TBI during deployment only, 680 TBI from both deployment and non-deployment settings, 507 had TBI solely in non-deployment settings, and 343 individuals had no history of TBI.

Measures

The primary outcome, behavioral dyscontrol, was assessed by self-report using the 10-item Traumatic Brain Injury Quality of Life (TBIQOL) questionnaire, which measures emotional and behavioral dyscontrol, including disinhibition, emotional lability, irritability, impatience, and impulsiveness (11, 12)—the primary characteristics of behavioral dyscontrol. The total score ranges from 10 to 50, with higher scores indicating higher levels of dyscontrol (12).

Independent variables

History of deployment-related mild TBI was evaluated using the Virginia Commonwealth University Retrospective Concussion Diagnostic Interview (VCU-rCDI)—a structured interview developed for the PLS to facilitate the classification of all potential concussive events (PCEs) experienced throughout an individual's lifetime (13). PCEs are first identified via a modified OSU TBI ID interview version (13). Each PCE is evaluated with the VCU-rCDI to determine if it meets the criteria for mild TBI and to gather information on setting, mechanism, and other clinical characteristics (13). Diagnostic determinations were consistent with the VA/ Department of Defense (DoD) standard definition of mild TBI and the American Congress of Rehabilitation Medicine guidelines (14, 15). Variables utilized for this analysis included deployment and non-deployment designation for each mild TBI based on whether the TBI occurred during a combat deployment or some other time during life.

PTSD symptom severity was assessed using the PTSD Checklist for the Diagnostic and Statistical Manual, 5th edition (PCL-5) (16). This 20-item self-report measure utilizes a 5-point Likert scale to evaluate how bothered an individual has been by symptoms associated with PTSD in the past 30 days. Total scores range from 0 to 80, with greater scores indicating greater symptom severity (16). Participants scoring 33 or higher on the PCL-5 were classified as positive for probable PTSD (16).

Covariates

Previous studies have identified key symptoms associated with PTSD, mild TBI, and behavioral dyscontrol (17, 18) that were chosen as covariates for the present analysis.

The Euroqol 5 measures pain/discomfort on a 5-point ordinal scale, allowing respondents to assess their current pain as none, slight, moderate, severe, or extreme (19). Meanwhile, the TBI Qol Pain Interference Short-Form comprises a 10-item questionnaire prompting participants to rate the extent of pain interference across functions like family life, daily tasks, mental health, and overall quality of life. Responses are noted on a 5-point ordinal scale (1–5), and total scores range from 10 to 50 points, with higher scores reflecting greater interference (19).

General Self-Efficacy (GSE) was measured using a 10-item self-reported questionnaire that measures an individual's perceived ability to solve problems and achieve their goals (20). Response options range from 1 (Not at all true) to 5 (Exactly true), with a total score range of 10–50 (20).

The Deployment Risk and Resilience Inventory-2 (DRRI-2) Social Support subscale is a comprehensive self-report assessment tool designed to evaluate the degree of social support available to individuals, particularly those who have experienced military deployment and related challenges (21). It encompasses a range of factors that contribute to an individual's perception of social support, including emotional, instrumental, and informational assistance from family members, friends, and peers (21). The subscale aims to quantify the extent to which individuals perceive themselves as having access to a robust support network during and after deployment. Respondents are asked to rate their level of agreement or frequency on a Likert-type scale from 1 to 5, where higher scores indicate higher levels of perceived social support (21).

Lifetime Mild TBI history is assessed in LIMBIC-CENC PLS using a validated process, cataloging each participant's potential concussive events through a modified Ohio State University TBI Identification (OSU TBI-ID) (12). A retrospective Concussion Diagnostic Interview generates a preliminary algorithm based TBI diagnosis, which undergoes rigorous review against medical records by a centralized expert committee. Final determinations align with the VA/DoD common definition of mild TBI.

Blast mechanisms are classified as blast-related or not, and if blast-related, as pure blast or mixed blast-blunt. Subclassifications for analysis include 1–2 mild TBIs vs. 3+ (repetitive mild TBI), mild TBIs with or without PTA, blast-related or not, and pure blast vs. non-blast/ mixed blast-blunt mild TBIs (12).

We also included sociodemographic factors (age, sex, education, and race/ethnicity) selected based on the existing literature to adjust for their potential impact in multivariable analysis.

Statistical methods

Demographic and clinical outcomes are reported using means and standard deviation (SD), medians and interquartile ranges (IQR), ranges for continuous variables, and counts and percentages for categorical variables. To compare these variables between deployment-related mild TBI exposure (yes/no) group, we used non-parametric Wilcoxon rank sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate. There were no independent or interaction effects of non-deployment-related mild TBI on behavioral dyscontrol; therefore, non-deployment TBI was excluded from the analysis. Univariable and multivariable linear regression models assessed independent and interactive associations between variables of interest and behavioral dyscontrol. The multivariable model included the interaction term and adjusted for age, sex, ethnicity, race, Euroqol 5 – pain dimension scores, DRRI-2 Social Support scores, and GSE scores. Multicollinearity was considered tolerable if the generalized variance inflation factor (GVIF) was <2.24 (22). Johnson-Neyman analysis probed significant interaction effects. We report Betas (B) with 95% confidence intervals (CI) for each

analysis. Statistical significance was assessed at the 0.05 level, and all analyses were performed using R v. 4.1.2 (23).

Results

In our analytic sample of 1,808 individuals, 53% ($n = 958$) had deployment-related mild TBI, and 47% ($n = 850$) had no history of deployment mild TBI. Studying both deployment- and non-deployment-related mild TBI is fundamental for a comprehensive understanding of the diverse causes, mechanisms, and long-term impacts of TBI and the individuals affected by these injuries (24, 25). Table 1 presents the demographic characteristics of the sample, stratified by deployment-related mild TBI status. Most participants were male (87.0%) and White (73.0%), with a median age of 39 years (IQR: 33, 48). There were significant differences in behavioral dyscontrol scores between SM/Vs with ($M = 23.6$, SD = 6.8) versus without ($M = 20.4$, SD = 6.9) history of deployment-related mild TBI. Social support scores were higher among SM/Vs without ($M = 40.1$, SD = 7.9) compared to those with a history of deployment-related mild TBI ($M = 38.1$, SD = 8.1). Finally, SM/Vs without a history of deployment-related mild TBI reported greater self-efficacy ($M = 32.7$, SD = 4.7) than SM/Vs with a history of deployment-related mild TBI ($M = 31.4$, SD = 4.8).

Table 2 presents linear regression models among SM/Vs with deployment-related mild TBI. In the univariable analyses, the presence of deployment-related mild TBI ($B = 3.27$, $p < 0.001$ CI [2.63, 3.90]) and PTSD symptom severity (Beta = 0.23, 95% CI: 0.22, 0.25, $p < 0.001$) were each independently associated with behavioral dyscontrol. Multivariable analysis indicated a significant interaction effect ($B = -0.03$, 95% CI: −0.06, −0.01, $p < 0.001$) between deployment-related mild TBI and PTSD symptom severity. Johnson-Neyman analysis (see Figure 1) indicated a critical score of 22.96, such that the interaction effect was significant when PCL-5 scores were between 0 and 22.96. This indicates that the impact of deployment-related mild TBI was significantly associated with behavioral dyscontrol when PCL-5 scores were ≤ 22.96.

Among SM/Vs who experienced both blast and non-blast deployment-related mild TBI, but no PTSD, dyscontrol scores were found to be 1.04 points higher compared to those with blast-only deployment-related mild TBI ($B = 1.04$, 95% CI: 0.09, 1.98, $p = 0.005$).

Dyscontrol scores among SM/Vs with deployment-related mild TBI but no PTSD symptoms, were 1.38 points higher than those with deployment-related mild TBI after adjusting for other covariates ($B = 1.38$, 95% CI: 0.36, 2.41, $p = 0.005$). Among SM/Vs without deployment-related TBI (reference group), each one-point increase in the PTSD total score was associated with a 0.21-point increase in dyscontrol scores ($B = 0.21$, 95% CI: 0.18, 0.23, $p < 0.001$). Furthermore, accounting for other variables, there was a decrease of 0.24 points in dyscontrol scores ($B = -0.24$, 95% CI: −0.30, −0.17, $p < 0.001$) for every one-point increase in general self-efficacy scores. Similar findings were obtained for social support scores ($B = -0.06$, 95% CI: −0.09, −0.02, $p < 0.001$).

Figure 2 interaction effect between deployment-related mild TBI status and PTSD symptom severity scores on behavioral dyscontrol. The slope of PTSD severity scores is steeper in SM/Vs without deployment-related mild TBI than those with no deployment-related mild TBI have lower observed behavioral dyscontrol total scores.

Discussion

We hypothesized that SM/Vs with greater PTSD symptom severity and deployment-related mild TBI would report increased behavioral dyscontrol. Our results partially supported this hypothesis, demonstrating that PTSD symptom severity and deployment-related mild TBI were associated with behavioral dyscontrol in univariable and multivariable models adjusting for race, ethnicity, and sex. Further, results indicated a significant interaction effect between deployment-related mild TBI and PTSD symptoms, in which the effect of deployment-related mild TBI was significant only among those with *lower* severity of PTSD symptoms (PCL-5 scores of 0–23). This finding suggests a clear effect of deployment-related mild TBI when PTSD symptoms are lower, but that when PTSD symptoms are more severe, PTSD symptoms likely account for effects on behavioral dyscontrol. Moreover, those with high social support and self-efficacy scores also reported significantly lower scores on behavioral dyscontrol.

The observed elevation in dyscontrol scores among SM/Vs with both blast and non-blast deployment-related mild TBI, as opposed to those with blast-only TBI, provides a noteworthy point of discussion in the broader context of TBI research. The documented difference in dyscontrol scores, even after adjusting for other relevant factors, underscores the complexity of deployment-related mild TBI-related outcomes and the importance of considering injury mechanisms. The distinct neurological effects associated with blast and non-blast injuries may contribute uniquely to dyscontrol, reflecting the complex interplay between injury characteristics and resulting behavioral sequelae. Moreover, the absence of PTSD symptoms in the studied population emphasizes the specific impact of TBI subtypes on dyscontrol, independent of comorbid psychological conditions.

The association between elevated social support scores and diminished behavioral dyscontrol scores among SM/Vs emphasizes the potential importance of social support as a protective factor. Existing research demonstrates that social support from the military unit, friends, and family buffer the relationship between stressor exposure and posttraumatic stress symptoms. Social support from familial, peer, or community relationships is a stabilizing force that helps SM/V navigate the complexities of life after military service (26). Support networks can offer emotional reassurance, facilitate coping strategies, and provide a sense of belonging and understanding (26). Wilks and colleagues analyzed 2,467 Iraq/Afghanistan-era Veterans and found that TBI was associated with suicidal ideation, and social support was negatively associated with suicide ideation. Conversely, limited social support has been linked to heightened levels of stress, increased symptom severity, and a more challenging rehabilitation journey (27, 28). These findings, coupled with the findings in our study, help explain the connections between PTSD symptom severity and behavioral dyscontrol symptoms, and may bolster the need for additional social and family support as treatment adjuncts to lower the risk of these adverse outcomes.

Similarly, our results suggest that greater self-efficacy may also be protective and lead to decreased behavioral dyscontrol. The ability to effectively navigate challenges impacts cognitive, behavioral, affective, and functional outcomes and demonstrates a significant protective influence (29, 30). Research consistently demonstrates that high levels of self-efficacy increase resiliency among SM/Vs and are closely associated with better mental health outcomes (29, 30). Self-efficacy may also be an important factor in treatment. In one study of

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TABLE 1 Summary of demographic variables stratified by deployment-related mild TBI.

Variable	All ($N = 1808$)	No deployment-related mild TBI: $N = 850$	Deployment-related mild TBI: $N = 958$	p-value
Age at baseline (yr)				
Mean (SD)	41.2 (10.0)	42.1 (10.4)	40.3 (9.5)	<0.001[k]
Median (IQR)	39.0 (33.0, 48.0)	41.0 (34.0, 50.0)	39.0 (33.0, 47.0)	–
Range	(22.0, 76.0)	(23.0, 76.0)	(22.0, 72.0)	–
Ethnicity				
Hispanic or Latino	299 (17%)	122 (14.4%)	177 (18.5%)	0.014[c]
Not Hispanic or Latino	1486 (82%)	721 (84.8%)	765 (79.9%)	–
Not Hispanic or Latino	23 (1%)	7 (0.8%)	16 (1.7%)	–
Race				
White	1314 (73%)	618 (72.7%)	696 (72.7%)	0.052[c]
Black/African American	328 (18%)	159 (18.7%)	169 (17.6%)	–
Asian/American Indian/Alaska Native/ or Pacific Islander	59 (3%)	34 (4%)	25 (2.6%)	–
Don't know/Not sure/Refused/Other	107 (6%)	39 (4.6%)	68 (7.1%)	–
Gender				
Female	233 (13%)	156 (18.4%)	77 (8%)	0.001[c]
male	1574 (87%)	694 (81.6%)	880 (91.9%)	–
Marital status				
Never married	264 (15%)	134 (15.8%)	130 (13.6%)	0.005[s]
A member of an unmarried couple	25 (1%)	17 (2%)	8 (0.8%)	–
Married	1101 (61%)	514 (60.5%)	587 (61.3%)	–
Divorced	326 (18%)	150 (17.6%)	176 (18.4%)	–
Separated	75 (4%)	25 (2.9%)	50 (5.2%)	–
Widowed	14 (1%)	10 (1.2%)	4 (0.4%)	–
Refused	3 (0%)	0 (0%)	3 (0.3%)	–
Emotional and behavioral dyscontrol total score				
Mean (SD)	22.1 (7.0)	20.4 (6.9)	23.6 (6.8)	<0.001[k]
Median (IQR)	22.0 (17.0, 27.0)	20.0 (15.0, 25.0)	23.0 (18.0, 28.0)	–
Range	(10.0, 45.0)	(10.0, 42.0)	(10.0, 45.0)	–
Pain / Discomfort dimension				
Mean (SD)	2.4 (0.9)	2.2 (0.9)	2.6 (0.9)	<0.001[k]
Median (IQR)	2.0 (2.0, 3.0)	2.0 (1.0, 3.0)	2.0 (2.0, 3.0)	–
Range	(1.0, 5.0)	(1.0, 5.0)	(1.0, 5.0)	–
Social support				
Mean (SD)	39.1 (8.1)	40.1 (7.9)	38.1 (8.1)	<0.001[k]
Median (IQR)	40.0 (34.0, 45.0)	41.0 (36.0, 46.0)	39.0 (33.0, 44.0)	–
Range	(10.0, 50.0)	(10.0, 50.0)	(10.0, 50.0)	–
General self-efficacy				
Mean (SD)	32.0 (4.8)	32.7 (4.7)	31.4 (4.8)	<0.001[k]
Median (IQR)	32.0 (29.0, 36.0)	32.0 (30.0, 37.0)	31.0 (29.0, 35.0)	–
Range	(12.0, 40.0)	(12.0, 40.0)	(14.0, 40.0)	–

(Continued)

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TABLE 1 (Continued)

Variable	All ($N = 1808$)	No deployment-related mild TBI: $N = 850$	Deployment-related mild TBI: $N = 958$	p-value
PTSD				
No	1214 (67%)	669 (78.7%)	545 (56.9%)	<0.001[c]
Yes	594 (33%)	181 (21.3%)	413 (43.1%)	–
PTSD symptom severity score				
Total PTSD symptom severity score (out of 80 pts) PCL5_TOT: Mean (SD)	25.1 (18.4)	18.9 (16.9)	30.6 (18.0)	<0.001[k]
Median (IQR)	22.0 (10.0, 38.0)	14.0 (5.0, 29.0)	29.0 (16.0, 44.0)	–
Range	(0.0, 78.0)	(0.0, 76.0)	(0.0, 78.0)	–

Number of missing values in the No Deployment-related mild TBI/Deployment-related mild TBI groups: Gender: = n = 0/n = 1, Pain / discomfort dimension: n = 0/n = 1, PTSD symptom severity score (out of 80 pts): n = 10/n = 6. [c] Chi-squared test, [k] Kruskal-Wallis test, [f] Fisher's exact test, [s] Chi-squared test by Montecarlo simulation.

TABLE 2 Behavioral dyscontrol score by deployment-related mild and PTSD.

Variable	Univariable coefficient (95% CI)	p-value	N used	Multivariable coefficient (95% CI)	p-value
Deployment-related TBI	3.27 (2.63, 3.90)	<0.001	1808	1.38 (0.36, 2.41)	0.008
PTSD	0.23 (0.22, 0.25)	<0.001	1800	0.21 (0.18, 0.23)	<0.001
Deployment-related TBI × PTSD	–	–	–	−0.03 (−0.06, 0.00)	0.046
Age at baseline (yr)	−0.06 (−0.09, −0.03)	<0.001	1808	−0.02 (−0.06, 0.02)	0.34
Pain/Discomfort dimension	2.45 (2.11, 2.79)	<0.001	1807	0.26 (−0.06, 0.57)	0.11
Social Support	−0.29 (−0.33, −0.26)	<0.001	1808	−0.06 (−0.09, −0.02)	<0.001
Ethnicity					
Not Hispanic or Latino	−0.68 (−1.55, 0.19)	0.13	1808	0.60 (−0.12, 1.31)	0.10
Do not know/Not sure/Refused	−1.43 (−4.41, 1.55)	0.35	1808	−0.35 (−2.69, 2.00)	0.77
Hispanic	Reference			Reference	
Race					
Asian/Pacific Islander/American Indian or Alaska Native	−0.61 (−2.45, 1.22)	0.51	1808	0.15 (−1.26, 1.55)	0.84
Black or African American	−0.48 (−1.33, 0.37)	0.27	1808	−1.79 (−2.46, −1.13)	<0.001
Do not know/Not sure/Refused/Other	0.17 (−1.22, 1.55)	0.81	1808	−0.35 (−1.53, 0.83)	0.56
White	Reference			Reference	
Gender: Male	0.19 (−0.78, 1.15)	0.71	1807	0.25 (−0.52, 1.02)	0.52
General Self-Efficacy	−0.64 (−0.70, −0.58)	<0.001	1808	−0.24 (−0.30, −0.17)	<0.001
Number of mild TBI[a]	0.64 (0.47, 0.80)	<0.001	1808	–	–
Blast-related TBI					
No TBI at all	−3.69 (−4.95, −2.43)	<0.001	1808	0.80 (−0.43, 2.03)	0.20
Non-Blast only	−1.46 (−2.60, −0.33)	0.012	1808	1.50 (0.51, 2.50)	0.003
Blast and Non-blast	0.22 (−0.98, 1.42)	0.72	1808	1.04 (0.09, 1.98)	0.031
Blast only	Reference			Reference	
Years of service	−0.06 (−0.10, −0.03)	<0.001	1807	0.00 (−0.0.4, 0.04)	0.98
Mental health treatment in the past 6 months					
- No response/Don't know/Not sure	−2.96 (−10.58, 4.66)	0.45	1808	−1.00 (−8.47, 6.47)	0.79
Yes	4.09 (3.47, 4.71)	<0.001	1808	−0.06 (−0.63, 0.51)	0.83
No	Reference			Reference	

[a] The number of mild TBI is the same as number of lifetime TBI if none of the TBIs are moderate-severe.

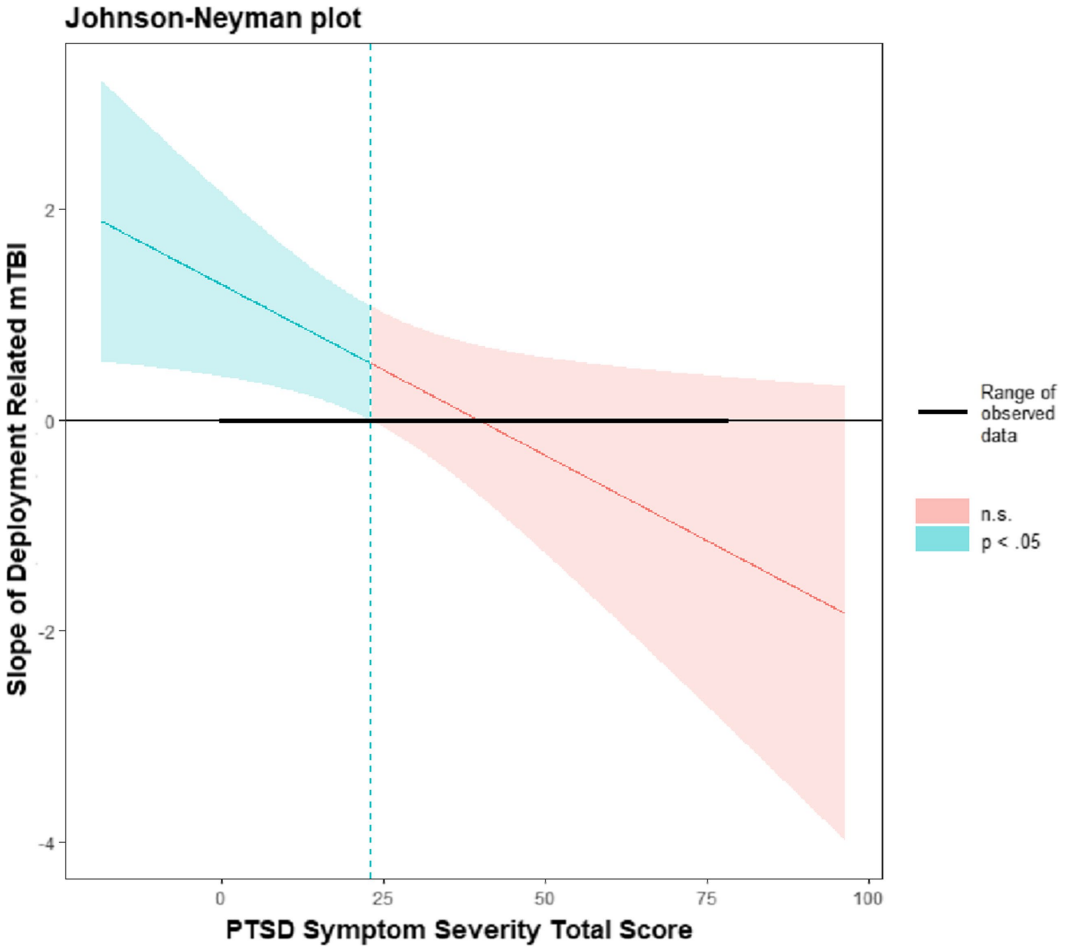

FIGURE 1
Johnson-Neyman intervals.

SMs receiving cognitive rehabilitation treatment (29), perceived self-efficacy at the beginning of treatment was associated with treatment engagement, suggesting self-efficacy mediates treatment outcomes. Increasing patients' level of self-efficacy may be important for successful treatment of psychological distress in SM/Vs (30). Greater self-efficacy is associated with better mental health outcomes, such as enhanced coping skills, increased resilience, and reduced levels of anxiety and depression (29). The perception of being capable of resolving problems and attaining personal goals may empower SM/Vs to exert greater control over their actions and reactions, subsequently mitigating symptoms of behavioral dyscontrol (31).

Study strengths

The present analysis has several inherent strengths. The sample size was substantial, representing 1,808 well-characterized SM/Vs with combat exposure from the LIMBIC-CENC multi-center cohort. This ensured robustness as we rigorously evaluated their lifetime mild TBI histories and benefited from the extensive data collected in the comprehensive assessments. The study controlled for symptom validity by excluding participants with non-credible symptom profiles on a validated measure.

Study limitations

While our study sheds light on the effects of PTSD and deployment-related mild TBI on behavioral dyscontrol, it is essential to acknowledge several limitations. A significant limitation is that many of the study measures were self-reported and therefore cannot provide definitive clinical diagnoses. Additionally, inherent to the cross-sectional design, causal inferences and temporal dynamics remain constrained. Notably, the study lacks a systematic assessment of structural brain abnormalities, medications, and psychological evaluations at baseline which may have explained variance in our results.

Implications for future research

Further research is warranted to identify how self-efficacy and social support influence behavioral dyscontrol in SM/Vs with PTSD and/or deployment-related mild TBI. Longitudinal studies can contribute to understanding the temporal relationship between self-efficacy and behavioral dyscontrol symptoms, elucidating whether changes in self-efficacy precede or follow improvements in behavioral regulation. Investigating the influence of social

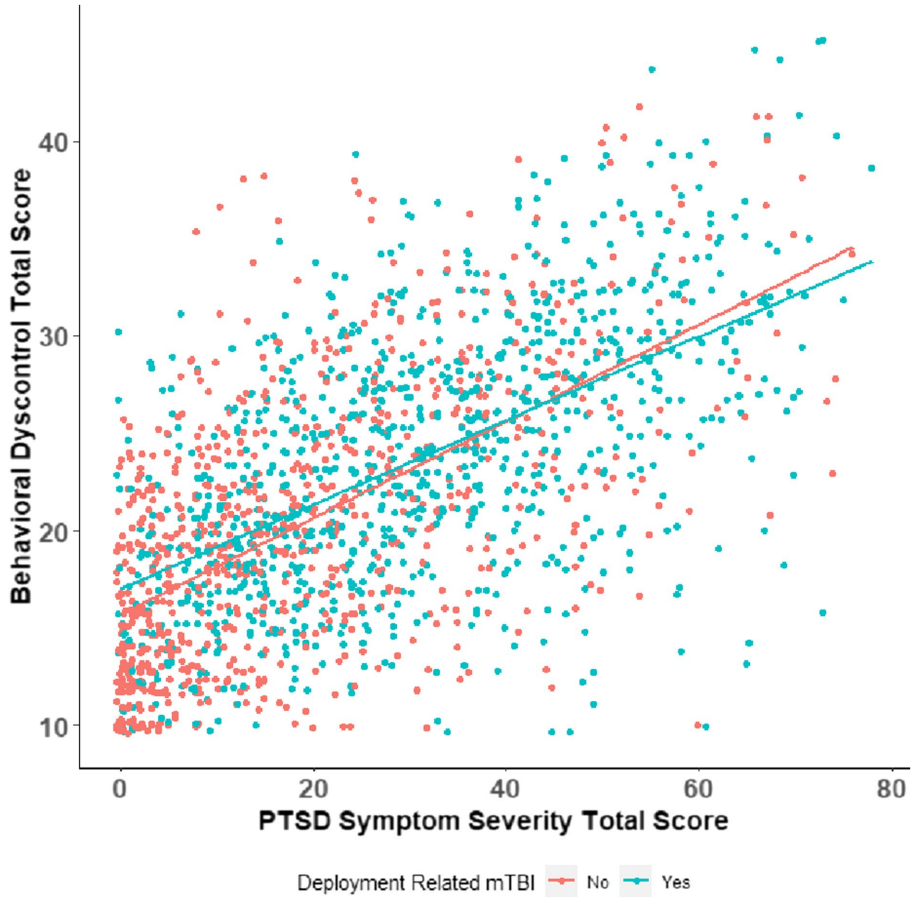

FIGURE 2
Interaction plot of deployment mild TBI and PTSD symptom severity.

support can provide valuable insights into the interpersonal factors that contribute to behavioral dyscontrol symptoms and may inform interventions to improve behavioral regulation. Examining the types of support (e.g., emotional, instrumental, informational) and the sources of support (e.g., family, friends, healthcare providers) can provide a comprehensive understanding of how different aspects of social support impact behavioral regulation (32). A thorough exploration is critical to understanding the complex relationship of deployment-related mild TBI, PTSD symptom severity, and related psychosocial constructs in shaping behavioral dyscontrol among SM/Vs. Future research using longitudinal designs should provide a more comprehensive understanding of the temporal dynamics between deployment-related mild TBI, PTSD, and dyscontrol, which may influence the observed associations between these conditions.

Conclusion

PTSD and mild TBI are commonly diagnosed during or following military deployments, and both are associated with behavioral dyscontrol in SM/Vs. The present analysis demonstrated that PTSD symptom severity and deployment-related mild TBI were each associated with behavioral dyscontrol in univariable and multivariable models adjusting for race, ethnicity, and sex. Deployment-related mild TBI primarily contributes to behavioral dyscontrol in the absence of prominent PTSD symptom severity. The findings highlight the complex relationship between PTSD symptoms and mild TBI resulting from deployment, particularly with regard to behavioral dyscontrol. Consequently, there is a pressing need for a comprehensive understanding and targeted interventions within clinical, research, and policy spheres, given the interdependence of these conditions.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System. https://fitbir.nih.gov/.

Ethics statement

The studies involving humans were approved by the local Institutional Review Boards at all eleven prospective longitudinal study enrollment sites. The studies were conducted in accordance with

the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

KS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. SMa: Formal analysis, Methodology, Visualization, Writing – review & editing. WW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing – review & editing. ZO: Conceptualization, Data curation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. TP: Methodology, Writing – review & editing. SMi: Methodology, Writing – review & editing. CD-G: Writing – review & editing. KC: Writing – review & editing, Methodology. JR: Formal analysis, Methodology, Writing – review & editing. MO'N: Writing – review & editing, Investigation, Methodology. MP: Conceptualization, Investigation, Methodology, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The economic impact of cannabis use disorder and dementia diagnosis in veterans diagnosed with traumatic brain injury

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Background: Studies have demonstrated that individuals diagnosed with traumatic brain injury (TBI) frequently use medical and recreational cannabis to treat persistent symptoms of TBI, such as chronic pain and sleep disturbances, which can lead to cannabis use disorder (CUD). We aimed to determine the Veterans Health Administration (VHA) healthcare utilization and costs associated with CUD and dementia diagnosis in veterans with TBI.

Methods: This observational study used administrative datasets from the population of post-9/11 veterans from the Long-term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium and the VA Data Warehouse. We compared the differential VHA costs among the following cohorts of veterans: (1) No dementia diagnosis and No CUD group, (2) Dementia diagnosis only (Dementia only), (3) CUD only, and (4) comorbid dementia diagnosis and CUD (Dementia and CUD). Generalized estimating equations and negative binomial regression models were used to estimate total annual costs (inflation-adjusted) and the incidence rate of healthcare utilization, respectively, by dementia diagnosis and CUD status.

Results: Data from 387,770 veterans with TBI (88.4% men; median [interquartile range (IQR)] age at the time of TBI: 30 [14] years; 63.5% white) were followed from 2000 to 2020. Overall, we observed a trend of gradually increasing healthcare costs 5 years after TBI onset. Interestingly, in this cohort of veterans within 5 years of TBI, we observed substantial healthcare costs in the Dementia only group (peak = $46,808) that were not observed in the CUD and dementia group. Relative to those without either condition, the annual total VHA costs were $3,368 higher in the CUD only group, while no significant differences were observed in the Dementia only and Dementia and CUD groups.

Discussion: The findings suggest that those in the Dementia only group might be getting their healthcare needs met more quickly and within 5 years of TBI diagnosis, whereas veterans in the Dementia and CUD group are not receiving early care, resulting in higher long-term healthcare costs. Further investigations should examine what impact the timing of dementia and CUD diagnoses have

on specific categories of inpatient and outpatient care in VA and community care facilities.

KEYWORDS

traumatic brain injury, cannabis use disorder, dementia, veterans, costs, economic burden, healthcare utilization

Introduction

Acute traumatic brain injury (TBI) is associated with a decline in cognition involving one or more domains (learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition) (1), and TBI-related symptoms may persist for more than 6 months post-injury (2). The economic impact of TBI on the United States Department of Veterans Affairs (VA) has been shown to extend over a decade (≥15 years) (3); however, TBI-related costs in the Department of Defense (DOD) or VA may even be underestimated compared with the civilian sector considering that service members and veterans face a higher risk of TBI within their lifetime (4) and are more likely to suffer from injury-related comorbidities, such as chronic pain, post-traumatic stress disorder (PTSD), and other mental health conditions (5–8). Up to 20% of more than 2.5 million deployed service members since 2003 are estimated to have sustained at least one TBI (9, 10). Comorbid mental health diagnosis, substance use disorders, general medical disorders, TBI, history of violent events, and suicide attempts increase the risk of post-injury recurrent hospitalizations and deaths (8).

Mild cognitive impairment prevalence in the US is 6.7% for ages 60–64 years, 8.4% for 65–69 years, and increases to 25.2% for 80–84 years (11). Dementia, a disease of older age, has an overall prevalence of 7.3% among the VA healthcare system users older than 65 years old (12). However, TBI is considered a risk factor for dementia diagnosis (13) and early onset dementia in veterans, defined as dementia onset in age less than 65 years (14). Veterans with comorbid TBI and dementia have a higher healthcare cost burden relative to TBI alone or those with no diagnosis, and older veterans with comorbid TBI and dementia have been shown to have higher annual total Veteran Health Administration (VHA) costs (3).

Individuals with TBI who suffer from chronic pain are at a higher risk of substance and/or opioid use disorder (OUD) (15), and the presence of a TBI history should be considered in clinical decision-making regarding the long-term use of opioids (16, 17). Approximately 23% of individuals with OUD appear to also use cannabis (18). Despite the lack of proven efficacy, cannabis is frequently used to self-treat a wide array of symptoms and conditions associated with post-TBI injury (e.g., chronic pain, headache, sleep disturbances, anxiety, and irritability) (19–21). Cannabis use disorder (CUD) presents as a problematic pattern of cannabis use, with either abuse or dependence, that results in clinically significant functional impairment or distress. Following the cannabis legalization process, similar to the general population, access to cannabis and cannabinoids has increased substantially among VA patients (22). The estimated prevalence of cannabis use in veterans increased from 9% in 2014 to nearly 12% in 2020 (23); however, its efficacy and safety profile remains uncertain (24, 25). While the antioxidant and anti-inflammatory properties of cannabidiol suggest protective effects of cannabis on dementia progression (26), dementia-like structural changes to the brain have also been observed in heavy, chronic cannabis users (27–31).

Dementia is a possible long-term comorbidity of TBI, potentially accelerated by the presence of chronic pain, and secondary substance and cannabis use may have a specific, critical role in the dementia process after TBI. All of these factors individually and in combination are likely to have overlapping and additive health effects that necessitate the availability and use of general and targeted VA healthcare resources. This study aimed to determine the VA healthcare costs associated with CUD and dementia diagnosis in veterans with TBI.

Methods

Participants and data source

Our cohort included participants from the Long-term Impact of Military-Relevant Brain Injury Consortium–Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) phenotype study, which has been described in detail previously (32). The LIMBIC phenotype longitudinal cohort is a large cohort of post-9/11 (including Operation Enduring Freedom and Operation Iraqi Freedom) current and former US military persons who received care in the DoD for at least 3 years, including those exposed and unexposed to TBI(s). The goal of this cohort is to identify chronic sequelae and neurologic comorbidities (cognitive, behavioral, and physical). Sources for this study included healthcare data during deployment (e.g., DoD Trauma Registry [DoDTR] and Theatre Management Data Store [TMDS]), DoD, VA, and non-VA community inpatient and outpatient data.

To ensure accurate TBI status and sufficient data to identify dementia, we included all the participants who enrolled in the Veterans Health Administration (VHA) during the study period, completed the TBI screening, and underwent the VA comprehensive TBI evaluation (CTBIE). The LIMBIC-CENC consortium verified the definition for the TBI severity categories. We used a hierarchical approach to identify TBI and its severity by prioritizing data from DoDTR and TMDS, followed by self-reported data from the CTBIE data collected in the process of clinical care, in the alteration of consciousness or post-traumatic amnesia, and according to ICD-9/10-CM diagnosis codes from the 2012 Armed Forces Health Surveillance System algorithm (33, 35, 36). We also considered ICD codes for post-concussive syndrome as evidence of mild TBI history among veterans without another indicator of a TBI diagnosis. The veterans who did not enroll in VHA and did not complete the initial VA screening for CTBIE were excluded from the study. The index date for TBI was the first date of diagnosis or the date of the CTBIE

assessment; for those with more than one TBI documented, we used the date of the most severe TBI. The research protocol was reviewed and approved by the institutional review boards of the University of Utah and Stanford and was conducted in accordance with all applicable federal regulations.

Measures and outcomes

VA health services costs

Annual per veteran total costs for both VA and non-VA facilities were obtained for fiscal years 2000 through 2020, the last available year for VA cost data. VA national costs are estimated by the Health Economics Resource Center using actual cost data from VA facilities, including adjustments for labor cost differentials across regions (34). Non-VA facility costs were based on reimbursement by VA to non-VA facilities. In our study, the immediate healthcare costs after acute TBI, which may have been paid by the DoD while the veterans were in service, are not captured. All cost data were adjusted for inflation to 2022-dollar values (37).

Dementia diagnosis was identified using ICD-9/10 codes provided by VHA geriatrics and extended care (Supplementary Table S1). ICD 9/10 codes used to identify dementia in older patients have been found to be inaccurate when used in patients under the age of 65 years (38, 39). CUD was identified using ICD-9 (304.3: Cannabis dependence, and 305.2: Nondependent cannabis abuse) and ICD-10 codes (F12: Cannabis-related disorders). We compared the differential VHA costs among the following groups of veterans with a history of TBI: (1) No Dementia diagnosis and No CUD (control group), (2) Dementia diagnosis only (Dementia only), (3) CUD only, and (4) comorbid dementia diagnosis and CUD (Dementia and CUD).

We used a quality-cost conceptual framework to select the covariates and risk factors associated with TBI, dementia, and CUD health services costs (40). The sociodemographic and military characteristics (sex, age at TBI diagnosis (baseline), race, education, marital status, branch, rank, rurality, VA service-connected disability percent, and district/region) were obtained from the VA and DoD Identity Repository (VADIR). Years of TBI diagnosis were captured by the total number of years since the first TBI diagnosis and enrolled in VHA. Other covariates were defined using ICD-9/10 codes from VINCI and DOD VA Informatics and Computing Infrastructure (DaVINCI) and are defined in Supplementary Table S1. These measured conditions have a complex multifactorial etiology and are risk factors for dementia, CUD, and TBI (14, 41, 42).

Statistical analysis

We conducted descriptive analyses of demographic characteristics and risk behaviors from baseline data by CUD and dementia diagnosis status. To evaluate the healthcare cost trajectories over time by dementia and CUD status, we plotted the annual total costs after the TBI index date. We have also presented the trajectories of the dementia and CUD cost stratified by TBI severity. We assessed the association between total healthcare costs and CUD or dementia diagnosis status and the 95% confidence interval (CI), using crude and adjusted generalized estimating equation (GEE) models. The incidence rate ratio of healthcare utilization by CUD or dementia diagnosis status was reported using a negative binomial regression model. The following covariates in the adjusted model included sociodemographic and military characteristics (years of TBI diagnosis, biological sex, age at the time of TBI, TBI severity, race/ethnicity, highest education level completed at baseline, marital status, military branch, rank, rurality, service-connected disability percentage, US district (region), and death), and health conditions (see more details in Supplementary Table S1). We repeated the GEE-adjusted model for veterans with at least two dementia diagnosis codes for a sensitivity analysis. The association between healthcare costs and utilization and TBI severity in these adjusted models is also reported. Using the standardized mean difference, the risk profile of dementia and CUD have been separately evaluated, and we report the clinical and structural population differences for measured covariates in Supplementary Table S2 (43, 44). All analyses were conducted using Stata version 17 (StataCorp LP, College Station, Texas).

Results

Sociodemographic/military and clinical characteristics

Table 1 presents the demographic and medical conditions characteristics for four groups of veterans diagnosed with TBI: (1) No Dementia diagnosis and No CUD group ($n = 341,324$; 88.02%), (2) Dementia only ($n = 4,572$;1.18%), (3) CUD only ($n = 40,873$; 10.54%), and (4) Dementia and CUD ($n = 1,001$; 0.26%). The median [interquartile range] age at the time of TBI was 30 [14] years. The majority of the veterans (65.54%) in our cohort presented with mild TBI (Table 1). Veterans diagnosed with TBI who were diagnosed with dementia and CUD were predominantly non-Hispanic white people, men, and former army service members with up to a high school education. They had relatively high rates of non-headache chronic pain and insomnia as well as severe mental illness and other mental health diagnoses such as depression, anxiety, and personality disorders. They also had relatively high rates of alcohol use disorder and OUD. The clinical and structural population differences for measured covariates indicate substantial differences between dementia and non-dementia as well as the CUD and non-CUD groups (see Supplementary Table S2). The time from TBI to dementia was approximately 1 year longer in the Dementia and CUD group (mean (SD) = 4.36 (4.18) years) compared with the Dementia only group (mean (SD) = 5.31 (4.10) years), as shown in Figure 1.

Healthcare (VA and non-VA) costs after TBI injury

Figure 1 shows the trend of annual total healthcare costs per veteran after documented TBI over a time span of 19 years. The total costs for the Dementia only and Dementia and CUD groups showed two important trajectories over time (Figure 1). First, we observed substantial healthcare costs in the Dementia only group (peak = $46,808) within 5 years of TBI onset, which was not noticed in other groups (in particular, the Dementia and CUD group). The TBI severity subgroup evaluation showed that the substantial healthcare costs in the Dementia only group were driven by veterans with moderate/severe and penetrating TBI (Figure 2). Second, we observed the gradually increasing trend of healthcare costs after 5 years of TBI onset (Figure 1). However, compared with the two other

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TABLE 1 Demographic and clinical characteristics of veterans with a history of TBI by dementia diagnosis and CUD status (*N* = 387,770).

	No Dementia and No CUD *N* (%)	Dementia only *N* (%)	CUD only *N* (%)	Dementia and CUD *N* (%)	Total *N* (%)
Overall	341,324 (88.02)	4,572 (1.18)	40,873 (10.54)	1,001 (0.26)	387,770 (100.00)
Male sex	300,291 (87.98)	4,078 (89.2)	37,319 (91.3)	924 (92.31)	342,612 (88.35)
Age ≥ 65	2,228 (0.65)	316 (6.91)	27 (0.07)	4 (0.40)	2,575 (0.66)
Race and ethnicity					
White	217,674 (63.77)	2,887 (63.15)	25,167 (61.57)	629 (62.84)	246,357 (63.53)
Black/African American	54,081 (15.84)	800 (17.5)	7,042 (17.23)	169 (16.88)	62,092 (16.01)
Hispanic or Latino	35,339 (10.35)	432 (9.45)	3,543 (8.67)	86 (8.59)	39,400 (10.16)
Other	32,957 (9.66)	446 (9.76)	5,036 (12.32)	114 (11.39)	38,553 (9.94)
Unknown	1,273 (0.37)	7 (0.15)	85 (0.21)	3 (0.30)	1,368 (0.35)
Education					
College and above	81,834 (23.98)	1,679 (36.72)	4,349 (10.64)	142 (14.19)	88,004 (22.69)
High school and less	258,910 (75.85)	2,873 (62.84)	36,474 (89.24)	856 (85.51)	299,113 (77.14)
Unknown	580 (0.17)	20 (0.44)	50 (0.12)	3 (0.30)	653 (0.17)
Marital status					
Unmarried	161,077 (47.19)	1,763 (38.56)	26,386 (64.56)	614 (61.34)	189,840 (48.96)
Married	180,067 (52.76)	2,808 (61.42)	14,471 (35.4)	386 (38.56)	197,732 (50.99)
Unknown	180 (0.05)	1 (0.02)	16 (0.04)	1 (0.1)	198 (0.05)
Military branch					
Air Force	33,398 (9.78)	686 (15)	2,399 (5.87)	88 (8.79)	36,571 (9.43)
Army	204,047 (59.78)	2,615 (57.2)	27,442 (67.14)	658 (65.73)	234,762 (60.54)
Marines	61,003 (17.87)	551 (12.05)	6,822 (16.69)	135 (13.49)	68,511 (17.67)
Navy/Coast guard	42,725 (12.52)	708 (15.49)	4,208 (10.3)	120 (11.99)	47,761 (12.32)
Other	151 (0.04)	12 (0.26)	2 (0)	0 (0)	165 (0.04)
Rank					
Enlisted	317,218 (92.95)	3,916 (85.65)	40,288 (98.57)	974 (97.3)	362,396 (93.46)
Officer	20,407 (5.98)	562 (12.29)	484 (1.18)	24 (2.4)	21,477 (5.54)
Warrant	3,670 (1.08)	94 (2.06)	99 (0.24)	3 (0.3)	3,866 (1)
Rurality					
Rural	108,255 (31.72)	1,455 (31.82)	12,632 (30.91)	309 (30.87)	122,651 (31.63)
Urban	231,902 (67.94)	3,109 (68)	28,151 (68.87)	689 (68.83)	263,851 (68.04)
Unknown	1,167 (0.34)	8 (0.17)	90 (0.22)	3 (0.3)	1,268 (0.33)
VA SCD% (0)	38,954 (11.41)	665 (14.55)	4,928 (12.06)	132 (13.19)	44,679 (11.52)
10 to 40%	24,126 (7.07)	157 (3.43)	1,821 (4.46)	10 (1)	26,114 (6.73)
≥50%	278,244 (81.52)	3,750 (82.02)	34,124 (83.49)	859 (85.81)	316,977 (81.74)
District					
North Atlantic	70,682 (20.71)	956 (20.91)	8,177 (20.01)	188 (18.78)	80,003 (20.63)
Southeast	66,029 (19.35)	1,090 (23.84)	7,634 (18.68)	198 (19.78)	74,951 (19.33)
Midwest	69,456 (20.35)	854 (18.68)	8,524 (20.85)	177 (17.68)	79,011 (20.38)
Continental	72,831 (21.34)	1,042 (22.79)	8,722 (21.34)	260 (25.97)	82,855 (21.37)
Pacific	62,318 (18.26)	630 (13.78)	7,816 (19.12)	178 (17.78)	70,942 (18.3)
Comorbid conditions					
Headache	194,574 (57.01)	3,178 (69.51)	24,497 (59.93)	729 (72.83)	222,978 (57.5)
Other chronic pain	309,908 (90.8)	4,386 (95.93)	38,233 (93.54)	964 (96.3)	353,491 (91.16)
MAT (recent)	18,957 (5.55)	335 (7.33)	11,333 (27.73)	317 (31.67)	30,942 (7.98)

(Continued)

TABLE 1 (Continued)

	No Dementia and No CUD *N* (%)	Dementia only *N* (%)	CUD only *N* (%)	Dementia and CUD *N* (%)	Total *N* (%)
Oncology	4,257 (1.25)	152 (3.32)	611 (1.49)	20 (2)	5,040 (1.3)
SMI	80,657 (23.63)	2,184 (47.77)	24,516 (59.98)	786 (78.52)	108,143 (27.89)
Depression	187,134 (54.83)	3,614 (79.05)	34,257 (83.81)	940 (93.91)	225,945 (58.27)
PTSD	222,236 (65.11)	3,058 (66.89)	35,512 (86.88)	895 (89.41)	261,701 (67.49)
Personality disorder	15,343 (4.5)	474 (10.37)	9,748 (23.85)	375 (37.46)	25,940 (6.69)
Alcohol use disorder	120,007 (35.16)	1,967 (43.02)	33,786 (82.66)	886 (88.51)	156,646 (40.4)
OUD	20,292 (5.95)	532 (11.64)	18,187 (44.5)	533 (53.25)	39,544 (10.2)
Other drug use disorder	23,526 (6.89)	624 (13.65)	26,766 (65.49)	790 (78.92)	51,706 (13.33)
Nicotine use disorder	91,915 (26.93)	1,494 (32.68)	23,006 (56.29)	676 (67.53)	117,091 (30.2)
Anxiety	171,582 (50.27)	3,098 (67.76)	30,976 (75.79)	867 (86.61)	206,523 (53.26)
Insomnia	114,882 (33.66)	2,246 (49.13)	16,147 (39.51)	557 (55.64)	133,832 (34.51)
CHF	6,880 (2.02)	504 (11.02)	794 (1.94)	70 (6.99)	8,248 (2.13)
Peripheral vascular disease	12,441 (3.64)	840 (18.37)	1,152 (2.82)	93 (9.29)	14,526 (3.75)
Cardiac disease	48,580 (14.23)	1,618 (35.39)	7,806 (19.1)	372 (37.16)	58,376 (15.05)
Stroke	12,634 (3.7)	1,145 (25.04)	1,538 (3.76)	187 (18.68)	15,504 (4)
DM	37,526 (10.99)	1,219 (26.66)	2,985 (7.3)	178 (17.78)	41,908 (10.81)
Diabetes with chronic complication	21,038 (6.16)	795 (17.39)	1,600 (3.91)	99 (9.89)	23,532 (6.07)
Epilepsy	85,489 (25.05)	2,186 (47.81)	19,406 (47.48)	664 (66.33)	107,745 (27.79)
Other neurologic disorders (no epilepsy)	6,515 (1.91)	889 (19.44)	992 (2.43)	139 (13.89)	8,535 (2.2)
Liver disease	12,905 (3.78)	325 (7.11)	1,810 (4.43)	83 (8.29)	15,123 (3.9)
CKD	6,233 (1.83)	302 (6.61)	801 (1.96)	43 (4.3)	7,379 (1.9)
Death	10,068 (2.95)	647 (14.15)	2,561 (6.27)	119 (11.89)	13,395 (3.45)
TBI severity and evidence of TBI					
Mild	223,940 (65.61)	2,304 (50.39)	27,358 (66.93)	539 (53.85)	254,141 (65.54)
Moderate/Severe	44,421 (13.01)	955 (20.89)	6,069 (14.85)	233 (23.28)	51,678 (13.33)
Penetrating	11,582 (3.39)	702 (15.35)	1,450 (3.55)	137 (13.69)	13,871 (3.58)
Unclassified	61,381 (17.98)	611 (13.36)	5,996 (14.67)	92 (9.19)	68,080 (17.56)

CUD, cannabis use disorder; SCD, service-connected disability; TBI, traumatic brain injury; MAT, medication-assisted treatment; CHF, congestive heart failure; CKD, chronic kidney disease; PTSD, post traumatic stress disorder; SMI, severe mental illness; DM, diabetes mellitus.

non-dementia groups, we observed that the increasing trend of healthcare costs in the Dementia and CUD and Dementia only groups declined after approximately 14 years (peak = $44,983 and $21,954 for Dementia and CUD and Dementia only, respectively). We observed a constant increase in the total healthcare costs (VA and non-VA) for the No Dementia and No CUD group and CUD only group, with a higher cost following TBI over time for the CUD only group.

The association between healthcare costs and CUD and dementia diagnosis status

Table 2 shows the association between healthcare utilization costs and CUD and dementia diagnosis status in veterans with a history of TBI. After controlling for sociodemographic/military characteristics and clinical conditions (Model 2), the total healthcare costs were USD$ 3,368 higher in the CUD only group (95% CI: 3,090–3,645) than in the No Dementia and No CUD group. We did not observe any association between the annualized total healthcare costs in dementia-related subgroups (Dementia only and Dementia and CUD groups), compared with the No Dementia and No CUD group.

Table 2 also shows the healthcare utilization incidence rate ratio by CUD and dementia diagnosis status in veterans with a history of TBI. Compared with the No Dementia and No CUD group, the total healthcare utilization was lower in the Dementia only [incidence rate ratio (IRR) = 0.25 (CI95%: 0.24, 0.25)], Dementia and CUD [IRR = 0.25 (CI95%: 0.24, 0.26)], and CUD only [IRR = 0.99 (CI95%: 0.98, 0.99)] groups.

The association between healthcare costs and TBI severity

After controlling for sociodemographic/military characteristics and clinical conditions (Model 2), veterans with penetrating TBI have the highest average annual costs of approximately USD$ 2,600 (95% CI:

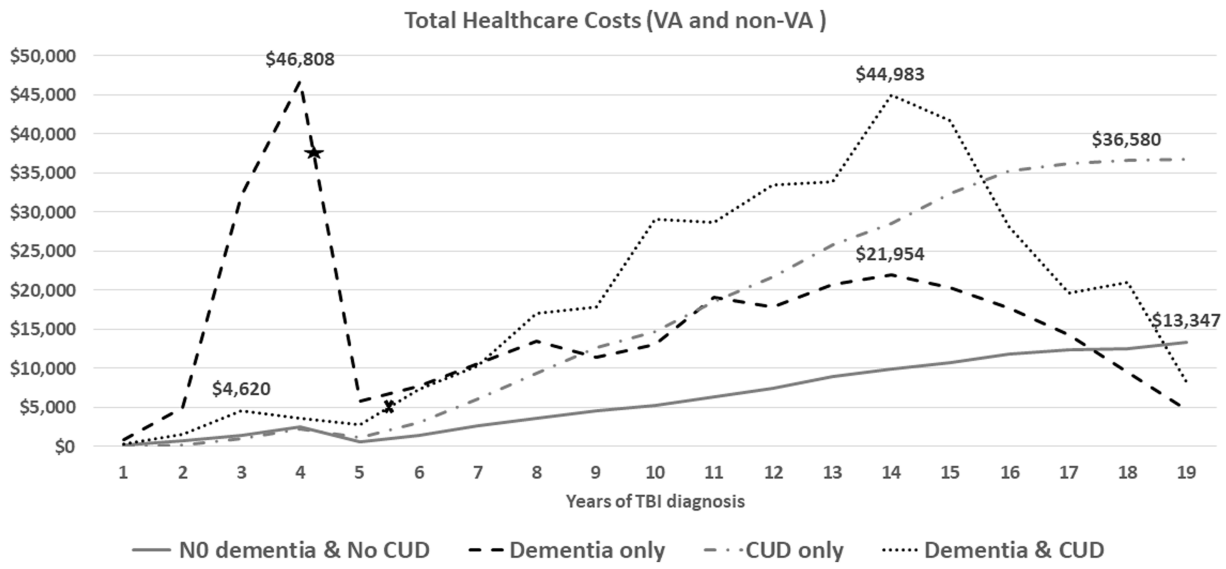

FIGURE 1
The average of annual total health care costs (VA and non-VA) after TBI injury (time zero). The average time from TBI event to dementia diagnosis was 4.36 years for veterans in the dementia only (star) and 5.31 years for veterans in the dementia and CUD group (x).

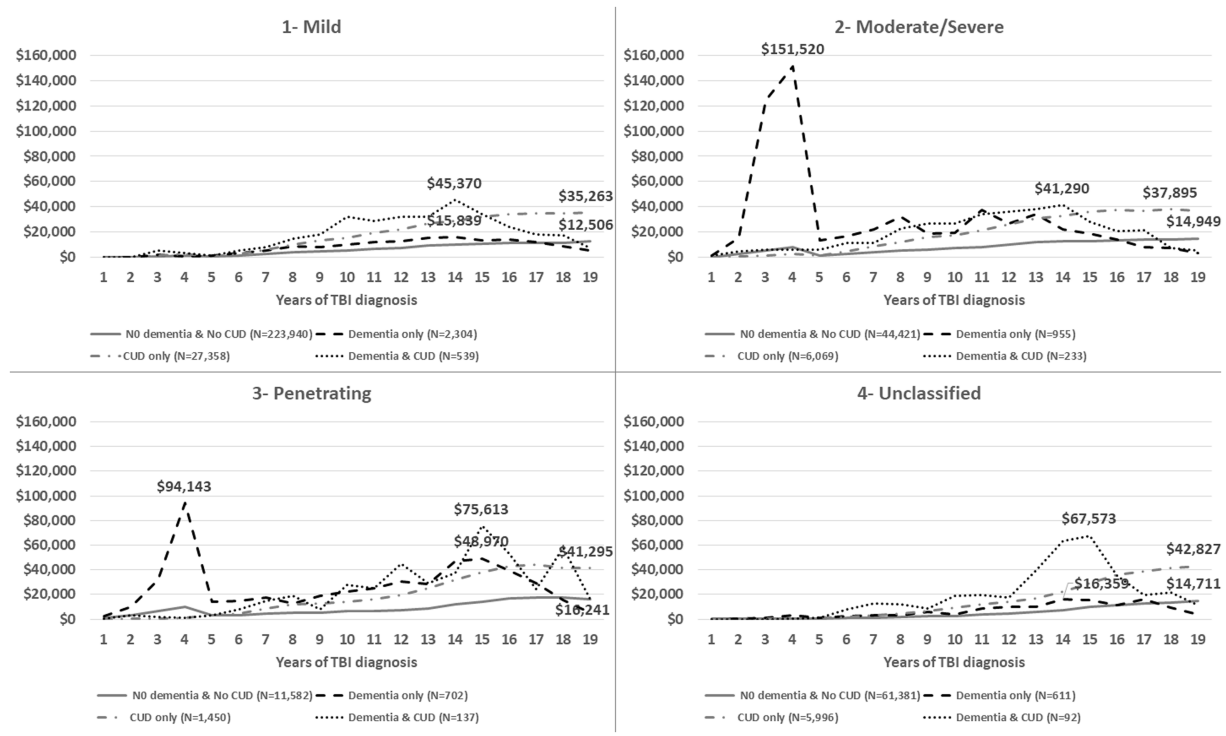

FIGURE 2
The average of annual total healthcare costs (VA and non-VA) after TBI injury (time zero), stratified by TBI severity (1—mild, 2—moderate/severe, 3—penetrating, 4—post-concussive syndrome, 5—unclassified).

1,936–3,265), followed by moderate/severe TBI [USD$ 1,466 (95% CI: 1,032–1,900)] compared with veterans with mild TBI (Table 3). However, compared with mild TBI, veterans with moderate/severe TBI (IRR = 0.91 (95% CI: 0.91–0.92)) have the highest average annual care utilization, followed by the penetrating TBI [IRR = 0.71 (95% CI: 0.71–0.72)].

Discussion

Compared with the No Dementia and No CUD group of veterans with confirmed TBI diagnosis, the highest annual total healthcare cost in VA and non-VA facilities was in veterans in the CUD only, which

TABLE 2 The association between healthcare costs or utilization and CUD and dementia diagnosis status in veterans with a history of TBI.

	Crude regression (Model 1)		Adjusted model (Model 2)		Confirmed dementia Adjusted model (Model 3)	
	Coefficient/IRR (95 CI%)	*p*	Coefficient/IRR (95 CI%)	*p*	Coefficient/IRR (95 CI%)	Value of *p*
Total healthcare costs, compared with the No Dementia and No CUD group (coefficient)						
No Dementia and No CUD	Reference		Reference		Reference	
Dementia only	9,294 (4,747, 13,841)	<0.001	1,071 (−3,204, 5,347)	0.623	−344 (−3,023, 2,334)	0.801
CUD only	10,840 (10,597, 11,084)	<0.001	3,368 (3,090, 3,645)	<0.001	3,273 (3,000, 3,545)	<0.001
Dementia and CUD	12,515 (10,753, 14,278)	<0.001	−1,667 (−3,456, 121)	0.068	−116 (−3,109, 2,877)	0.939
Total healthcare utilizations, compared with No Dementia and No CUD group (IRR)						
No Dementia and No CUD	Reference		Reference		Reference	
Dementia only	0.36 (0.35, 0.37)	<0.001	0.25 (0.24, 0.25)	<0.001	0.24 (0.24, 0.25)	<0.001
CUD Only	1.12 (1.12, 1.13)	<0.001	0.99 (0.98, 0.99)	<0.001	0.98 (0.98, 0.99)	<0.001
Dementia and CUD	0.38 (0.37, 0.39)	<0.001	0.25 (0.24, 0.26)	<0.001	0.26 (0.25, 0.27)	<0.001

We used the generalized estimating equations model to estimate the healthcare costs by dementia diagnosis or CUD status. We used the negative binomial regression model to estimate the incidence rate ratio of healthcare utilizations by dementia diagnosis or CUD status. The covariates included in the adjusted model: year with TBI, gender, age at the time of TBI, TBI severity, race, education, marital status, branch, rank, rurality, service connected disabilities (percent), district, headache, chronic pain, medication-assisted treatment (recent), oncology, severe mental illness, depression, post-traumatic stress disorder, personality disorder, alcohol use disorder, OUD, other SUD, nicotine use disorder, anxiety, insomnia, congestive heart failure, perivascular disease, cardiac disease, stroke, diabetes mellitus (DM), DM with complications, epilepsy, neurologic disorder (no epilepsy), liver disease, chronic kidney disease, and death. CUD, cannabis use disorder; SCD, service-connected disability; TBI, traumatic brain injury; IRR, incidence rate ratio.

TABLE 3 The association between healthcare costs or utilization and TBI severity in veterans with a history of TBI.

	Adjusted model (Model 2)		Confirmed dementia adjusted model (Model 3)	
	Coefficient/IRR (CI%95)	*p*	Coefficient/IRR (CI%95)	*p*
Total healthcare costs (coefficient)				
Mild	Reference		Reference	
Moderate/Severe	1,466 (1,032, 1,900)	<0.001	1,466 (1,022, 1,910)	<0.001
Penetrating	2,600 (1,936, 3,265)	<0.001	2,622 (1,989, 3,256)	<0.001
Unclassified	294 (156, 432)	<0.001	294 (156, 433)	<0.001
Total healthcare utilization (IRR)				
Mild	Reference		Reference	
Moderate/severe	0.91 (0.91, 0.92)	<0.001	0.91 (0.91, 0.91)	<0.001
Penetrating	0.71 (0.71, 0.72)	<0.001	0.7 (0.7, 0.71)	<0.001
Unclassified	0.72 (0.72, 0.72)	<0.001	0.72 (0.72, 0.72)	<0.001

We used the generalized estimating equations model to estimate the healthcare costs by dementia diagnosis or CUD status to provide healthcare costs by TBI severity. We used the negative binomial regression model to estimate the incidence rate ratio of healthcare utilizations by dementia diagnosis or CUD status to provide healthcare utilizations by TBI severity. The covariates included in the adjusted model: year with TBI, gender, age at the time of TBI, race, education, marital status, branch, rank, rurality, service connected disabilities (percent), district, headache, chronic pain, medication-assisted treatment (recent), oncology, severe mental illness, depression, post-traumatic stress disorder, personality disorder, alcohol use disorder, OUD, other SUD, nicotine use disorder, anxiety, insomnia, congestive heart failure, perivascular disease, cardiac disease, stroke, diabetes mellitus (DM), DM with complications, epilepsy, neurologic disorder (no epilepsy), liver disease, chronic kidney disease, and death. CUD, cannabis use disorder; SCD, service-connected disability; TBI, traumatic brain injury; IRR, incidence rate ratio.

was associated with 1% less healthcare utilization. However, we observed the incidence rate of healthcare utilization in the dementia-related subgroups (Dementia only and Dementia and CUD groups) was 75% less than the No Dementia and No CUD group. Prior research has demonstrated that, compared with veterans without either TBI or dementia, veterans with TBI and dementia have the highest average annual costs of approximately USD$ 20,408, followed by the Dementia only (USD$ 4,822) and TBI only (USD$ 3,344) groups (3). Our findings suggest higher average healthcare costs in veterans with TBI and CUD compared with TBI and dementia. Cognitive dysfunction or impairment may reduce help-seeking intentions (45) and should be considered as a possible reason for lower dementia-related healthcare utilization. The significantly lower healthcare utilization without cost differences in veterans with a dementia diagnosis is consistent with higher dementia-related total costs that were found in long-term rehabilitation and domiciliary inpatient services (46). Despite the high prevalence and numerous associated adverse health consequences in individuals with CUD (47) and other individuals with substance use disorders (48, 49), other studies have found that veterans with CUD did not appear to seek

treatment. In our study, compared with veterans with TBI but without dementia or CUD, veterans with TBI and CUD had the highest average annual healthcare costs, despite 1% lower healthcare utilization.

The timing of costs revealed the highest initial 5-year costs after TBI diagnosis were in the Dementia only group, which was driven by penetrating and moderate/severe TBI. Since the DoD healthcare costs were not included in our study, the immediate and expensive healthcare costs for penetrating and moderate/severe TBI are not reflected at the time of TBI. Other contributors to costs may include the persistence of TBI-related symptoms for more than 6 months post-injury (2) and the related needs of those veterans at high risk of various short- and long-term sequelae (50). Valuating the healthcare costs by subcategories in VA and non-VA facilities was beyond the focus of this study. However, relatively very high costs in the first 5 years (peak = $46,808 in year 4) could be explained by high-cost diagnostic tests, such as neuroimaging (51). The average time from TBI event to dementia diagnosis was 4.36 years for veterans in the dementia only group. Therefore, the highest initial in this group are less likely related to the prodromal phase of dementia where the veteran/family tries to find an answer to the cognitive difficulties, which needs further evaluation. While the burden of CUD costs is notable after 5 years following TBI, we did not observe extraordinary total healthcare costs in veterans with combined TBI, dementia, and CUD compared with those with dementia only in the first 5 years. These findings suggest that veterans with TBI and dementia only may be getting their healthcare needs met more quickly (i.e., in the first 5 years) while those with TBI, dementia, and CUD were not receiving sufficient initial care, resulting in higher healthcare costs after 5 years. Moreover, the absence of a high burden of healthcare costs in veterans with dementia and CUD in the short term (first 5 years) could be explained by the protective or regulatory effects of cannabis use (52, 53). The specific "causative" factors involved need further investigation, and it is possible that the antioxidant and anti-inflammatory properties of cannabidiol products (26) lead to a delay in seeking care in the first 5 years. Of note, after this initial period, costs of all types become much higher in those with dementia and CUD. Finally, dementia is a clinical diagnosis defined as at least two impaired mental functions that interfere with daily activities (54). Therefore, the documented dementia diagnosis may not represent all of the actual dementia cases. The sample sizes of veterans with TBI, CUD, and early onset dementia, diagnoses that have a high positive predictive value, were not large enough to replicate a sensitivity analysis from prior research (14). To overcome this limitation, we conducted a sensitivity analysis with confirmed dementia cases by identifying at least two dementia diagnoses. The sensitivity analysis only showed heterogeneity in the costs of dementia-related subgroups and warrants further evaluation.

This population-based study provides a broad view of the association of TBI, dementia, CUD, and VHA costs; however, as with any large database study, there were limitations. These results are limited to characteristics and conditions measured and stored in electronic health records (EHRs), which means that cannabis exposure information is limited to documented ICD codes in VA and DoD, which likely under-represents dosage and the chronicity of cannabis exposure. Of note, the EHR system in VHA allowed the inclusion of reliable study measures, such as the frequency of CUD and identification of the TBI index date relative to the documented development of CUD, strengthening our assessment of the associations between CUD, TBI, and dementia. While there are adequate techniques available to account for potential structural population differences in comorbidities and other expenditure-related factors to establish a proper cause-and-effect relationship (55), our study primarily relied on controlling for all measured covariates to focus on the excess burden of CUD in total healthcare costs and trajectories after TBI, providing a broader perspective on CUD costs for VHA. Nevertheless, in Supplementary Table S2, we provide an estimate of the potential extent of structural population differences based on dementia and CUD status. The ascertainment of the timing of TBI is problematic in our cohort and based on only the first time that a TBI diagnosis is noted in VA medical records. There is limited information on events such as lifetime TBI history and other variables such as type of brain injury (diffuse vs. focal), repetitive exposures, and mechanism of injury. Thus, TBIs reported here are not necessarily representative of service-connected injury (i.e., from deployed settings and/or related to military service) alone but may also include TBIs that occurred from a range of causes after leaving DoD (e.g., motor vehicle crashes, sports injuries, assault, and falls). While LIMBIC-CENC has engaged in an extensive effort to overcome this limitation and provide reliable TBI-related information, there are always certain limitations to Big Data analyses (i.e., optimization and empowerment of the data by aggregating information from different sources such as DoD and the diverse VA health system data sources; having an overpowered dataset; and using a dataset that was not originally designed to address the study question). Additionally, although private-sector care reimbursed by the VA is included in the analysis, private-sector care paid for by other third-party payers is not included.

Overall, healthcare costs in the TBI group that was identified as CUD only were higher than the dementia-related (Dementia only, Dementia, and CUD) groups. Lower healthcare utilization in the dementia-related groups could be explained by cognitive impairment and behavioral changes, limiting access to or perceived need for care in veterans suffering from dementia. The healthcare cost reduction after 14 years of TBI onset could also be explained by death in the dementia-related subgroups. A better appreciation of the timing and the types of services that are needed and/or accessed by these different subgroups of veterans is vital to optimize the availability and provision of the services. Given the constraints in overall resources across the VA system, it is important to assess the quality of supportive care in outpatient facilities by VA clinicians and administrators and to identify effective approaches to maximize cost-efficient strategies for veterans with TBI and at risk of dementia (11). The impact of the growing number of potential pharmacologic management options for dementia (56) and the extent to which such treatments may delay the need for healthcare services is unknown. Further investigation is needed to examine the impact of the timing of dementia and CUD diagnoses on veterans with TBI, with specific attention to the specific categories of inpatient and outpatient care in VA and community care facilities.

Data availability statement

The datasets presented in this article are not readily available due to VA Regulations indicating data behind the firewall. Requests to access the datasets should be directed to: VINCI@VA.GOV.

Ethics statement

The studies involving humans were approved by the University of Utah and Stanford University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AE: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. TP: Writing – review & editing. MA: Data curation, Software, Formal analysis, Project administration, Writing – review & editing. CG: Project administration, Resources, Software, Writing – review & editing. AN: Writing – review & editing. MM: Project administration, Data curation, Software, Writing – review & editing. MP: Investigation, Supervision, Validation, Writing – review & editing. DC: Supervision, Writing – review & editing. CD-G: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2023.1261144/full#supplementary-material

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Cannabis use disorder contributes to cognitive dysfunction in Veterans with traumatic brain injury

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Background: While emerging evidence supports a link between traumatic brain injury (TBI) and progressive cognitive dysfunction in Veterans, there is insufficient information on the impact of cannabis use disorder (CUD) on long-term cognitive disorders. This study aimed to examine the incidences of cognitive disorders in Veterans with TBI and CUD and to evaluate their relationship.

Methods: This retrospective cohort study used the US Department of Veterans Affairs and Department of Defense administrative data from the Long-term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium Phenotype study. Diagnoses suggesting cognitive disorders after a TBI index date were identified using inpatient and outpatient data from 2003 to 2022. We compared the differential cognitive disorders incidence in Veterans who had the following: (1) no CUD or TBI (control group), (2) CUD only, (3) TBI only, and (4) comorbid CUD+TBI. Kaplan-Meier analyses were used to estimate the overall cognitive disorders incidence in the above study groups. The crude and adjusted Cox proportional hazards models were used to estimate crude and adjusted hazard ratios (HRs) for cognitive disorders.

Results: A total of 1,560,556 Veterans [82.32% male, median (IQR) age at the time of TBI, 34.51 (11.29) years, and 61.35% white] were evaluated. The cognitive disorder incidence rates were estimated as 0.68 (95% CI, 0.62, 0.75) for CUD only and 1.03 (95% CI, 1.00, 1.06) for TBI only per 10,000 person-months of observations, with the highest estimated cognitive disorder incidence observed in participants with both TBI and CUD [1.83 (95% CI, 1.72, 1.95)]. Relative to the control group, the highest hazard of cognitive disorders was observed in Veterans with CUD+TBI [hazard ratio (HR), 3.26; 95% CI, 2.91, 3.65], followed by those with TBI only (2.32; 95 CI%, 2.13, 2.53) and with CUD (1.79; 95 CI%, 1.60, 2.00). Of note, in the CUD only subgroup, we also observed the highest risk of an early onset cognitive disorder other than Alzheimer's disease and Frontotemporal dementia.

Discussion: The results of this analysis suggest that individuals with comorbid TBI and CUD may be at increased risk for early onset cognitive disorders, including dementia.

KEYWORDS

traumatic brain injury, cannabis use disorder, dementia, Veterans, Cox proportional hazards model

Introduction

Individuals with traumatic brain injury (TBI), independent of severity, are at increased risk for dementia (1) a neurodegenerative disorder that is characterized by a decline in one or more cognitive domains (2) and profoundly affects mortality, quality of life, caregiver stress, and economic burden (3). The risk of dementia is of particular concern for Veterans with TBI since they frequently present with other associated risk factors for dementia, including post-traumatic stress disorder (PTSD), depression, and sleep impairment that may compound risk and accelerate neurodegenerative processes (4, 5). TBI has been a central focus of morbidity in recent war efforts, as nearly 20% of the more than 2.5 million deployed U.S. military Service Members and Veterans (SMVs) since 2003 sustained at least one TBI (6, 7). Importantly, more than 80% of the TBIs are mild in severity (mTBI) and up to 8% of all Veterans who have sustained TBI are expected to have persistent symptoms related to the event more than 6 months post-injury (8, 9). Difficulty with cognitive, affective, somatosensory, and vestibular symptoms are common post-TBI complaints (10, 11). Post-9/11 combat-deployed service members are at risk of single and repetitive blast and non-blast injuries, in particular mild TBIs (12). Although yet to be fully defined, the mechanisms by which TBI promotes neurodegeneration may be modulated by an array of processes manifesting from insult related neuropathological changes that may be further exacerbated by repetitive injury (13, 14). A history of TBI exposure may also accelerate the time to dementia diagnosis (15), evidenced by a recent study showing an increased risk for early-onset dementia in young post-9/11 Veterans with prior TBI (16).

No study has demonstrated the beneficial effects of smoking marijuana (17). To date, the United States Food and Drug Administration (FDA) has not recommended cannabis for the treatment of any disease or condition (18). Cannabis use disorder (CUD) is defined as problematic marijuana use that causes impairment or distress, without necessarily leading to addiction (19, 20). Zehra et al. (21) suggested that CUD possesses addictive properties akin to other drugs of abuse. Despite the lack of efficacy, cannabis is frequently used to self-treat a wide array of symptoms and conditions, including those associated with persistent post-concussion symptoms (e.g., chronic pain, headache, insomnia, anxiety, irritability, etc.) (22–25). Owing to expanded legalization, lower perceptions of risk, and the absence of established medication regimens (26), the use of cannabis for symptom management following TBI has likely increased (25, 27) in parallel with growing trends in overall use in both the general U.S. population (28) and in Veterans (29–32). Cannabinoids may regulate some of the processes that lead to neurodegeneration (33), and therefore may be useful in the treatment of neurodegenerative dementias such as Alzheimer's disease (AD), in particular for symptoms of agitation (34, 35). However, to date, systematic reviews have noted that available data evaluating cannabinoids for the treatment of dementia progression are insufficient to draw clear conclusions (36, 37). Additionally, studies have shown that cannabis use acutely impairs cognitive functions including attention, concentration, episodic memory, and associative learning in a dose-dependent fashion (38, 39). As observed in some types of dementia, structural changes, such as decreases in regional brain volume in the hippocampus, amygdala, and striatum have also been linked to heavy, chronic cannabis use (40–45). The existence of these non-conclusive and contradictory studies on effectiveness of cannabis on dementia treatment warrant further study. The objective of this study was to examine the association of CUD in the emergence of cognitive disorders in Post-9/11 Veterans diagnosed with TBI.

Methods

Participants and data source

The cohort for this retrospective analysis included participants from the Long-term Impact of Military-Relevant Brain Injury Consortium–Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) Phenotype study. As described in detail previously (46), this is a large cohort of Post-9/11 active duty and veteran U.S. military persons who received care in the Department of Defense (DoD) for at least 3 years, including those exposed and unexposed to TBI(s). Data for this study included healthcare data during deployment [e.g., DoD Trauma Registry (DoDTR) and Theater Management Data Store (TMDS)], DoD, VA, and Non-VA community inpatient and outpatient data. To ensure accurate TBI status and sufficient data to identify cognitive disorder, we included only those participants who also had 2 years of care in the Veterans Health Administration (VHA) during the study period. The research protocol was reviewed and approved by the University of Utah and Stanford institutional review board (IRB) and was conducted in accordance with all applicable federal regulations.

Measures and outcomes

Development of study groups

We used a hierarchical approach to identify TBI by prioritizing data from DoDTR and TMDS (Glasgow Coma Scale score, Abbreviated Injury Severity Score, and ICD-9-CM and ICD-10-CM codes), followed by self-reported data from the comprehensive TBI evaluation (CTBIE) data collected in the process of clinical care loss of consciousness (mild, $\leq$30 min; moderate to severe, $>$30 min), alteration of consciousness or posttraumatic amnesia (mild$<$24 h; moderate to severe, $\geq$24 h 16), and ICD-9/10-CM diagnosis codes from the Armed Forces Health Surveillance Division algorithm (47). The *index date* for TBI was the first date of diagnosis or the date of the CTBIE assessment; for those with more than one TBI documented we used the date of the most severe TBI. Veterans who did not enroll in VHA and did not complete the initial VA screening for TBI were excluded from the study (Figure 1). For those without TBI we calculated simulated TBI index dates using a Monte Carlo simulation to generate age-correlated index dates (16). To establish comparable analysis time windows across groups, it was necessary to assign a simulated index date to each individual in the non-TBI group. The simulated index dates were drawn at random from the real distribution of injury dates. To further refine this approach, the simulated index dates were only sampled from a subset of those

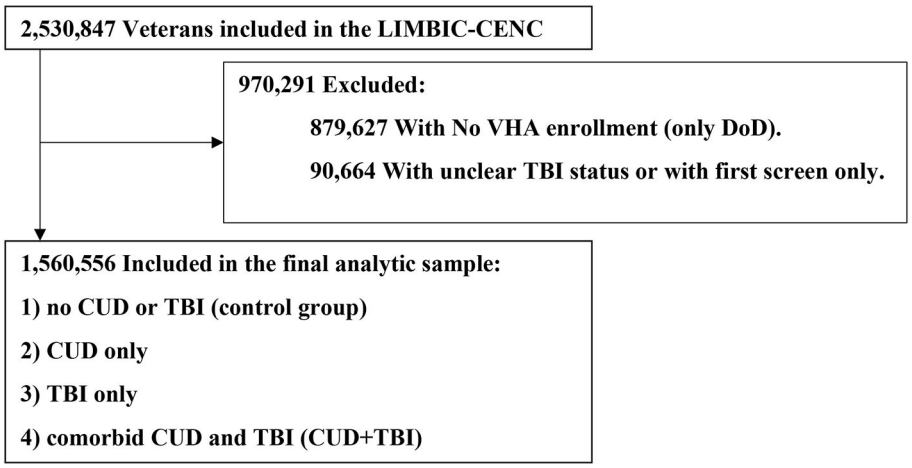

FIGURE 1
Study flow chart for impact of cannabis on cognitive disorder in Veteran patients with TBI. CUD, Cannabis Use Disorder; DoD, Department of Defense; LIMBIC-CENC, Long-term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium; TBI, Traumatic Brain Injury; VHA, Veterans Health Administration.

in the TBI group who were of a similar age as the TBI negative individual (within 5 years) (16).

Cognitive disorder was indicated by ICD-9/10 diagnosis codes used to identify dementia by VHA Geriatrics and Extended Care (Supplementary Table 3); ascertainment required a single ICD-9/10 dementia diagnosis code after TBI index date through September 11, 2022. Since prior research indicates that these diagnoses are not accurate for individuals under age 65 (48, 49), we classified these diagnoses simply as a "cognitive disorder." To increase confidence in confirmed dementia cases, we performed a sensitivity analysis on the cohort with at least two ICD-9/10 codes for dementia diagnosis and in the subgroup of 1) early onset of dementia (EOD) (16), consisting of AD (ICD10 = G30.0), and Frontotemporal dementia (FTD) and 2) non-EOD subgroups consisting of early onset cognitive disorder other than AD and FTD.

Primary outcome

The primary outcome, time from TBI index date to cognitive disorder diagnosis, was calculated using the TBI/simulated index date and the first documented diagnosis indicating cognitive disorder. To evaluate the associations among CUD and cognitive disorder emergence following TBI, we categorized the cohort into four groups: (1) Neither CUD nor TBI (control group), (2) TBI only, (3) CUD only, and (4) comorbid CUD and TBI (CUD+TBI). Cannabis CUD was identified using ICD-9 (304.3: Cannabis dependence, and 305.2: Non-dependent cannabis abuse), and ICD-10 codes (F12: Cannabis-related disorders including F12.1 Cannabis abuse, F12.2 Cannabis dependence, and F12.9 Cannabis use, unspecified) for any ICD-9/10 diagnoses after TBI index date.

Covariates

Sociodemographic and military characteristics, including biological sex, age at index date, race/ethnicity, education, marital status, branch, rank, rural/urban location of Veteran residence, and VA service-connected disability group were obtained from the VA DoD Identity Repository (VADIR; FY00-FY19) at the time of military discharge.

Clinical characteristics

We identified comorbid conditions using ICD-9 and 10 codes obtained from the VA Corporate Data Warehouse (CDW) and the DoD and VA Infrastructure for Clinical Intelligence (DaVINCI). Conditions were identified using algorithms provided in Supplementary Table 3 when individuals had one or more ICD-9 and 10 diagnoses between TBI index date to September 11, 2022. We identified the Medication-assisted treatment (MAT) after the TBI index date using the algorithm provided by VA Pharmacy Benefits Management Services (Supplementary Table 3). The U.S. district/region is identified using the VA medical center (stations) that was assigned based on the Veteran home address (Veteran residence).

Statistical analysis

Descriptive analyses of demographic characteristics and risk behaviors from baseline data by CUD and TBI status were conducted. We estimated the cognitive disorder incidence rates (IRs) using Kaplan-Meier methods for the overall cohort and for each of the four groups. Participants were censored at the date of their last health care system encounter or September 11, 2022 (whichever came first). We used Cox proportional hazards models to calculate the crude and adjusted CUD and TBI-specific hazard ratio (HR) for cognitive disorder incidence using CUD+TBI as the main exposure, controlling for sociodemographic and clinical characteristics. To increase confidence in confirmed dementia cases, we performed a sensitivity analysis by re-running the Cox proportional hazards models in the EOD and Non-EOD cohort (Table 2). All analyses

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TABLE 1 Demographic and clinical characteristics of veterans by CUD and TBI status ($N = 1,560,556$).

	Control *N* (%)	TBI only *N* (%)	CUD only *N* (%)	CUD + TBI *N* (%)	Total *N* (%)
Overall	1,12,4686 (72.07)	3,45,896 (22.16)	48,100 (3.08)	41,874 (2.68)	1,560,556 (100)
Male	9,02,228 (80.22)	3,04,369 (87.99)	39,783 (82.71)	38,243 (91.33)	1,284,623 (82.32)
Age at TBI (Mean ± SD)	35.36 (11.60)	33.30 (10.42)	28.43 (8.07)	28.58 (7.29)	34.51 (11.29)
Race/ethnicity (White)	6,84,525 (60.86)	2,20,561 (63.77)	26,501 (55.1)	25,796 (61.6)	9,57,383 (61.35)
Black or African American	2,32,517 (20.67)	54,881 (15.87)	13,172 (27.38)	7,211 (17.22)	3,07,781 (19.72)
Hispanic or Latino	1,15,010 (10.23)	35,771 (10.34)	4,353 (9.05)	3,629 (8.67)	1,58,763 (10.17)
Other	86,198 (7.66)	33,403 (9.66)	3,901 (8.11)	5,150 (12.3)	1,28,652 (8.24)
Unknown	6,436 (0.57)	1,280 (0.37)	173 (0.36)	88 (0.21)	7,977 (0.51)
Education (college and above)	3,46,404 (30.8)	83,513 (24.14)	5,730 (11.91)	4,491 (10.73)	4,40,138 (28.2)
High school and less	7,74,755 (68.89)	2,61,783 (75.68)	42,282 (87.9)	37,330 (89.15)	1,116,150 (71.52)
Unknown	3,527 (0.31)	600 (0.17)	88 (0.18)	53 (0.13)	4,268 (0.27)
Marital status (not married)	5,44,334 (48.4)	1,62,840 (47.08)	33,069 (68.75)	27,000 (64.48)	7,67,243 (49.16)
Married	5,79,138 (51.49)	1,82,875 (52.87)	15,001 (31.19)	14,857 (35.48)	7,91,871 (50.74)
Unknown	1,214 (0.11)	181 (0.05)	30 (0.06)	17 (0.04)	1,442 (0.09)
Branch (air force)	2,08,515 (18.54)	34,084 (9.85)	5,661 (11.77)	2,487 (5.94)	2,50,747 (16.07)
Army	5,10,432 (45.38)	2,06,662 (59.75)	26,205 (54.48)	28,100 (67.11)	7,71,399 (49.43)
Marines	1,61,454 (14.36)	61,554 (17.8)	6,953 (14.46)	6,957 (16.61)	2,36,918 (15.18)
Navy/coast guard	2,43,312 (21.63)	43,433 (12.56)	9,275 (19.28)	4,328 (10.34)	30,0348 (19.25)
Other	973 (0.09)	163 (0.05)	6 (0.01)	2 (0)	1,144 (0.07)
Rank (enlisted)	1,004,715 (89.34)	3,21,134 (92.85)	47,300 (98.34)	41,262 (98.54)	1,414,411 (90.64)
Officer	1,05,095 (9.34)	20,969 (6.06)	672 (1.4)	508 (1.21)	1,27,244 (8.15)
Warrant	14,812 (1.32)	3,764 (1.09)	124 (0.26)	102 (0.24)	18,802 (1.2)
Rurality (Rural)	3,13,229 (27.85)	1,09,710 (31.72)	12,344 (25.66)	12,941 (30.9)	4,48,224 (28.72)
Urban	8,06,537 (71.71)	2,35,011 (67.94)	35,677 (74.17)	28,840 (68.87)	1,106,065 (70.88)
Unknown	4,920 (0.44)	1,175 (0.34)	79 (0.16)	93 (0.22)	6,267 (0.4)
VA SCD None/0%	2,54,515 (22.63)	39,619 (11.45)	10,384 (21.59)	5,060 (12.08)	30,9578 (19.84)
10-40 percent	1,85,725 (16.51)	24,283 (7.02)	4,943 (10.28)	1,831 (4.37)	2,16,782 (13.89)
≥50 percent	6,84,446 (60.86)	2,81,994 (81.53)	32,773 (68.14)	34,983 (83.54)	1,034,196 (66.27)
District (North Atlantic)	2,46,134 (21.89)	71,638 (20.71)	9,963 (20.71)	8,365 (19.98)	3,36,100 (21.54)
Southeast	2,29,057 (20.37)	67,119 (19.4)	10,061 (20.92)	7,832 (18.7)	3,14,069 (20.13)
Midwest	2,17,771 (19.36)	70,310 (20.33)	9,437 (19.62)	8,701 (20.78)	3,06,219 (19.62)
Continental	2,26,839 (20.17)	73,873 (21.36)	9,917 (20.62)	8,982 (21.45)	3,19,611 (20.48)
Pacific	2,04,855 (18.21)	62,948 (18.2)	8,720 (18.13)	7,994 (19.09)	2,84,517 (18.23)
Headache	2,82,990 (25.16)	1,97,752 (57.17)	14,821 (30.81)	25,226 (60.24)	5,20,789 (33.37)
Other chronic pain	8,84,584 (78.65)	3,14,294 (90.86)	41,360 (85.99)	39,197 (93.61)	1,279,435 (81.99)
EOD (AD and FTD disease)	845 (0.08)	527 (0.15)	38 (0.08)	59 (0.14)	1,469 (0.09)
MAT (recent)	29,563 (2.63)	19,292 (5.58)	10,485 (21.8)	11,650 (27.82)	70,990 (4.55)
Severe mental illness	1,28,519 (11.43)	82,841 (23.95)	23,283 (48.41)	25,302 (60.42)	2,59,945 (16.66)
Depression	3,89,215 (34.61)	1,90,748 (55.15)	36,809 (76.53)	35,197 (84.05)	6,51,969 (41.78)
PTSD	2,92,631 (26.02)	2,25,294 (65.13)	28,998 (60.29)	36,407 (86.94)	5,83,330 (37.38)
Personality disorder	22,613 (2.01)	15,817 (4.57)	8,488 (17.65)	10,123 (24.17)	57,041 (3.66)

(Continued)

TABLE 1 (Continued)

	Control *N* (%)	TBI only *N* (%)	CUD only *N* (%)	CUD + TBI *N* (%)	Total *N* (%)
Alcohol use disorder	2,09,531 (18.63)	1,21,974 (35.26)	34,111 (70.92)	34,672 (82.8)	4,00,288 (25.65)
Opioid use disorder	24,459 (2.17)	20,824 (6.02)	14,697 (30.56)	18,720 (44.71)	78,700 (5.04)
Other drug use disorder	28,869 (2.57)	24,150 (6.98)	28,052 (58.32)	27,556 (65.81)	1,08,627 (6.96)
Nicotine use disorder	1,78,754 (15.89)	93,409 (27)	20,290 (42.18)	23,682 (56.56)	3,16,135 (20.26)
Anxiety	3,63,430 (32.31)	1,74,680 (50.5)	32,448 (67.46)	31,843 (76.04)	6,02,401 (38.6)
Insomnia	2,07,220 (18.42)	1,17,128 (33.86)	10,998 (22.86)	16,704 (39.89)	3,52,050 (22.56)
Memory loss	14,928 (1.33)	56,855 (16.44)	1,072 (2.23)	8,023 (19.16)	80,878 (5.18)
CHF	20,709 (1.84)	7,384 (2.13)	801 (1.67)	864 (2.06)	29,758 (1.91)
Cardiac disease	1,12,527 (10.01)	50,198 (14.51)	5,921 (12.31)	8,178 (19.53)	1,76,824 (11.33)
Stroke	15,412 (1.37)	13,779 (3.98)	588 (1.22)	1,725 (4.12)	31,504 (2.02)
Convulsions disorders	91,835 (8.17)	87,675 (25.35)	11,772 (24.47)	20,070 (47.93)	2,11,352 (13.54)
CKD	19,286 (1.71)	6,535 (1.89)	860 (1.79)	844 (2.02)	27,525 (1.76)

SCD, Service Connected Disability; TBI, Traumatic Brain Injury; CUD, Cannabis Use Disorder; MAT, Medication-Assisted Treatment; CHF, Congestive Heart Failure; CKD, Chronic Kidney Disease; PTSD, Post-Traumatic Stress Disorder; EOD, Early Onset Dementia; AD, Alzheimer's disease; FTD, Frontotemporal dementia. The statistical difference is significant for all variables ($p < 0.005$).

were conducted using Stata version 17 (StataCorp LP, College Station, TX).

Results

Sociodemographic and clinical characteristics

A total of 1,560,556 Veterans were included in the analysis and stratified by TBI and CUD status. Table 1 presents some of the key demographic and health characteristics of each of the four groups. A fuller range of these variables may be seen in Supplementary Table 1, which also includes standardized mean differences between the clinical and population differences by TBI and CUD status. The median (IQR) age at the time of TBI was 34.51 (11.29) years. Veterans with CUD+TBI tended to be male, with a high school education or less, were enlisted in the Army, and had higher service-connected disability percentages compared with the other 3 groups (Table 1). The TBI-CUD group also had higher rates of diagnoses for headache, other chronic pain, participation in MAT programs, mental health conditions [i.e., severe mental illness (such as schizophrenia, Bipolar II disorder), depression, PTSD, personality disorder, anxiety, insomnia], and alcohol, opioid, and other substance use disorders compared with the other groups.

Cognitive disorder IR and hazard ratio by TBI and CUD status

The cognitive disorder IR and corresponding HR by TBI and CUD status are shown in Table 2. Overall, we identified 9,844 Veterans with a history of any type of cognitive disorder. The overall cognitive disorder IR was estimated as 0.52 (95% CI: 0.51, 0.53) per 10,000 person months of observations (PMO). After controlling for all demographic and risk factors, the hazard of cognitive disorder was 2.32 (95% CI: 2.13, 2.53), 1.79 (95% CI: 1.60, 2.00), and 3.26 (95% CI: 2.91, 3.65) for Veterans with TBI only, CUD only, and CUD+TBI, respectively, compared to the control group. Figure 2 shows the time from TBI to cognitive disorder by subgroup. Despite a very low incidence of cognitive disorder in our cohort, the risk of cognitive disorder was significantly higher in Veterans with CUD+TBI. The cognitive disorder rate was 0.25%, 0.30%, and 4.4% at 5, 10, and 15 years after TBI, respectively, in Veterans with CUD + TBI. After controlling for all demographic and risk factors, the modifying effect (interaction term) between CUD and TBI on the progression of dementia was <22% the expected rate for the combined risks of TBI and CUD [Supplementary Table 2, HR = 0.78 (95% CI: 0.69, 0.89)] in Veterans diagnosed with TBI.

EOD vs. non-EOD

Among the 9,844 Veterans with an assigned diagnosis of cognitive disorder, 5,360 were identified as early onset cognitive disorder with at least 2 documented dementia diagnoses (1,053 and 4,307 Veterans with EOD and non-EOD, respectively, Table 2). The crude and adjusted HRs of the CUD+TBI, CUD only, and TBI only groups, relative to the control groups, were lower in the EOD subgroup relative to the Non-EOD group. We did not observe any significant differences in the hazard of EOD between the CUD only and control groups.

EOD and non-EOD among Veterans with TBI

We examined factors related to EOD and Non-EOD development among Veterans with TBI, after adjusting for

TABLE 2 Cognitive disorder incidence rate (overall and by TBI and CUD status), and hazard ratio of dementia by CUD and TBI status.

	Person-time	Failures (Documented cognitive disorder)	IR (95% CI) per 10000 PMO	Crude	Adjusted model*
				HR (95% CI)	HR (95% CI)
All types of cognitive disorder					
Overall	190,800,000	9,844	0.52 (0.51, 0.53)		
Control	136,600,000	4,053	0.30 (0.29, 0.31)	Ref	Ref
TBI only	4,255,8896	4,381	1.03 (1.00, 1.06)	3.47 (3.33, 3.62)	2.32 (2.13, 2.53)
CUD only	6213722.8	423	0.68 (0.62, 0.75)	2.31 (2.09, 2.55)	1.79 (1.60, 2.00)
CUD+TBI	5386415.6	987	1.83 (1.72, 1.95)	6.21 (5.79, 6.65)	3.26 (2.91, 3.65)
EOD (AD and FTD disease)					
Overall	191,300,000	1,053	0.06 (0.05, 0.06)		
Control	136,800,000	646	0.05 (0.04, 0.05)	Ref	Ref
TBI only	42,866,265	354	0.08 (0.07, 0.09)	1.75 (1.54, 1.99)	1.75 (1.3, 2.35)
CUD only	6237732.1	20	0.03 (0.02, 0.05)	0.68 (0.44, 1.07)	1.49 (0.93, 2.39)
CUD+TBI	5458252.4	33	0.06 (0.04, 0.09)	1.29 (0.91, 1.83)	2.81 (1.74, 4.53)
All other early onset cognitive disorder (Non-EOD)					
Overall	191,100,000	4,307	0.23 (0.22, 0.23)		
Control	136,700,000	1,529	0.11 (0.11, 0.12)	Ref	Ref
TBI only	42,696,148	2,195	0.51 (0.49, 0.54)	4.61 (4.32, 4.92)	3.04 (2.68, 3.44)
CUD only	6228235.2	157	0.25 (0.22, 0.29)	2.27 (1.93, 2.68)	1.84 (1.54, 2.20)
CUD+TBI	5426337.5	426	0.79 (0.71, 0.86)	7.08 (6.36, 7.88)	3.95 (3.33, 4.67)

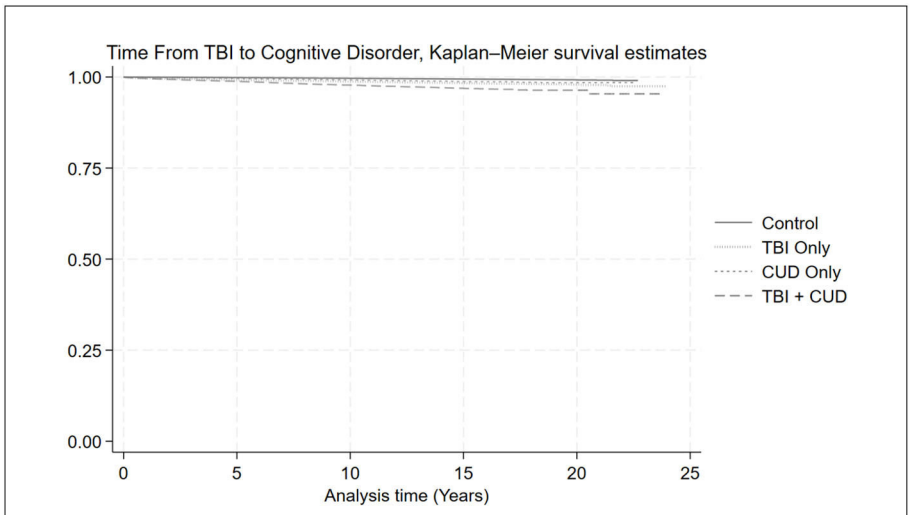
HR, Hazard Ratio; IR, Incidence Rate; CI, Confidence Interval; EOD, Early Onset Dementia; TBI, Traumatic Brain Injury; CUD, Cannabis Use Disorder; PMO, Person Months of Observations; Ref, Reference. The covariates included in the adjusted model: CUD, TBI, sex, age at the time of TBI, TBI severity, race, education, marital status, branch, rank, rurality, service-connected disability groups, District, Headache, Chronic Pain, MAT (recent), Oncology, Severe Mental Illness, Depression, PTSD, Personality Disorder, Alcohol Use Disorder, Opioid Use Disorder, Other SUD, Nicotine Use disorder, anxiety, insomnia, CHF, Perivascular disease, Cardiac disease, Stroke, Diabetes Mellitus (DM), DM with complications, convulsions disorders, Neurologic disorder (No Convulsions disorders), Liver Disease, CKD, and death. *The covariates included in the adjusted model.

select variables: TBI severity, sex, race/ethnicity, and education, as shown in Table 3. More severe categories of TBI were associated with higher risk of dementia development, as observed with penetrating and moderate/severe TBI; and conversely, less severe TBI, specifically mild TBI and post concussive syndrome (which is indicative of mild TBI), were associated with lower risk of EOD and non-EOD development relative to no TBI. Other factors related to increased risk of EOD were being male, older age at time of TBI, and Hispanic or Latino ethnicity (relative to White). Other factors related to Non-EOD development were being male, older age at time of TBI, Black or African American (relative to White), and having up to a high school education (relative to completing college or higher).

Discussion

Among a large cohort of Post-9/11 Veterans, incidence rates of cognitive disorder were highest among those with a history of TBI and concomitant CUD followed by those with TBI only, CUD only, and those without a history of TBI or CUD. Veterans with CUD + TBI had a 3.26 times higher hazard for cognitive disorder compared with those in the control group. Prior studies have established the association between TBI and dementia (1, 50) and potential mechanisms linking the two conditions (14, 51, 52). As expected, Veterans with TBI only had a 2.32 times higher hazard for cognitive disorder compared with those in the control group. While we are not able to assess a dose-response association between CUD and cognitive disorder, we found a higher hazard of cognitive disorder in those with CUD only and CUD+TBI, compared with the control group. Depending on the type and severity, TBI may be exhibited by focal brain damage causing 'shearing and stretching' injuries in cerebral brain tissues (53, 54) or diffuse axonal injury that may involve subcortical and deeper white matter tissues such as the brainstem and corpus callosum (55). Conversely, the distribution of cannabinoids in the brain, regardless of the intake route, occurs after modifying the deleterious effects on the blood–brain barrier (56). Although the brain's blood supply originates in the base of the skull (the brainstem, amygdala, and hypothalamus) and terminates in the cortical area, a previous study demonstrated that cannabis users exhibited significantly increased blood volumes in the frontal, temporal, and cerebellar areas (57).

While our finding is consistent with a previous study indicating higher risk of EOD in Veterans with TBI (16), our data also suggests that CUD is an independent risk factor for cognitive disorder only in the non-EOD group. Compared with the control group, the CUD-only group exhibited a 79% higher hazard for cognitive disorders, primarily driven by the non-EOD subgroup (excluding



Life Table, the Cognitive Disorder failure rate (95%CI)	5 Years	10 Years	15 Years
Control	0.02 (0.01, 0.02)	0.02 (0.02, 0.03)	0.7 (0.68, 0.72)
TBI only	0.24 (0.22, 0.26)	0.28 (0.26, 0.30)	2.35 (2.28, 2.42)
CUD only	0.04 (0.03, 0.06)	0.06 (0.05, 0.09)	1.68 (1.53, 1.85)
CUD+TBI	0.25 (0.21, 0.30)	0.3 (0.25, 0.36)	4.4 (4.14, 4.68)

FIGURE 2
The time from TBI (or TBI index date in the control group) to cognitive disorder, Kaplan–Meier survival estimate and life table, in four groups: Control, TBI only, CUD only, and CUD+TBI. TBI, Traumatic Brain Injury; CUD, Cannabis Use Disorder.

AD and FTD). A previous systematic review of brain imaging studies among adolescent cannabis users revealed functional and structural evidence of lesions in the frontoparietal, frontolimbic, frontostriatal, and cerebellum regions (58). The results are also consistent with previous studies demonstrating that cannabis use is associated with cognitive functional disorder and bilateral hippocampal and amygdala volume reduction in midlife patients with heavy, chronic cannabis use (40, 45). Our findings indicate AD and FTD are less likely to be observed in the CUD patients, which may be explained by intact cortical areas in cannabis users but need further investigation. Since AD is characteristically a disease of older age (59) and those who were older tended to have lower cannabis quantity use and fewer consequences associated with cannabis use (60, 61), other considerations include possible age-related behavioral changes among those with CUD. Additional factors not measured in these analyses, including social, structural, and biological characteristics, may contribute to dementia susceptibility in Veterans with non-EOD and co-occurring CUD.

The hazard ratio for dementia diagnosis across all categories was more pronounced in individuals with non-EOD, compared with EOD, which could be explained by genetic risk factors and the physiopathology of TBI and CUD in the progression of dementia. The genetic risk factors may pave the way to approach the hypothesis behind the dissimilarity in our EOD vs. non-EOD results. Previous studies addressed the potential roles of several missense mutations and known variant genes in the pathogenesis of early-onset AD (62) and decreased levels of dopaminergic neurotransmitters in patients with AD (63). Conversely, distinct genetic factors for CUD might concurrently initiate underlying pathways related to AD (64). Cannabinoids have been shown to increase mesolimbic dopamine transmission in the short term (65). The risk factors underlying CUD development likely involve multiple genes that interact with each other and the environment, ultimately leading to cognitive disorders. TBI is defined as an impact, penetration, or rapid movement of the brain within the skull and the event can be classified as either impact (direct contact of the head with an object) or non-impact (encountering non-impact forces like blast waves or rapid acceleration and deceleration) (66).

Limitations

This study has several limitations. The results were restricted to Veterans and based on characteristics and conditions measured and stored in electronic health records (EHRs). Therefore, they may not represent other patient populations. We attempted to account for the difficulties associated with obtaining chronicity and severity of cannabis use by examining both DoD and VA records and limiting cannabis exposures to ICD codes related to CUD. The EHR system in VHA allowed us to identify a CUD diagnosis after the TBI index date, further strengthening the methodology. However, we note that we were not able to quantify the route of cannabis intake (i.e., inhalation vs. ingestion), which is an area for further exploration. While our approach focused on cognitive disorders due to inaccuracy of dementia codes in younger individuals,

TABLE 3 The impact of selected demographic and clinical characteristics on cognitive disorder (adjusted cox proportional hazards model) among veterans with TBI ($N = 1,554,319$).

	All	EOD	Non-EOD
TBI severity (No TBI)	**Ref**	**Ref**	**Ref**
Mild	0.81 (0.75, 0.89)	0.76 (0.56, 1.04)	0.76 (0.67, 0.86)
Moderate/Severe	1.31 (1.19, 1.44)	1.00 (0.70, 1.45)	1.30 (1.13, 1.49)
Penetrating	2.88 (2.6, 3.2)	1.61 (1.09, 2.38)	3.33 (2.89, 3.85)
Post concussive syndrome	0.40 (0.28, 0.57)	0.45 (0.14, 1.46)	0.42 (0.25, 0.69)
Male	1.31 (1.23, 1.4)	1.22 (1.01, 1.48)	1.52 (1.38, 1.68)
Age at the time of TBI	1.08 (1.08, 1.08)	1.17 (1.16, 1.18)	1.08 (1.07, 1.08)
Race (White)	Ref	Ref	Ref
Black or African American	1.04 (0.99, 1.10)	0.99 (0.83, 1.18)	1.11 (1.02, 1.20)
Hispanic or Latino	1.07 (0.99, 1.14)	1.33 (1.08, 1.64)	1.02 (0.91, 1.13)
Other	0.99 (0.92, 1.07)	0.89 (0.69, 1.14)	1.04 (0.93, 1.16)
Unknown	0.93 (0.64, 1.37)	0.40 (0.06, 2.85)	0.89 (0.48, 1.65)
Education (college or higher)	Ref	Ref	Ref
High School and Less	1.14 (1.09, 1.20)	1.04 (0.90, 1.20)	1.19 (1.11, 1.29)
Unknown	1.1 (0.81, 1.50)	0.87 (0.43, 1.77)	1.01 (0.62, 1.64)
Alcohol use disorder	1.08 (1.02, 1.14)	0.94 (0.78, 1.15)	1.08 (0.99, 1.18)
Opioid use disorder	0.82 (0.76, 0.88)	0.71 (0.53, 0.94)	0.78 (0.7, 0.87)
Other drug use disorder	1.47 (1.37, 1.58)	1.26 (0.95, 1.67)	1.43 (1.28, 1.59)
Nicotine use disorder	0.91 (0.86, 0.96)	0.82 (0.68, 1.00)	0.90 (0.83, 0.98)

TBI, Traumatic Brain Injury; CUD, Cannabis Use Disorder; EOD, Early Onset Dementia; Ref, Reference.

further analysis is warranted in other older cohorts, and subsequent analyses as this longitudinal cohort ages.

Conclusions

The results of our study suggest that CUD and TBI are independent risk factors for cognitive disorder and the highest incidence of cognitive disorder is observed in Veterans with comorbid CUD+TBI. TBI and CUD are both independently associated with cognitive impairment. Cognitive impairment is a common post-TBI symptom that may last more than 6 months post-injury (8, 9). Acute inhaled cannabis use is associated with cognitive impairment that may last at least 5 h (38). However, the timing of cognitive disorders is the key point in our study (i.e., time from TBI to ICD codes for dementia diagnosis) and likely indicates permanent cognitive dysfunction after TBI insult. The heterogeneity in impact of CUD on emergence of EOD and Non-EOD subgroup in our cohort, who were relatively young at the time of TBI, may be indicative of the potential harms of cannabis use on long-term cognitive dysfunction. Given that cannabis receptor (CB1R) is enriched in the mesocorticolimbic system (67) and cannabis exposure increases long-term vulnerability to cognitive impairments (68, 69), our results support the long-term harmful effect of cannabis use in patients with cognitive disorder and dementia subtypes that involved brain areas other than frontal and temporal lobes (AD and FTD). Cannabis users showed that the cerebral blood flow reduced in cortical regions and increased in the right precuneus at baseline (70). Also, in the experimental animal's study, noxious effects of chronic cannabis exposure led to higher THC and cannabidiol concentrations in cerebellum and occipital cortex of squirrel monkeys and persisted after discontinuation of the treatment (71). Further studies is needed to evaluate the impact of the chronic cannabis use and structural changes in medial temporal structures and midbrain (40–45). Given the findings of this analysis and the increasing awareness of the potential long-term impacts of combat-related and civilian TBI and the growing rates of CUD, further investigations are warranted.

Data availability statement

The datasets presented in this article are not readily available because VA regulation required the dataset behind the firewall. Requests to access the datasets should be directed to vinci@va.gov.

Ethics statement

The studies involving humans were approved by the University of Utah and Stanford University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal

guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AE: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. CD-G: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing. TP: Investigation, Methodology, Writing – review & editing. MA: Data curation, Software, Writing – review & editing. CG: Project administration, Resources, Writing – review & editing. AD: Investigation, Writing – review & editing. MM: Project administration, Writing – review & editing. EK: Writing – review & editing, Data curation, Methodology, Validation. DC: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing. MP: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1261249/full#supplementary-material

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Sleep duration and perceptions of sleep quality in British Army recruits during basic training - an observational analysis

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Introduction: Sleep is critical to the health, wellbeing and performance of military personnel during basic training. This two-part study evaluated sleep-wake patterns and sleep disturbances in junior soldiers (JS) and infantry recruits in Autumn 2021 (study 1), and non-infantry recruits in spring 2022 (study 2).

Methods: During studies 1 and 2, validated wearable technology combined with a sleep diary was used to quantify sleep-wake indices, sleep disturbances and perceptions of sleep quality. Sleep diary data was analysed descriptively. A series of repeated-measures ANOVAs examined differences in objective sleep-wake indices. Correlation analysis determined associations between time in bed (TIB) and total sleep time (TST).

Results: Significant ($p < 0.05$) differences in most sleep-wake indices were observed between weeks of basic training for all cohorts. Strong positive correlations between TIB and TST were observed for each cohort across basic training ($r = 0.681 - 0.970$, $p < 0.001$), with longer TST associated with greater TIB. The mean±SD sleep duration (hours and mins [hm]) for JS (06:22 ± 00:27hm), non-infantry (05:41 ± 00:47hm) and infantry (05:46 ± 00:34hm) recruits across basic training was consistently below national recommendations. The mean±SD bed and wake times for JS (bedtime: 23:01 ± 00:32hm; awake: 05:34 ± 00:10hm), non-infantry (bedtime: 23:38 ± 01:09hm; awake: 04:47 ± 00:58hm), and infantry (bedtime: 23:13 ± 00:29hm; awake: 05:38 ± 00:26hm) recruits varied across weeks of basic training, with over 80% reporting "fairly bad" or "very bad" sleep quality and frequent periods of "dozing off" during daytime activity. The most commonly reported sleep disturbing factors identified during basic training involved: late-night military admin (e.g., ironing, boot cleaning, kit set up etc), early morning wake times, extraneous noise, light and hot room temperatures within the primary sleeping environment, bed/mattress discomfort, muscle soreness and feelings of stress and anxiety.

Discussion/Conclusion: Our findings contribute to the existing evidence that long-term sleep loss is pervasive during initial military training programmes. The average sleep durations indicate chronic and unrecoverable sleep loss which would be expected to significantly impair physical and cognitive military performance, and increase the risk of injury, illness and attrition rates during basic training. Changes in the design and scheduling of basic training programmes to enable, at the least, minimum sleep recommendations to be met, and to improve sleep hygiene in the primary sleeping environment are warranted.

KEYWORDS
recruit, sleep duration, sleep loss, military training, adolescence

Introduction

The primary aim of basic training is to transform civilians into trained soldiers. Recruits are required to internalize core professional values, master technical skills and improve physical fitness to meet the required standards of basic training. Failure to meet these standards can negatively impact first time pass rates and subsequent progression into the field Army as a fully trained soldier. Poor health and performance during basic training has been associated with a number of risk factors (e.g., low fitness, prior injury, cognitive dissonance and stress, aggressive coping strategies, poor mental health, smoking, body mass index) (1–4). However, a component of basic training that serves to promote several physiological and cognitive functions, and therefore, could significantly undermine recruit health and performance during basic training if impaired, is sleep.

Good quality sleep is dependent on achieving sufficient duration and is essential for recovery from training and operational stressors (5). The negative implications of poor sleep on mental health (6, 7), immune function and infection (8), physical adaptation and performance (9), injury risk (10, 11), emotional regulation (12), cognitive and higher-order functioning (13), and job performance (14) are well established in civilians (both adult and adolescent) and military personnel. However, despite a growing awareness of the importance of sleep, military culture largely accepts sleep deprivation as a normal part of military training, with reports indicating that military leaders and, by extension, their subordinates perceive the need for sleep as a "weakness" (15, 16) or as a means of "hardening" recruits as part of their socialization into the military (17). These actions are despite prior research demonstrating the importance of leadership's role in subordinates' sleep health, particularly recruits who include the youngest and least experienced members of the military (17, 18).

According to expert consensus statements (19) and the National Sleep Foundation (NSF) recommendations for sleep duration (20), healthy young adults [18–25 years (yrs)] and adolescents (13-18 yrs) (representative of recruits and Junior Soldiers [JS] undergoing regular basic training) require 7–9 h (hr) and 8–10 h of sleep per night to support optimal health and performance, respectively. Despite these recommendations, it is becoming increasingly evident that military recruits are likely to experience chronic and unrecoverable sleep loss during basic training (21–23), and therefore, placing them at greater risk of injury, illness, and impaired cognitive and military specific performance (10, 13, 24). Evidence of inadequate sleep duration in British Army Officer Cadets (5.5 h per night) and Infantry recruits (6 h per night) has been reported (8, 25). However, these studies only assessed a small number of days (7–14) relative to training course length (14–40 weeks), did not include an assessment of sleep hygiene of the primary sleeping environment, and were unable to evaluate sleep from other basic training populations (e.g., non-infantry or junior soldiers).

To date, no assessment of sleep–wake patterns of non-infantry recruits and JS during basic training has been conducted. The average age of a JS commencing basic training is 16 yrs., and of the many changes that occur during maturation, changes in the adolescent sleep–wake cycle are among the most dramatic (26–28). Coinciding with pubertal onset and throughout maturation, adolescents experience a phase delay (i.e., a shift in chronotype preference) in their sleep–wake cycle as reflected by delayed bedtimes, later awakenings and longer sleep periods (27, 29, 30). These biologically determined adaptations in adolescent sleep–wake patterns dictate a net increase of 0.5–1.25 h, which corresponds to 8.5–9.25 h of required sleep per night, irrespective of adolescent age or maturation stage (17, 31). Poor understanding of the sleep–wake changes and requirements of adolescents combined with chronic and unrecoverable sleep loss risks the presentation of significant health, performance and developmental issues during maturation (29, 32). As such, better understanding of the current sleep–wake patterns of JS during training is warranted given the health and performance implications related to poor and unrecoverable sleep loss as demonstrated within civilian populations (30).

Our current understanding of sleep across different training populations is limited, and therefore, unable to adequately support evidence-based practice/policy changes related to sleep and recovery of recruits and JS during basic training. The aim of this study was to evaluate sleep–wake patterns and perceptions of sleep quality, including potential sleep hygiene issues, in JS, non-infantry and infantry recruits during their respective basic training. We hypothesized that all recruits and JS would demonstrate inadequate sleep duration relative to minimum national sleep recommendations, poor perceptions of sleep quality, and suboptimal sleep hygiene within the primary sleeping environment.

Methods

Study 1 and 2 conducted an assessment of sleep duration and perceptions of sleep quality during basic training. Study 1, conducted in autumn 2021, used wrist-based actigraphy (wGT3X-BT, Actigraph, Pensacola, United States) and the National Sleep Foundation (NSF) sleep diary during weeks 1, 2, 6 and 11 of basic training in line infantry recruits (Infantry Training Center, Catterick) and Junior Soldiers (JS) (Army Foundation College, Harrogate). Study 2, conducted in spring 2022 used a sleep ring (Oura health, Finland) and the same NSF sleep diary during 12 weeks of basic training in non-infantry recruits (Army Training Center, Pirbright). To note, study 2 was part of a wider internal service evaluation on program design, explaining why the sample size for this group was greater compared to JS and infantry recruits. Participants who volunteered to take part in this study provided informed consent. Ethical approval was granted by the United Kingdom Ministry of Defense Research Ethics Committee (924/MODREC/18). Height and weight were recorded using a stadiometer and digital weighing scales (SECA 703, Birmingham, United Kingdom). Body mass index was calculated and interpreted as per Nuttall (33) (Table 1).

TABLE 1 Participant demographics.

Basic training cohort	Age (yrs)	Height (cm)	Body mass (kg)	BMI (kg/m^2)
Non-infantry recruits (*n* 208)	23.2 ± 4.8	175.9 ± 8.4	75.8 ± 5.4	24.2 ± 4.1
Junior Soldiers (*n* 37)	16.2 ± 0.4	164.4 ± 35.1	71.7 ± 10.7	24.5 ± 3.1
Line Infantry recruits (*n* 19)	22.8 ± 4.4	175.7 ± 8.5	73.2 ± 9.6	23.8 ± 3.2

Values are mean ± SD.

TABLE 2 Sleep–wake indices.

Sleep variable	Definition (units)
Total sleep time	Actual time spent asleep from sleep start and end, minus any wake time (hours: mins [hm])
Time in bed	Difference between bedtime and awakening time (hm)
Sleep onset latency	The time it takes to transition from full wakefulness to sleep onset (hm)
Wake after sleep onset	The total number of hours and mins marked awake after sleep onset (hm)
Sleep efficiency	The sleep duration expressed as a percentage of time asleep from bedtime to wake (%)
Sleep fragmentation index	A measure of restlessness based on physical movement and expressed as a percentage (%)

A description of the sleep indices collected from the wearable technology used in both study 1 and 2.

Experimental design

The sleep–wake indices recorded from the wearable technology during both study 1 and 2 are defined in Table 2 (34, 35).

Study 1

The Actigraph wGT3X+ sleep watch (dimensions: 4.6 cm x 3.3 cm x 1.5 cm, weight: 19 g) was worn on the non-dominant wrist and used to record sleep–wake indices from infantry recruits and JS. The wGT3X+ has shown to produce valid estimates of sleep–wake indices when worn on the wrist compared to polysomnography (PSG) (36). Due to limited resources at the time of data collection, sleep–wake data was only measured (Monday to Friday) during weeks 1, 2, 6 and 11 of basic training. Actigraph watches were initialized to record sleep–wake data in 30-s epochs, with mean ± SD values reported across each week of basic training. Sleep–wake data was derived from proprietary software (ActiLife Software, v6.13.4, Pensacola, FL) using the Sadeh algorithm (37), which has shown reasonable to good levels of agreement for sleep–wake estimation compared to PSG (38). An online version (LimeSurvey, Community Edition Version 6.3.4) of the NSF sleep diary (completed on individual's mobile phones) was used to determine perceptions of sleep quality and sleep disturbing factors, involving a series of multiple-choice questions, including "*likeliness of dozing off during daytime*," "*ease of falling asleep at night*," "*overall rating of sleep quality*," "*perceived fatigue upon awakening*," and "*factors disturbing sleep at night.*" In both study 1 and 2, participants were provided with verbal instructions of the timing (i.e., AM between 0600–0700), how to complete the self-report measures, and were given example question/answer definitions to aid their understanding and interpretation.

Study 2

A sleep ring (OURA Gen 2), width: 7.9 mm; thickness: 2.6 mm; weight: 4-6 g was worn on the non-dominant index finger and used to record the same sleep–wake indices in study 1 each night of the 12-week course (~90 days). Estimates of sleep staging were not included due to low levels of accuracy and sensitivity reported for the Gen 2 ring when detecting rapid-eye-movement (REM) and non-REM sleep compared to gold standard (35, 39). Data from the sleep ring was extracted from proprietary software (Oura Teams, Finland) and mean ± SD reported across each week of basic training. Compared to gold-standard (i.e., PSG), the sleep ring demonstrates acceptable-to-high levels of accuracy and sensitivity in detecting sleep–wake indices and differences in sleep patterns in young healthy populations (35). The same online NSF sleep diary questions were used to determine perceptions of sleep quality and sleep disturbing factors only in weeks 1, 2, 6 and 12 to minimize study burden while providing comparable data.

Statistical analysis

Data was analyzed descriptively (mean ± SD) to summarize participants' demographics, objective sleep–wake indices and scores for each subjective response across the reporting weeks of basic training. The daily TST data derived from the sleep watch for infantry recruits and JS, and the sleep ring for non-infantry recruits were plotted against the NSF recommendations for young adults (18-25 yrs., i.e., non-infantry and infantry recruits) and adolescents (13-18 yrs., i.e., JS) (40). The R package 'vioplot' (Alder and Kelly, 2020) (V.0.3.6) in R Core Team software (V.4.0.4; Vienna, Austria) was used for preparation of the TST figures.

Sleep–wake variables collected from the sleep watch and ring were graphically examined for normality (normal Q-Q plots) prior to statistical analysis. Sample size was based on *a priori* power analysis using G*power (Dusseldorf, V 3.1). For a within-factors repeated-measures (RM) ANOVA, a minimum of 18 participants was required to achieve a medium effect size (np^2, 0.06) with $\alpha = 0.05$ and $\beta = 0.90$. A series of RM ANOVAs were conducted to determine differences in pseudo-objective sleep–wake indices between each week of training measured. Significant

main effects were followed up with *post hoc* (Bonferroni adjusted) analyses and mean differences between significant pairs were presented with corresponding effect sizes [Cohen's *d* criteria: ≤ 0.2 is considered trivial, 0.21–0.5 is small, 0.51–0.8 is moderate and ≥ 0.8 is large (41)]. A bivariate Pearson product–moment correction was conducted to determine the association between TIB and TST for each cohort and week of basic training [Pearson's r criteria: small 0.10–0.29; moderate 0.30–0.49; large 0.50–1.0 (41)].

Results

Study 1

Infantry recruits

Significant main effects for week of basic training were observed for sleep efficiency ($p = 0.017$, $\eta_p^2 = 0.21$), TIB ($p < 0.001$, $\eta_p^2 = 0.58$), TST ($p < 0.001$, $\eta_p^2 = 0.57$) and WASO ($p = 0.005$, $\eta_p^2 = 0.26$). No significant main effects were observed for sleep fragmentation ($p = 0.420$, $\eta_p^2 = 0.06$) or SOL ($p = 0.119$, $\eta_p^2 = 0.102$), however, the average sleep fragmentation and SOL was 22 ± 1.5% and 00:07 ± 00.06hm, respectively. *Post hoc* analysis (Supplementary Table S3) revealed significantly poorer sleep efficiency scores in week 1 when compared to week 11 of basic training ($p = 0.044$, 95%CI: 0.06, 5.77, $d = 1.4$, $\Delta = 3\%$). Despite these differences, sleep efficiency remained normal (i.e., >80%) (34) across each week of basic training measured. Infantry recruits had significantly less TIB during week 6 (05:29 ± 00:37hm) when compared to week 1 ($p < 0.001$, 95%CI: 43.11, 145.04, $d = 2.3$, $\Delta = 94$ min), week 2 ($p < 0.001$, 95%CI: 36.98, 108.79, $d = 1.8$, $\Delta = 72$ min) and week 11 ($p < 0.001$, 95%CI: 44.52, 103.44, $d = 1.8$, $\Delta = 73$ min). Similarly, significantly less TST was observed during week 6 (04:48 ± 00:33hm) compared to week 1 ($p < 0.001$, 95%CI: 32.93, 131.87, $d = 2.0$, $\Delta = 82$ min), week 2 ($p < 0.001$, 95%CI: 38.27, 107.84, $d = 1.8$, $\Delta = 73$ min) and week 11 ($p < 0.001$, 95%CI: 39.08, 117.21, $d = 1.9$, $\Delta = 78$ min) of training (Figure 1). Significantly longer WASO was observed in week 1 (00:41 ± 00:10) compared to week 11 ($p = 0.012$, 95%CI: 2.78, 25.90, $d = 1.4$, $\Delta = 14$ min). A strong positive correlation between TIB and TST was observed for each week of basic training Wk1: $r = 0.970$, $p < 0.001$; Wk2: $r = 0.915$, $p < 0.001$; Wk6: $r = 0.944$, $p < 0.001$; Wk11: $r = 0.829$, $p < 0.001$. Time in bed explained 91–98% of the variance in infantry recruit's TST during basic training.

Infantry recruits spent, on average, 01:20hm less TIB and 01:17hm less TST during week 6 of basic training when compared to all other reporting weeks. The national minimum sleep recommendations for TST were not met, on average, by 68% in week 1, 84% in week 2, 96% in week 6 and 85% in week 11. Average bed and wake times reflected TST and TIB results: week 1 (bedtime: 23:08 ± 00:33hm; wake-time: 06:12 ± 00:34hm), week 2 (bedtime: 23:13 ± 00:29hm; wake-time: 05:47 ± 00:24hm), week 6 (bedtime: 23:45 ± 00:35hm; wake-time: 05:15 ± 00:16hm) and week 11 (bedtime: 22:47 ± 00:28hm; wake-time: 05:20 ± 00:17hm).

The NSF sleep diary responses across the reporting weeks of basic training indicated that 38–69% of infantry recruits were "likely" and a further 39–58% "somewhat likely" to doze off during daytime activities. Sleep quality was "very bad" (56–82%) and "fairly bad" (10–34%); while the majority were able to fall asleep "easily" (60–83%) but felt only "somewhat refreshed" (44–59%) upon awakening (Figures 2A–D).

The proportion of the most common self-reported sleep disturbing factors reported by infantry recruits included, late-night military admin (e.g., ironing, boot cleaning, kit set up, weapon handling, studying) and early morning wake times (>85%), noise (36–42%) and light (34–50%) within and outside of the primary sleeping environment, and a hot room temperature (12%).

Junior soldiers

Significant main effects for week of basic training were observed for sleep efficiency ($p < 0.01$, $\eta_p^2 = 0.146$), TIB ($p < 0.001$, $\eta_p^2 = 0.275$), TST ($p < 0.001$, $\eta_p^2 = 0.319$), WASO ($p = 0.025$ $\eta_p^2 = 0.080$) and sleep fragmentation ($p = 0.002$, $\eta_p^2 = 0.130$). No significant main effects were observed for SOL ($p = 0.219$, $\eta_p^2 = 0.065$), with average SOL of 00:14 ± 00:09hm demonstrating a reasonably short SOL throughout basic training. *Post hoc* analysis (Supplementary Table S3) revealed significantly poorer sleep efficiency in week 12 compared to week 1 ($p = 0.010$, 95%CI: −3.84, −0.38, $d = 0.61$, $\Delta = 3\%$) and week 6 ($p = 0.047$, 95%CI: 0.01, 3.31, $d = 0.47$, $\Delta = 2\%$) of basic training. Despite these differences, sleep efficiency was considered normal (i.e., >80%) across the reporting weeks of basic training. Significantly less TIB was observed during week 12 (06:35 ± 00:40hm) compared to week 1 ($p < 0.01$, 95%CI: −44.2, −10.8, $d = 0.87$, $\Delta = 27$ min), week 2 ($p = 0.019$, 95%CI: −38.2, −2.43, $d = 0.72$, $\Delta = 20$ min) and week 6 ($p < 0.01$, 95%CI: −47.94, −11.91, $d = 1.10$, $\Delta = 26$ min). Similarly, significantly less TST was observed in week 12 (06:00 ± 00:43) compared to week 1 ($p < 0.001$, 95%CI: 14.91, 48.8, $d = 1.02$, $\Delta = 32$ min), week 2 ($p = 0.004$, 95%CI: 5.82, 40.51, $d = 0.74$, $\Delta = 23$ min) and week 6 ($p < 0.01$, 95%CI: 13.80, 51.23, $d = 1.04$, $\Delta = 33$ min) (Figure 3). Junior soldiers spent, on average, 00:26hm less TIB and 00:30hm less TST during week 12 when compared to all other weeks evaluated. A strong positive correlation between TST and TIB was observed for each week of basic training Wk1: $r = 0.809$, $p < 0.001$; Wk2: $r = 0.801$, $p < 0.001$; Wk6: $r = 0.901$, $p < 0.001$; Wk12: $r = 0.949$, $p < 0.001$. Time in bed explained 89–97% of the variance in JS TST during basic training.

Junior soldiers demonstrated significantly greater WASO in week 12 (00:33 ± 00:14hm) when compared to week 6 ($p = 0.017$, 95%CI: 0.75, 10.84, $d = 0.45$, $\Delta = 6$ min), and demonstrated significantly greater sleep fragmentation in week 12 compared to week 1 ($p = 0.032$, 95%CI: 0.22, 7.11, $d = 0.63$, $\Delta = 4\%$) and week 2 ($p < 0.01$, 95%CI: 0.89, 7.16, $d = 0.72$, $\Delta = 4\%$). The proportion of nights per week that recruits did not meet the minimum national sleep recommendations for adolescents (i.e., 8 h) was 100% (week 1), 98% (week 2), 96% (week 6) and 99% (week 12). Average bed and wake-times for JS differed across the reporting weeks of basic training; week 1 (bedtime: 22:46 ± 00:22hm; wake-time: 05:47 ± 00:09hm), week 2 (bedtime: 23:45 ± 00:14hm; wake-time: 05:22 ± 00:11hm), week 6 (bedtime: 22:30 ± 00:16hm; wake-time: 05:31 ± 00:16hm) and week 12 (bedtime: 23:06 ± 00:36hm; wake-time: 05:38 ± 00:10hm).

The majority of sleep diary responses across the reporting weeks of basic training indicated that JS were "likely" (28–36%) and "somewhat likely" (47–58%) to doze off during the daytime; they rated their sleep quality as "very bad" (66–87%) and "fairly bad" (11–26%); they were able to fall asleep "easily" (60–83%) and

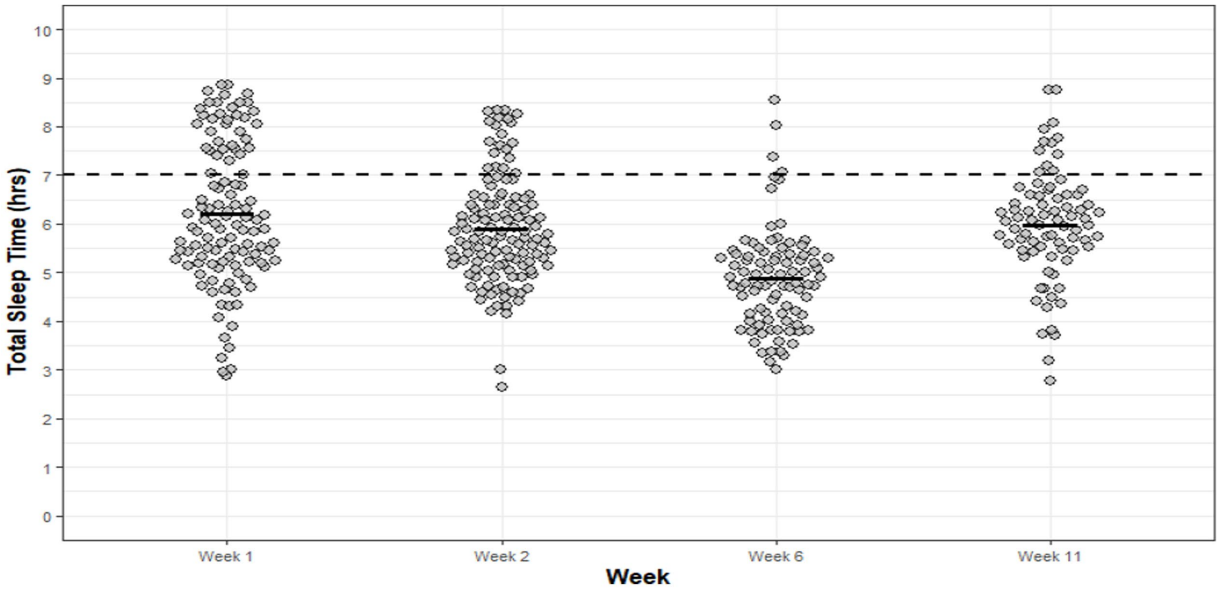

FIGURE 1
Infantry TST for each night of each week of basic training. Dots are individual nights within their respective week and the solid horizontal line represents the average weekly TST. The dashed horizontal line represents the minimum national sleep recommendations for young adults (7 h).

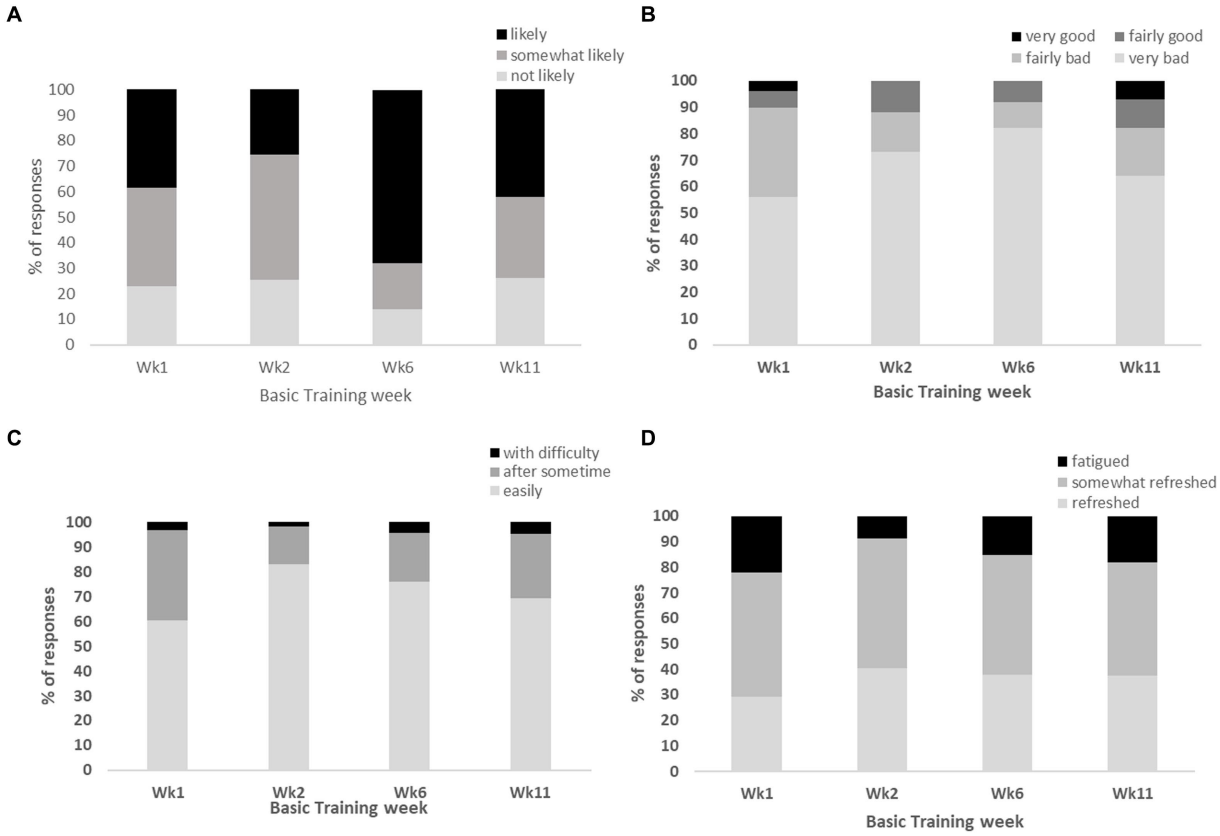

FIGURE 2
Represents the proportion (%) of responses from infantry recruits for the following NSF sleep diary questions, **(A)** "likeliness of dozing off during daytime"; **(B)** "overall rating of sleep quality"; **(C)** "ease of falling asleep at night"; **(D)** "perceived fatigue upon awakening".

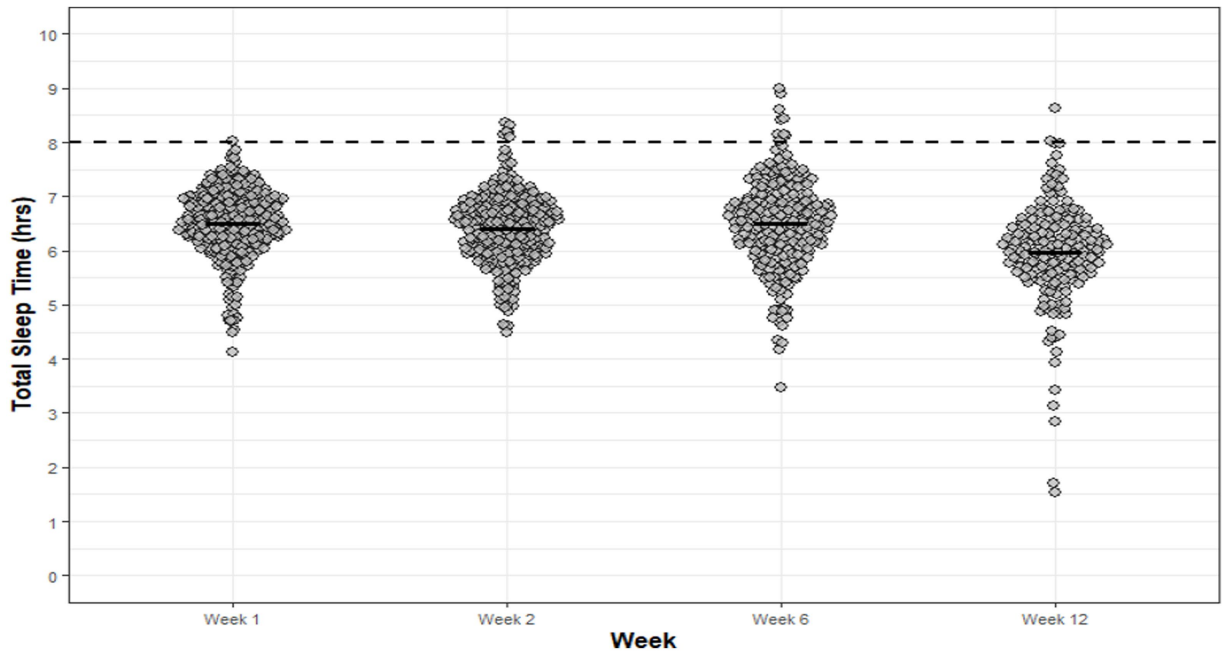

FIGURE 3
JS TST for each night of each week of basic training. Dots are individual nights within their respective week and the solid horizontal line represents the average weekly TST. The dashed horizontal line represents the minimum national sleep recommendations for adolescents (8 h).

"somewhat easily" (22–37%); and felt "somewhat refreshed" (48–51%) and "fatigued" (16–32%) upon awakening during basic training (Figures 4A–D).

The most common self-reported sleep disturbing factors reported by JS during the reporting weeks of basic training included noise (32–35%) within the primary sleeping environment, early-morning wake times (23–34%), bed discomfort (18–24%), and feelings of stress and anxiety (11–18%).

Study 2

Non infantry recruits

Significant main effects for week of basic training were observed for sleep efficiency ($p < 0.001$, $\eta_p^2 = 0.182$), TIB ($p < 0.001$, $\eta_p^2 = 0.176$), TST ($p < 0.001$, $\eta_p^2 = 0.188$), WASO ($p < 0.001$ $\eta_p^2 = 0.227$), SOL ($p < 0.01$, $\eta_p^2 = 0.171$) and sleep fragmentation ($p = < 0.001$, $\eta_p^2 = 0.087$). *Post hoc* analysis revealed significant differences ($p < 0.05$) for all sleep indices between weeks of basic training (Supplementary Table S3), ranging in moderate-to-large effects for significant pairs.

Sleep efficiency was similar across weeks, ranging between 81 and 88%, with the lowest scores observed for week 4. The average SOL across each week ranged from 00:08hm – 00:15hm, with weeks 4, 7 and 12 showing significantly shorter SOL compared to weeks 6, 9 and 10. The shortest average TIB for non-infantry recruits was observed during week 1 (05:53 ± 00:48hm) of basic training. For all other weeks, the average TIB ranged between 06:26 ± 01:15hm and 07:10 ± 00:38hm, with the longest TIB observed in week 10. The shortest average TST was observed in weeks 1, 4, 7 and 11, ranging from 05:09 ± 00:47hm to 05:21 ± 00:47hm. All other weeks demonstrated an average TST of between 05:43 ± 00:40hm and 06:06 ± 00:38hm, with the shortest and longest TST observed for week 1 and week 10 of basic training, respectively (Figure 5). The shortest average WASO was observed during week 1 (00:39 ± 00:15hm), however, WASO ranged between 00:52 ± 00:18hm to 01:18 ± 00:25hm for all remaining weeks of basic training. Sleep fragmentation was found to be greatest during week 12 (36 ± 9.8%), thus indicating greater restlessness, and by extension, sleep disturbance. For all remaining weeks, sleep fragmentation was similar, ranging between 30 ± 7.5% to 35 ± 9.8%. A strong positive correlation between TST and TIB was observed for weeks 1 to 11 of basic training, ranging $r = 0.681–0.901$, $p < 0.001$. Time in bed explained 83–95% of the variance in non-infantry recruit's TST during basic training. Week 12 showed a weak positive correlation ($r = 0.239$, $p = 0.034$), with TIB. However, explained 49% of the variance in TST.

The proportion of nights for each week that did not achieve the minimum national sleep recommendations for young adults (i.e., 7 h) was 80–98%. Additionally, average bed and wake-times varied between weeks of basic training, ranging from 22:10 ± 02:13hm to 23:55 ± 02:11hm and 04:47 ± 01:52hm to 06:34 ± 01:35hm, respectively.

The majority of sleep diary responses across the reporting weeks of basic training indicated that non-infantry recruits were "somewhat likely" (46–71%) and "likely" (24–37%) to doze off during the daytime; they rated their sleep quality as "very bad" (26–37%) and "fairly bad" (32–48%); they were able to fall asleep "easily" (71–90%) and "somewhat easily" (9–25%); and felt "somewhat refreshed" (52–54%) and "fatigued" (19–31%) upon awakening during basic training (Figures 6A–D).

The most common self-reported sleep disturbing factors reported by non-infantry recruits during basic training included late night military admin and early morning wake times (75–80%), noise within the primarily sleeping environment (43–45%), stress and anxiety (18–19%) and muscle soreness (12–14%).

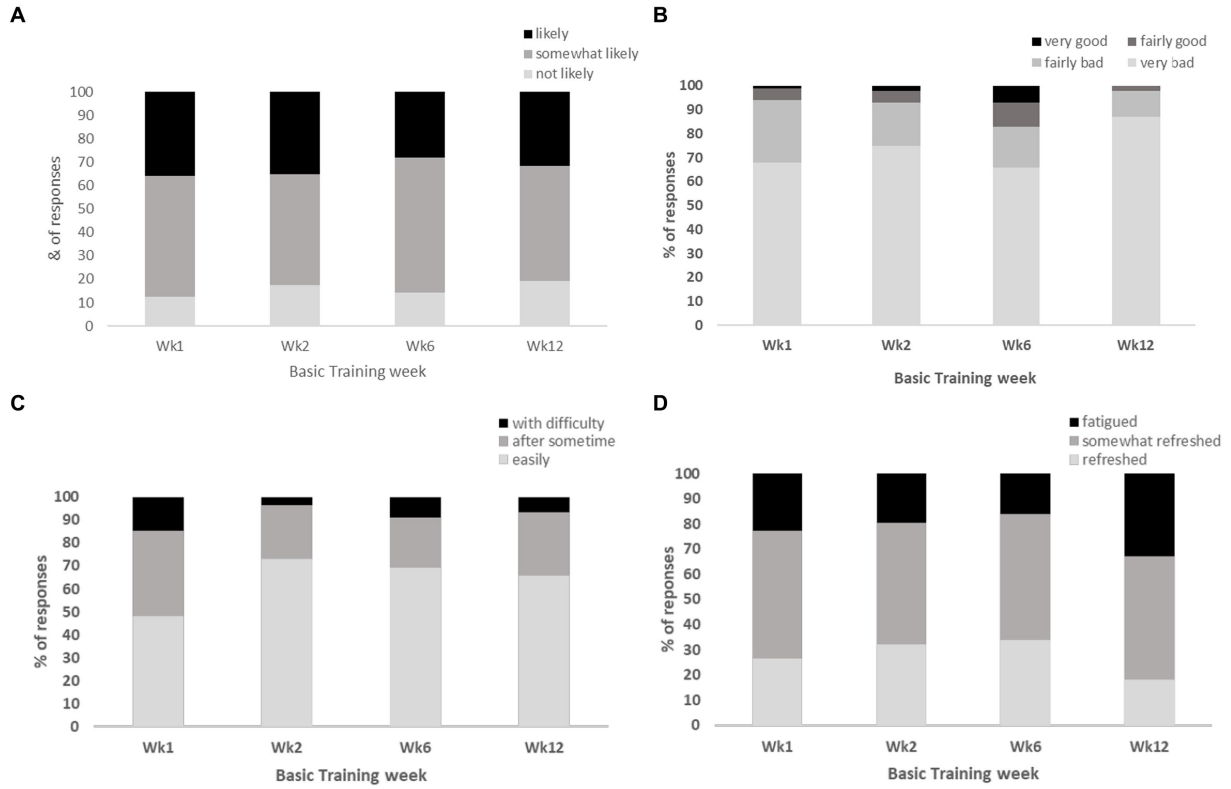

FIGURE 4
Represents the proportion (%) of responses from JS for the following NSF sleep diary questions, **(A)** "likeliness of dozing off during daytime"; **(B)** "overall rating of sleep quality"; **(C)** "ease of falling asleep at night"; **(D)** "perceived fatigue upon awakening".

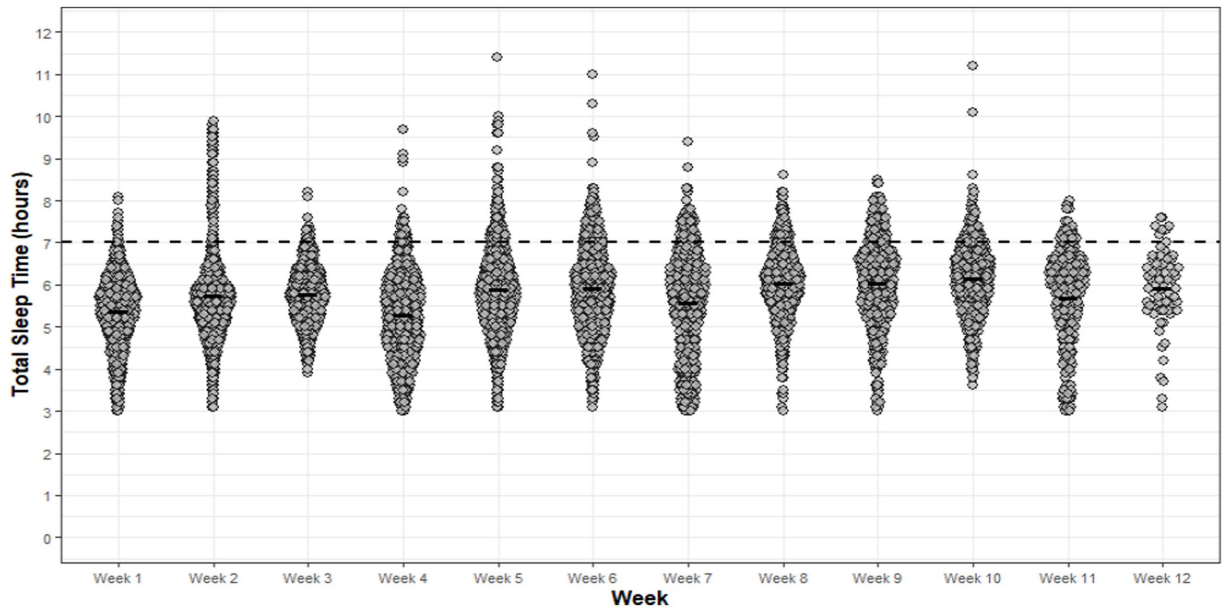

FIGURE 5
Non-infantry recruit TST achieved for each night of each week of basic training. Dots are individual nights within their respective week and the solid horizontal line represents the average weekly TST. The dashed horizontal line represents the minimum national sleep recommendations for young adults (7 h).

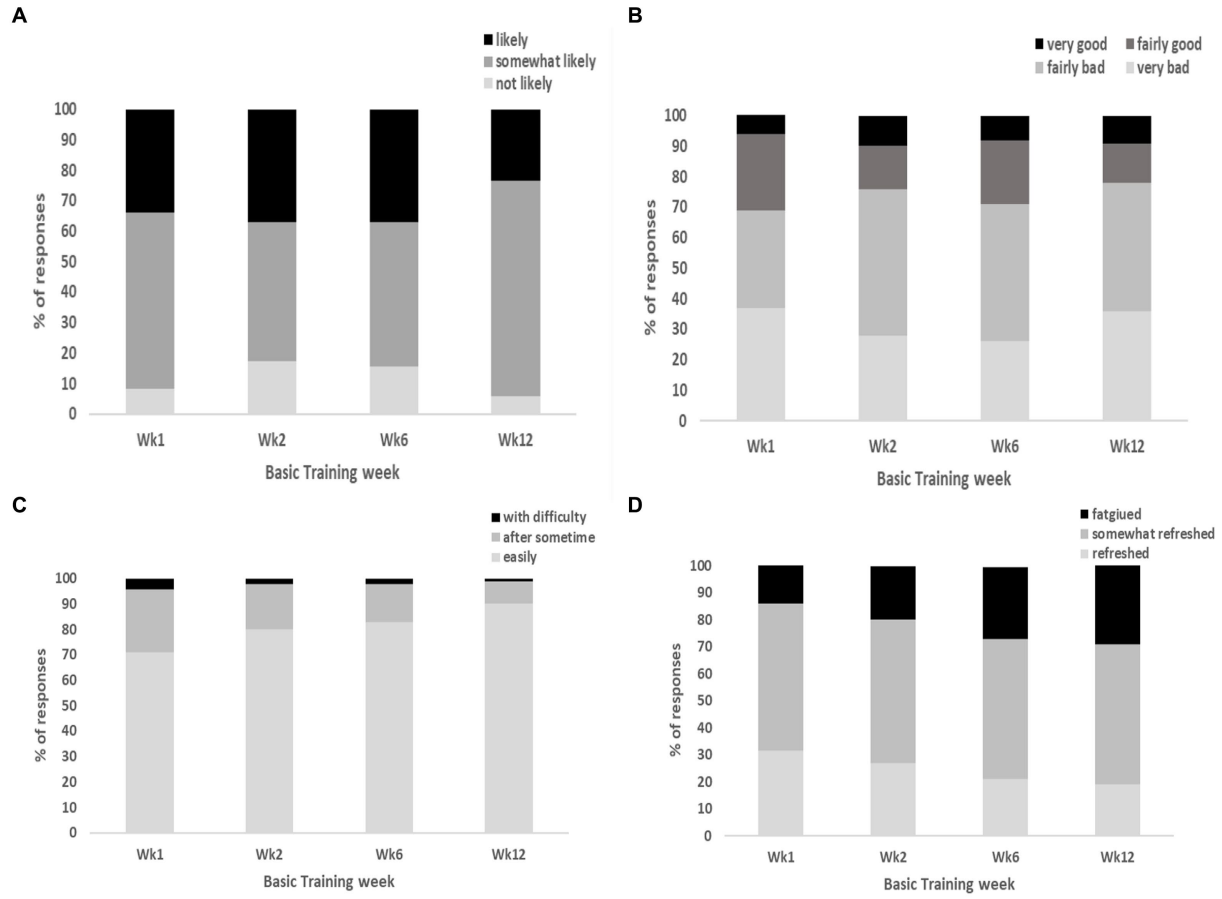

FIGURE 6
Represents the proportion (%) of responses from non-infantry recruits for the following NSF sleep diary questions, **(A)** "likeliness of dozing off during daytime"; **(B)** "overall rating of sleep quality"; **(C)** "ease of falling asleep at night"; **(D)** "perceived fatigue upon awakening".

Discussion

This study sought to evaluate the sleep–wake profiles of British Army JS, infantry and non-infantry recruits, and to quantify modifiable sleep disturbing factors during their respective basic training. Overall, and in agreement with our hypothesis, the average TST observed for JS, non-infantry and infantry recruits was consistently 1-2 h less than the minimum national sleep recommendations. The poor TST can be largely explained by the range in average TIB observed in JS (06:35 ± 00:40–07:04 ± 00:23hm), non-infantry (05:53 ± 00:48–07:10 ± 00:38) and infantry recruits (05:20 ± 00:31hm – 06:54 ± 00:50hm) during basic training. Recruits and JS undertake a number of over-night field-exercises, range activities (i.e., marksmanship) and summative assessments during basic training, most of which are designed to simulate operational demands, which inevitable result in varied sleep schedules. The varied scheduling of training activities explains, in part, the variability in bed and wake times across training for each group. For instance, infantry recruits during week 6 demonstrated ~1 h less average TST compared to other weeks (Figure 6). Upon review of the basic training schedule, it was confirmed that the later bedtimes and shorter TST were due to late-evening foot-drill training in preparation for a summative foot-drill exam scheduled at the end of week 6. Despite the poor average TST for each group across basic training, a small proportion (≤ 32%) achieved minimum sleep recommendations. It is unclear as to how some, over others, were able to achieve minimum sleep recommendations given the standardized nature of training, the unique sleep environment (i.e., 12-person dorms) and the extent of sleep disturbances reported by recruits and JS (i.e., late-night military admin, noise, light etc). However, it is thought that some individuals utilize their time more effectively during the day (when available) to conduct personal military admin (e.g., locker set up, kit cleaning etc.), enabling earlier bedtimes and longer sleep duration. It was also suggested that individuals placed on limited duties due to short-term illness and/or injury may have greater opportunity to achieve longer sleep periods. Nevertheless, further investigation is warranted to elucidate these observations.

Strong positive correlations were observed between TIB and TST for each week of basic training across all three cohorts, indicating that when given greater TIB, most, if not all JS, non-infantry and infantry recruits prioritized a longer TST. Nevertheless, a number of sleep disturbances preventing adequate sleep duration and quality were identified across each cohort, including extraneous light, noise and hot room temperatures within their primary sleeping environment, early-morning wake times and late-night military admin, muscle soreness, bed discomfort and feelings of stress and anxiety.

Furthermore, ~12% of JS, non-infantry and infantry recruits described sleeping on the floor next to their bed in fear of failing early-morning locker/kit inspections. The extent of these self-reported sleep disturbing factors are likely key contributors to the average WASO, sleep fragmentation, and reports of "fairly bad" and "very bad" sleep quality during basic training. Based on our observations, we have shown that JS, non-infantry and infantry recruits are achieving inadequate sleep duration with poor (self-reported) sleep quality, impacted by poor sleep hygiene and sleep schedules.

The chronic sleep restriction observed in our populations is similar to that reported in other recruit populations. Larsen et al. (23) and Bulmer et al. (21) conducted objective sleep evaluations of Australian recruits during a 12-week basic combat course and reported an average sleep duration of ~6.4 h per night. It was further reported that a relatively high proportion of recruits (42%) experienced chronic sleep restriction (i.e., <6 h per night on average). Crowley et al. (22) reported similar patterns of chronic sleep restriction in United States Army recruits during basic training who were averaging between 5 and 6 h sleep per night, which recruits reported as having a detrimental effect on their academic performances due to poor concentration, difficulty staying awake and poor retention of key information during class-based activity. As a consequence of restricted sleep, it is well-known that levels of simple (i.e., reaction time, short-memory recall) and complex (i.e., problem solving, critical thinking, learning) cognitive function are significantly improved with sufficient sleep (42, 43). For instance, Andrews (44) reported 11% better standardized academic test scores in US Army recruits that received 8 h sleep per night compared to those receiving 6 h sleep per night, highlighting the importance of sufficient sleep opportunity on academic performances. Sleep restriction has also shown to significantly increase the risk of injury and illness in military and adolescent civilian populations. Grier et al. (10) identified a dose–response relationship between sleep duration and musculoskeletal injury (MSKi) incidence in adult military personnel. Compared to those who slept >8 h per night, military personnel who slept ≤4 h, ≤ 5 h and ≤ 6 h per night were at a 2.35, 2.06- and 1.53-times greater risk of sustaining a MSKi during training, respectively. Similarly, Milewski et al. (24) determined the relationship between sleep and injury within a similarly aged athletic adolescent population and demonstrated that those who slept less than the minimum recommendations (i.e., 8 h per night) were at a 1.7 times greater risk of sustaining a MSKi compared to those achieving >8 h sleep per night. Sleeping <6 h per night during British Army basic training has shown recruits to be at a 3-times greater risk of being diagnosed with a respiratory illness (8), leading to lost training days, re-squadding and potential discharge from basic training. As such, our population are likely to also be at greater risk of injury, illness and overall poorer academic and military specific performances.

In our study, sleep efficiency scores were within normal ranges (45) throughout basic training, suggesting that JS, infantry and non-infantry recruits achieved relatively good sleep despite consistent reports of poor sleep quality and insufficient sleep duration. A possible reason for the discrepancy between the interpretation of sleep efficiency scores (and sleep reports) is likely a result of the short SOL: despite the potential negative health implications, a shorter SOL results in a higher (i.e., better) sleep efficiency score (34). The average SOL for JS, infantry and non-infantry recruits was considered short, ranging between 7 and 14 min. Notwithstanding individual differences, a SOL of ≤30 min is considered normal for a healthy individual, however, a SOL of ≤8 min is considered extremely short, indicating a high degree of sleep pressure due to sleep restriction and/or the existence of an underlying sleep problem (e.g., hypersomnia) (45). Similar to SOL, WASO is a key metric in the determination of sleep efficiency. While current guidelines do not specify a strict threshold (46) a WASO of >20 min may be indicative of poor sleep hygiene and/or an underlying sleep problem (45, 47). The average WASO observed for JS and infantry recruits was ~30 min, whereas non-infantry recruits experienced an average WASO of ~62 min, explaining, in part, the lower sleep efficiency scores compared to JS and infantry recruits. In contrast to Larsen et al. (23), our sleep efficiency scores were up to 14% greater than those reported in Australian Army recruits during basic training. This difference can partly be explained by the similar SOL (range: 16 – 18 min) and greater WASO (range: 85–123 min) observed in the Australian population, reporting lower sleep efficiency scores (< 79%) estimated from similar wearable technology (i.e., GT9X wrist monitor, Actigraph). The short SOL therefore suggests that sleep pressure is high and that recruits are experiencing a high degree of sleepiness which could be related to, and/or result in, an underlying sleep disorder. However, due to the extent of sleep restriction, any potential underlying disorders would be difficult to determine.

Although the majority of JS, infantry and non-infantry recruits fell asleep quickly once in bed, as demonstrated by the short SOL, the average WASO observed across the reporting weeks of basic training indicates a high degree of sleep disturbance after sleep onset. Although short periods of wakefulness (<20 min) after sleep onset are expected as part of the natural sleep–wake cycle (48), the extent of WASO observed while sleeping in their primary accommodation is likely a consequence of the poor sleep hygiene contributing to greater and more fragmented sleep patterns during basic training. The most common sleep disturbances observed are similarly reported by others during training (21–23), including early-morning wake times and late-night military admin, illness, bed discomfort, extraneous light, noise, and hot room temperatures. The use of personal electronic devices (PEDs) was also reported as a factor impeding adequate sleep during basic training, with many taking the opportunity to contact family and friends, many of whom resided oversees with vastly different time zones. Routine sleep disturbance resulting in fragmented sleep has been associated with decreased behavioral alertness and cognitive capacity (i.e., memory consolidation, learning), and increased negative mood changes (49–51). As such, efforts to improve sleep hygiene to enhance sleep quality are therefore warranted, including more comfortable mattresses/bedding, light and noise mitigations, better regulation of (cooler) room temperatures and relevant education to reduce the magnitude of external (i.e., PED usage) sleep disturbances. It is believed that many of the sleep hygiene issues identified in our study stems from the unique environment (albeit common to many training establishments) in which they sleep. The 12-person dorms that are frequently used to conduct early-morning and late-night military admin (e.g., ironing, boot cleaning, kit set up, weapon handling, studying etc.) must therefore be considered in any sleep intervention.

Muscle soreness was reported by JS, infantry and non-infantry recruits as a key factor contributing to disturbed sleep during basic training. Good quality sleep is well-known for its role in optimizing adaptation and recovery of numerous neuro-physiological processes

(52–55), and thus, with greater opportunity to recover from the physical stressors of basic training, one would expect reports of muscle soreness, and by extension, sleep disturbances to be reduced (52). Other key sleep disturbing factors included feelings of stress and anxiety. Indeed, reports of depressive symptoms are common during basic training, particularly during initial entry (56). Those entering basic training for the first time, the environment is a stark contrast to their prior home environments (e.g., including routine physical training and class-based lessons/education, communal living quarters, regimented mealtimes and sleep schedules, and chronic sleep restriction). Poor sleep quality due to sleep restriction is associated with higher psychological stress and maladaptive training responses during military training (57–59). For many, the psychological demand of adjusting to the basic training environment coupled with routine sleep restriction is likely to exacerbate the levels of psychological stress experienced during basic training, resulting in potentially lower mood, greater mental health-related problems, and by extension, undesirable attrition rates (22, 56, 59, 60). In some recruits this was compounded through the fear of failing their morning kit inspections, and as a result, conducting military admin (e.g., ironing) late into the evening and sleeping on the floor next to their bed. Simple educational and leadership interventions to reduce these types of counterproductive behaviors during basic training is warranted, alongside further work to understand how to better manage and/or structure the psychological demands of basic training.

Compared to non-infantry and infantry recruits, early-morning wake times were more commonly reported by JS as key sleep disturbing factors, and despite an allotted 8 h sleep period (less field exercise and ranges) during basic training (lights out: 2200, reveille: 0600), the average TST was 06:22hm, with average bed and wake times of 23:02 ± 00:32hm and 05:35 ± 00:10hm, respectively. Despite a growing awareness of adolescent sleep–wake requirements, there remains a common misconception among civilian and military members that adolescents should choose and/or be educated to go to sleep earlier than normal as to improve concentration and prevent sleep loss. However, biological changes in the homeostatic regulation of sleep (i.e., phase delay), which contribute to an increased rise in eveningness-chronotype, leads to extended wakefulness later in the evening (61). Therefore, adolescents will naturally fall asleep ~1-2 h later compared to their adult counterparts (62), which in turn results in later awakenings and demonstrates the futility of earlier bedtimes compared to extended-morning wake/start times on measures of improved physical, behavioral and cognitive function (29, 30, 63, 64). Similar to that of adolescent civilians (30, 55), our study has shown that JS are experiencing chronic sleep restriction throughout basic training, mainly from the interaction between biological adaptation (e.g., puberty, circadian and homeostatic adaptations) and environmental constraints (e.g., early basic training start times, poor sleep hygiene, societal pressures/demands), which is likely to lead to persistent and unrecoverable sleep loss. Failure to account for these biological changes can lead to the development and/or exacerbation of sleep disorders, impaired physical and mental health, increased potential for substance abuse (i.e., drugs, alcohol, smoking), greater risk taking behaviors and negative mood traits, and impaired neurobehavioral function (32, 65). Therefore, it is critical that interventions to improve sleep in JS during basic training (e.g., extended-morning wake times, improved sleep hygiene) must be considered relative to their specific sleep–wake physiology and independent of their adult counterparts.

A number of study limitations must be acknowledged. Our study was only able to evaluate sleep across the initial 12-weeks of JS basic training, and therefore, sleep–wake patterns and disturbances, and perceptions of sleep quality may differ as they progress through their 28-week or 49-week basic training course. Due to resource availability, two types of wearable technology (i.e., Actigraph watch and Oura ring) were used to measure sleep during the two studies, making direct cross-cohort comparisons difficult due to variations in the recorded data between the two technologies. Actigraphy is commonly used due to its levels of acceptability, low cost and utility in monitoring sleep in natural settings. However, actigraphy has shown to under-overestimate certain sleep wake-indices when compared to gold standard (i.e., polysomnography) (66) and therefore, validated wearable technology that incorporates biometric signals (e.g., heart rate) into sleep–wake detection algorithms to improve accuracy are recommended, along with the combined use of sleep diaries. Additionally, no measures of associated outcomes such as sleep disorders, components of psychological distress (i.e., stress, anxiety, depression) or training-related performances were included, and thus preventing a more detailed analysis. Although male and female recruits and JS sleep in single-sex dorms, no sex differences in objective sleep–wake indices were observed for JS or non-infantry recruits during basic training. These findings are likely due to the standardized (gender-free) scheduling and content of basic training. To note, no female infantry recruits were enrolled into basic training at the time of this study. Nevertheless, sex differences in the prevalence of certain sleep disorders (e.g., insomnia) and architecture (67) have been reported, indicating the influence of sex steroids and menstrual cycle on sleep–wake indices (67–69), and therefore, should be considered in subsequent sleep research.

Conclusion

Our findings demonstrate that sleep restriction is pervasive across basic training, regardless of unit type (i.e., JS, non-infantry and infantry recruits). Despite a growing awareness of the importance of sleep relative to the health, performance and wellbeing of military trainees, it is clear that greater efforts are required (i.e., practical and educational) to both increase sleep duration and improve sleep hygiene practices to reduce the magnitude of sleep disturbances. It is acknowledged that some aspects of basic training (i.e., field exercise) are designed to intentionally restrict sleep as a means of mimicking operational demands. However, based on our observations, sleep restriction is not constrained to field exercise. Rather, the average sleep duration is consistently below minimum sleep recommendations throughout basic training, leading to a high degree of chronic and unrecoverable sleep loss, which in turn is likely to significantly impair physical and cognitive military performance, and increase the risk of injury, illness and greater attrition rates. Changes in the design and scheduling of basic training programs to enable, at the least, minimum sleep recommendations to be met, and to improve sleep hygiene in the primary sleeping environment are warranted.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by United Kingdom Ministry of Defense Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AJR: Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. HT: Data curation, Project administration, Resources, Writing – review & editing. KH: Validation, Visualization, Writing – review & editing. KJ: Data curation, Project administration, Writing – review & editing. RH: Data curation, Writing – review & editing. SC: Data curation, Methodology, Project administration, Writing – review & editing. AnR: Methodology, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1321032/full#supplementary-material

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Identifying clinical phenotypes of frontotemporal dementia in post-9/11 era veterans using natural language processing

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Introduction: Frontotemporal dementia (FTD) encompasses a clinically and pathologically diverse group of neurodegenerative disorders, yet little work has quantified the unique phenotypic clinical presentations of FTD among post-9/11 era veterans. To identify phenotypes of FTD using natural language processing (NLP) aided medical chart reviews of post-9/11 era U.S. military Veterans diagnosed with FTD in Veterans Health Administration care.

Methods: A medical record chart review of clinician/provider notes was conducted using a Natural Language Processing (NLP) tool, which extracted features related to cognitive dysfunction. NLP features were further organized into seven Research Domain Criteria Initiative (RDoC) domains, which were clustered to identify distinct phenotypes.

Results: Veterans with FTD were more likely to have notes that reflected the RDoC domains, with cognitive and positive valence domains showing the greatest difference across groups. Clustering of domains identified three symptom phenotypes agnostic to time of an individual having FTD, categorized as Low (16.4%), Moderate (69.2%), and High (14.5%) distress. Comparison across distress groups showed significant differences in physical and psychological characteristics, particularly prior history of head injury, insomnia, cardiac issues, anxiety, and alcohol misuse. The clustering result within the FTD group demonstrated a phenotype variant that exhibited a combination of language and behavioral symptoms. This phenotype presented with manifestations indicative of both language-related impairments and behavioral changes, showcasing the coexistence of features from both domains within the same individual.

Discussion: This study suggests FTD also presents across a continuum of severity and symptom distress, both within and across variants. The intensity of distress evident in clinical notes tends to cluster with more co-occurring conditions. This examination of phenotypic heterogeneity in clinical notes indicates that sensitivity to FTD diagnosis may be correlated to overall symptom distress, and future work incorporating NLP and phenotyping may help promote strategies for early detection of FTD.

KEYWORDS

military health, frontotemporal dementia, phenotyping, veterans, natural language processing, traumatic brain injury

Introduction

Frontotemporal dementia (FTD) is a type of dementia that primarily affects the frontal and temporal lobes of the brain, leading to the progressive deterioration of behavior, personality, language abilities and executive dysfunction (1, 2). After Alzheimer's disease (AD), FTD is the second most common cause of early-onset dementia (3). Unlike Alzheimer's, which generally affects older individuals, FTD typically strikes at a younger age, with most cases occurring between 45 and 64 years of age (4). TBI and PTSD are both associated with an increased risk for neurodegenerative disorders, including FTD (5). Post-9/11 veterans represent a unique population with significant exposure to risk factors for FTD, as they are relatively young population and have a high prevalence of Traumatic Brain Injury (TBI) and Post-Traumatic Stress Disorder (PTSD) due to their military service experiences. The complexity of FTD presentation creates challenges for early detection, diagnosis, and treatment in this population.

FTD can manifest in two distinct clinical presentations; the behavioral variant of FTD (bvFTD) and the language variant (lvFTD). The behavioral variant is often marked by noticeable early-onset behavioral and by executive symptoms (2). The language variant is further classified into the semantic and non-fluent presentations of primary progressive aphasia (6). The behavioral and language signs and symptoms of FTD, however, often overlap in complex ways, and each individual symptom exists along a spectrum of severity. This makes FTD diagnosis challenging, and it is often misdiagnosed as a psychiatric disorder or stroke during the early stages (7). Therefore, an examination of the phenotypic heterogeneity of the disease is needed to improve identification. Clarifying the boundaries of FTD's various presentations could also help clinician's discriminate FTD from psychiatric disorders and stroke.

Identifying distinct phenotypes, defined as 'any traits or characteristics that distinguish a specific state 'could help to elucidate the heterogeneity of FTD case presentations (8). As FTD is heterogenous, FTD phenotyping demands particularly rich forms of data capable of discriminating subtle variations in FTD presentation. Natural Language Processing (NLP) presents a promising approach to phenotyping FTD because NLP can extract rich information from clinical notes across a patient's full medical history (9). Mature NLP tools can automate the extraction of valuable information about the symptomology and characteristics of FTD, which may not be evident in traditional structured data (10). In this study, NLP tools were used to identify and characterize FTD-related symptoms and features in patient's clinical notes. These features were then used to compare the histories of FTD cases to matched controls, and cluster distinct presentations within FTD cases.

Materials and methods

Cohort development

We initially identified post-9/11 era veterans who entered VA care between 2001–2012, had three or more years of VA care through the end of 2015, with one of those years being after 2007. Of those veterans, through 2019, $n = 86{,}960$ had an ICD9 code associated with cognitive dysfunction. Of the 86,960 patients identified, 98.98% of these cases ($n = 86{,}071$) were 65 years old or younger at the time of diagnosis. Those >65 years of age at the time of diagnosis were excluded. Because some of the ICD9 codes associated with cognitive dysfunction have poor predictive value in a population that is 65 years old or younger at the time of diagnosis (11). we only included those with ICD9 codes with a positive predictive value higher than 0.8 or that had been verified through expert chart review previously (11). The two ICD9 codes of Alzheimer's (331.0) and Frontotemporal Dementia (FTD, 331.1) have a positive predictive value of 0.85 and 0.95, respectively, in a younger population (11). Our approach, then, was to consider those with an Alzheimer's or FTD diagnosis positively validated ($n = 460$). We had 239 cases that had been validated by expert chart review in our previous study (11). This gave us a total of 699 cases that we treated as gold standards for training of our NLP system (Moonstone) (10). Since, the primary objective of our research was to discern whether it is possible to identify patients with TBI and cognitive dysfunction who are at heightened risk for developing FTD, it was essential to have a robust control group that mirrors the cases of interest in all respects. Therefore, cases were matched to at least one and up to four controls per case. Controls had to have a similar level of traumatic brain injury, if the case had a traumatic brain injury, but no indicator of cognitive dysfunction based on CTBIE and/or diagnosis codes. Cases were matched by age (± two years by birth year), gender, race, ethnicity, and year of first VA care. Nine of the cases of cognitive dysfunction lacked appropriate control matches, however, and were excluded leaving us with 690 cases and 2,624 control cases. We then randomly chose 200 FTD records with their matched controls ($n = 713$) for specific analysis of FTD (see Figure 1).

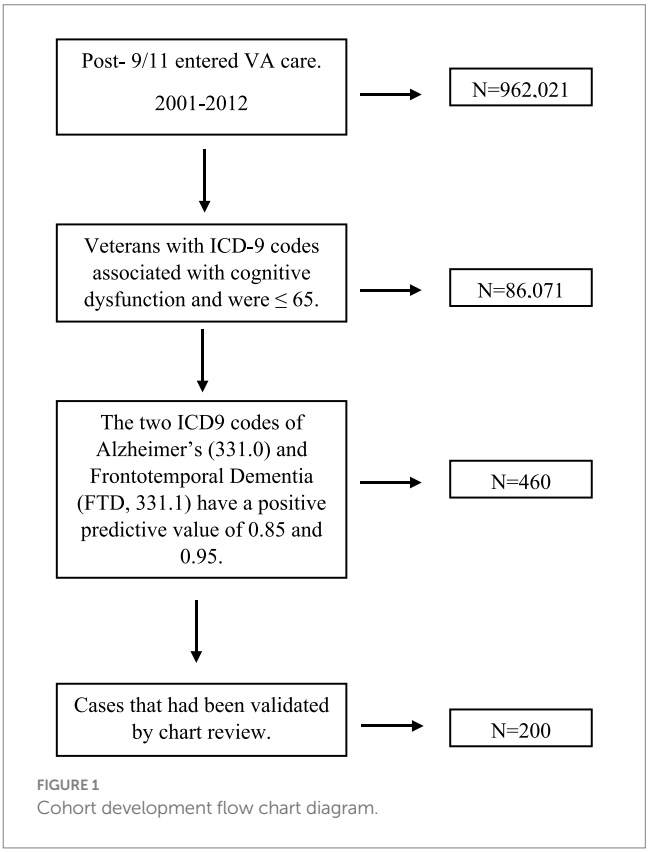

FIGURE 1
Cohort development flow chart diagram.

Moonstone ontology/grammar rule building

The Moonstone NLP platform (10) is designed to extract data from clinical text not just by capturing explicitly stated information but also by inferring complex concepts often embedded in the nuanced language of common narrative. Moonstone diverges from typical NLP systems that require unambiguous phrasing, as it was originally developed to recognize social risk factors (SRF) like housing status, whether a patient lives alone, and the presence of social support. The ontology within Moonstone denotes a concept hierarchy that includes both literal and inferred instances—'patient in communication with family' being a literal example, while 'social support' is more inferred (10).

Training of Moonstone for new NLP tasks involves the expansion of this ontology to encompass new concepts, supplemented by the creation of additional grammar rules until the system achieves satisfactory accuracy. For the purposes of our study, the ontology was augmented to include concepts pertaining to cognitive impairment, poor psychosocial function, and PTSD symptomatology. This enhancement was accomplished using two graphical tools: one for adding novel words and concepts to the ontology, and another for generating new grammar rules. This latter tool operates by allowing trainers to select from the array of "parse trees" that Moonstone produces when it processes sentences containing unknown words. From these trees, a new rule definition is extracted, to which a concept from the ontology is then attached. Consequently, this concept is applied to the interpretation of any phrase or sentence matching the new rule, thereby extending Moonstone's analytical reach.

The technique of expanding Moonstone's capabilities was meticulously applied to sentences from a set of reports, which were utilized to train the platform for this project. Through this iterative process, Moonstone's utility was refined, enabling it to more accurately parse and understand the complexities of clinical narratives related to cognitive and psychological assessments. After the ontology and grammar rule enhancement, and upon training Moonstone with the validated clinical notes, we employed a random forest classifier to identify cases with cognitive dysfunction. The classifier demonstrated a high level of precision, accurately identifying cases with an 88% success rate, further confirming the supervised nature of the learning paradigm employed by Moonstone (see Figure 2).

Clinical note type selection and training

Ontology and grammar rule building in Moonstone was trained with manual text annotation of clinical notes from 165 cases of cognitive dysfunction validated by chart review and consensus of three neuropsychologists in a prior study and which were considered "gold standard" for this work. All the gold standard cases had neuropsychologist consult notes and neuroimaging notes. Annotators reviewed 15,985 note title types that existed in the electronic health record for the 165 gold standard cases and determined the most relevant note types for FTD. Annotators chose 3,108 note types to review for possible inclusion. Two nurse practitioners reviewed and validated the clinical text of 20% of these 3,108 note types and determined 1,195 note title types for inclusion in this study for training the NLP software, Moonstone (10). The annotators validated these notes for sentence level evidence of cognitive dysfunction, poor psychosocial function, and PTSD symptomology, and symptoms relevant to traumatic brain injury. Then based on the ontology lexicon, Moonstone read the clinical text and counted the number of times each concept was found in each patient's history. Overall, 39 unique FTD-related concepts were identified by this process. Supplementary Table S1 provides a list of all 39 concepts.

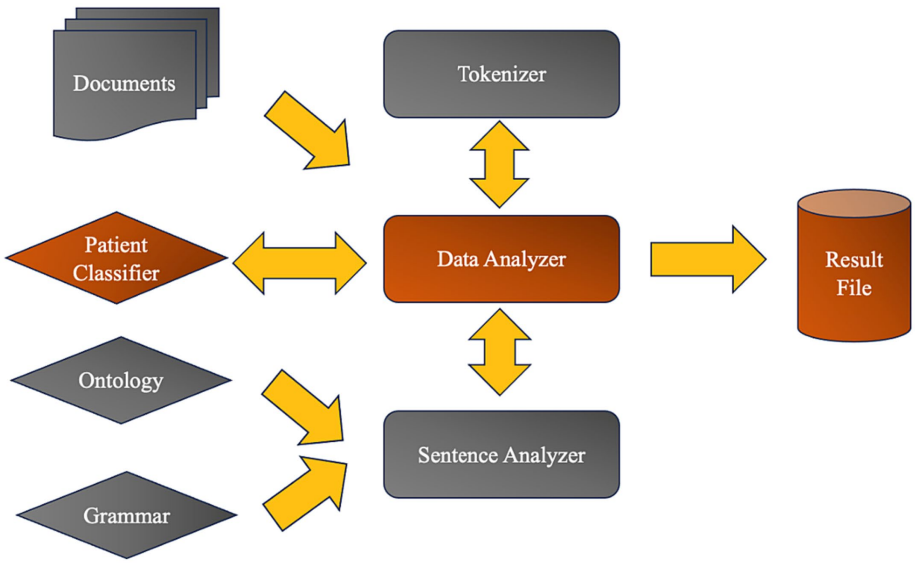

FIGURE 2
Moonstone system architecture.

RDoC domain

The 39 NLP-derived ontologies were grouped into Research Domain Criteria (RDoC) domains to improve interpretation. The RDoC framework is a comprehensive approach developed by the National Institute of Mental Health (NIMH) to understand mental disorders based on underlying neurobiological and behavioral dimensions (12). The RDoC framework consists of multiple domains that capture the fundamental dimensions of human functioning and psychopathology. These domains are Cognitive, Positive Valence, Negative Valence, Social Processes, Sensorimotor, Arousal-Regulatory (12). In this work we additionally added the domain of "Interpersonal Trauma" to increase specificity to some underlying PTSD ontologies. To translate individual's count of ontologies into a presence/absence of RDoC domains, we defined a domain as present in an individual's records if at least half of the domain's underlying ontologies were present in clinical notes.

Comorbidities

Comorbidities were selected based on the most common medical conditions that can coexist alongside the FTD diagnosis including psychiatric disorders (e.g., Depression, anxiety, bipolar disorder), physical conditions (e.g., Stroke, hypertension, diabetics, Headache) (13–18).

Analysis

Statistical analysis

All analyses were scripted in Python 3. We used Z tests for univariate analyses to test differences in proportions between FTD and Controls using the statsmodels feature.

Clustering

For clustering and dimensionality reduction, we employed the Uniform Manifold Approximation and Projection (UMAP) technique, utilizing frequency of 39 concepts extracted from the medical notes of our entire sample. UMAP is a manifold learning approach that facilitates the reduction of dimensions in the dataset. One of its key advantages lies in its ability to effectively preserve the global structure of high-dimensional data while simultaneously retaining the inter-sample distances. The subsequent clusters resulting from the UMAP-based analysis were assessed using the silhouette score method, a statistical measure that evaluates the effectiveness of a clustering technique by considering the defined subgroups' quality in relation to their number (19).

Word cloud

Word clouds are qualitative tools for visualizing the relative frequency of terms in text. Word cloud generating software was used to represent the relative frequency of symptom ontologies. The word cloud provides a summary overview of the most frequent FTD-specific concepts occurring in the medical notes for those with FTD relative to controls. In the word cloud, symptom ontologies that were more common in the FTD group are larger, and symptom ontologies that were equal across the two groups are represented in smaller text.

Results

Data summary

Table 1 presents sociodemographic and military measures for FTD cases and matched controls. After matching, the groups were statistically similar in terms of age, gender, education, race, ethnicity, and marital status, and military branch affiliations ($p > 0.05$). A significant difference emerged in the distribution of military rank, with the FTD group having a lower proportion of enlisted ($p < 0.001$) and a higher proportion of officers ($p < 0.01$).

Table 2 compares the incidence of comorbidities between the FTD group and matched controls. The FTD group showed significantly higher rates of overdose, depression, bipolar disorder, schizophrenia, suicidal ideation/attempt, stroke/CVD, cardiac issues, and seizures ($p < 0.001$).

Group comparison of NLP features

Table 3 compares the percentage of FTD cases and controls with evidence of each RDoC domain criteria in clinical notes. All RDoC

TABLE 1 Sociodemographic and military measures for FTD cases and matched controls.

Group	FTD	Control	*p*
Sample size (*n*)	200	713	
Age: mean years	56.0	54.9	*>0.05*
Mean age at 1st dementia dx	47.8	–	–
> 65 years	25.5%	22.2%	*>0.05*
Sex: male	89.0%	90.2%	*>0.05*
Female	11.0%	9.8%	*>0.05*
Education: high school	47.3%	52.1%	*>0.05*
Some college +	38.2%	42.5%	*>0.05*
Race: Black	15.5%	16.4%	*>0.05*
White	71.5%	72.7%	*>0.05*
Other	13.0%	10.9%	*>0.05*
Ethnicity: Hispanic/Latino	11.0%	10.7%	*>0.05*
Married/partnered: yes	62.0%	62.8%	*>0.05*
Military branch: army	62.0%	67.6%	*>0.05*
Marine corps	11.0%	8.1%	*>0.05*
Air force	15.5%	13.8%	*>0.05*
Navy	10.0%	9.5%	*>0.05*
Rank: enlisted	62.5%	75.7%	**<0.001**
Officer	13.5%	7.15%	**<0.01**
Others (warrant, unknown)	24%	17.11%	*>0.05*

Bold values are significant.

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TABLE 2 Comorbidity prevalence for the FTD group and matched controls.

Group	FTD	Control	*p*
Sample size (*n*)	200	713	
Substance misuse: alcohol abuse	28.0%	28.8%	*>0.05*
Substance abuse disorder	35.5%	34.1%	*>0.05*
Overdose, ever	11.5%	4.9%	**<0.001**
Mental health: depression	68.0%	54.1%%	**<0.001**
PTSD	53.0%	56.2%	*>0.05*
Anxiety	46.0%	38.7%	*>0.05*
Bipolar disorder	26.0%	14.9%	**<0.001**
Schizophrenia	4.0%	0.8%	**<0.01**
Suicidal ideation/attempt	15.5%	8.4%	**<0.01**
Physical health: any TBI	43.5%	47.7%	*>0.05*
Headache	48.5%	35.8%	*>0.05*
Brain tumor	1.0%	0.4%	*>0.05*
Stroke/CVD	24.0%	3.6%	**<0.001**
Cardiac	22.0%	10.9%	**<0.001**
Obesity	37.0%	35.1%	*>0.05*
Hypertension	47.5%	40.5%	*>0.05*
Seizure, any	20.0%	2.5%	**<0.001**
Insomnia	33.5%	25.4%	**<0.05**

Bold values are significant.

TABLE 3 Percentage incidence of ontologies that fall into the RDoC domains for the control and FTD groups, with *p*-values testing for groups differences per domain.

RDoC domain	Control	FTD	*p*
Cognitive	35.3%	82.0%	<0.0001*
Positive valence	35.6%	71.0%	<0.0001*
Negative valence	8.0%	24.5%	<0.0001*
Social processes	23.7%	46.4%	<0.0001*
Sensorimotor	1.8%	6.5%	0.0004*
Arousal-regulatory	11.8%	20.5%	0.0015*
Interpersonal trauma	8.6%	13.5%	0.036*

* indicates significance at <0.05.

domains showed significant percentage differences between the control group and the FTD group. The FTD group showed significantly higher percentages of individuals meeting the criteria for the cognitive, positive valence, negative valence, social processes, sensorimotor, arousal-regulatory, and interpersonal trauma domains. The cognitive-related ontologies showed the strongest association with FTD.

Figure 3 presents a word cloud of the most common behavioral characteristics among individuals with Frontotemporal Dementia (FTD) relative to matched controls. Dementia, impulsivity, executive symptoms, decision-making, and motor symptoms all featured prominently. A lack of recognition and motivation, alongside difficulties with social processes and interpersonal mannerisms featured moderately.

Phenotypes of FTD

Figure 4 shows a two-dimensional representation of the seven RDoC domains produced using UMAP dimensional reduction (20). In Figure 4A, a UMAP dimensional reduction is shown color coded by group membership (FTD, n = 200, blue circles. Controls, n = 713, white circles) where the distance between points is a preserved estimate of the distance between individuals across all RDoC domains. In Figure 4B, the average percentage of all ontologies present in notes is shown against the percentage of veterans with FTD. Both measures were derived by iterating a boundary of inclusion across the ontology space in Figure 4C. There is a strong positive correlation between percentage with FTD and frequency of sign/symptom ontologies in clinical notes. For example, given a cluster where 70% are FTD+, then 71% of the 39 ontologies are present on average in clinical notes.

Table 4 represents the incidence of demographic and clinical characteristics across three phenotypes identified by the clustering approach (see method section): low distress ($N = 149$), moderate distress ($N = 632$), and high distress ($N = 132$). High distress individuals had a significantly higher incidence of FTD, 71.97% compared to 8.05 and 14.71% in the low and moderate distress groups, respectively ($p < 0.001$). Similar patterns were observed with total behavioral symptoms and various clinical characteristics like traumatic brain injury (TBI), cardiac issues, insomnia, obesity, stroke, headache, and seizures, with all showing a significantly higher prevalence in the high distress group ($p < 0.001$). Clinical conditions like schizophrenia, anxiety, bipolar disorder, depression, PTSD, overdose, substance abuse disorder, alcohol abuse, and suicide showed significantly higher incidence rates in the high distress group ($p < 0.001$). The average age was significantly lower in the high and moderate distress groups, and there were differences in racial distribution, with significantly more Hispanic and Black individuals in the high distress group.

Figure 5 assess whether distinct subtypes are identified through clustering. The UMAP dimensional reduction of RDoC domains was performed specifically for the FTD group, comprising 200 cases, resulting in a 2D 'symptom space'. Next, two indices were created: (1) Behavioral concepts (e.g., impulsivity, disinhibition, apathy, and behavioral traits), and (2) Language concepts (e.g., language, speech, learning, executive functions, and memory). The ratio of these two symptom sets was calculated for each individual, and a color code was assigned based on the ratio: records with more behavioral symptoms were marked as RED, while those with more language-related issues in text notes were labeled BLUE. Subsequently, the distribution of these color-coded ratios was evaluated across the RDoC space, where clustering of colors would indicate the presence of subtypes.

Discussion

In this study, NLP-aided medical chart reviews successfully identified distinct phenotypes of FTD and provided a novel signature of RDoC domain distress. Prior research has leveraged unsupervised learning and clustering approaches applied to dementia cohorts. These include clusters of cognitive impairment using biomarkers, anatomical cluster identification and genetic variant mapping, although no clustering studies have specifically evaluated post-9/11 era veterans with FTD (8, 21). Our findings align with prior work by demonstrating

FIGURE 3
This figure provides a summary overview of the difference in words used in medical notes that were classified based on the FTD ontologies between patients with FTD and controls. For example, the largest words represent words that were classified by the ontologies far more frequently for those with FTD relative to controls. The smaller words represent concepts that were classified by the ontologies about the same frequency for people with FTD in relative to controls.

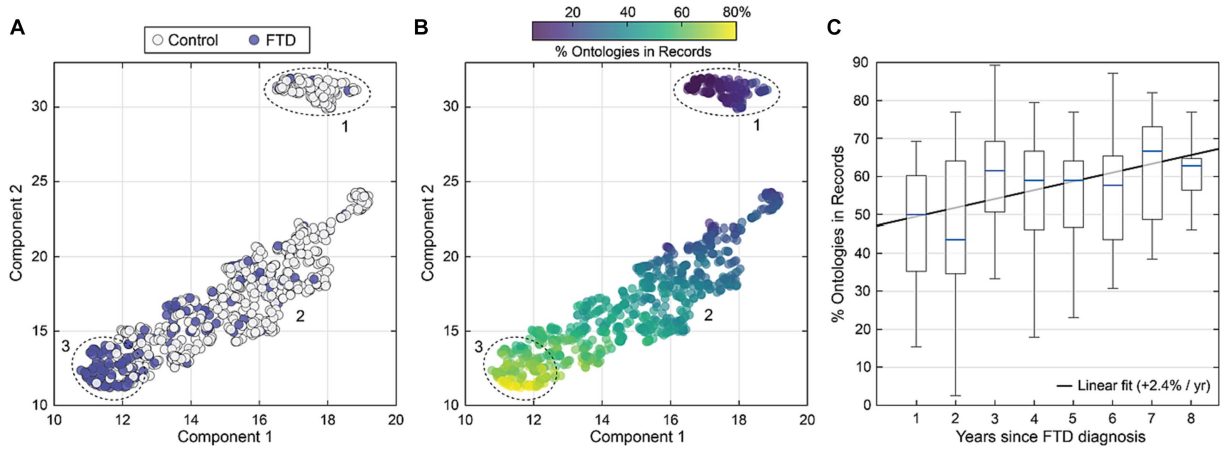

FIGURE 4
(A) A reduced dimensional representation of all sign/symptom ontologies is shown for all individuals, color coded by group membership (FTD, $n = 200$, blue circles. Controls, $n = 713$, white circles). Three regions showing individuals with similar symptomology are enumerated (1–3). **(B)** Like **(A)** showing the percentage of symptom ontologies present in clinical records per individual. Most FTD ontologies are present for those in region 3, whereas group 1 shows low rates of ontologies in records. **(C)** The percentage of all ontologies in records is shown as a function of time since first FTD diagnosis. Boxplots broken out per year indicate more FTD-related signs and symptoms in health records are evident for those with more time since first FTD diagnosis.

the presence of distinct phenotypes within the FTD group, as evidenced by the clustering of clinical text features. The identification of Low, Moderate, and High distress phenotypes in our study expands upon prior work and provides further evidence for the existence of diverse clinical subgroups within FTD.

The diagnosis of Early onset FTD poses challenges due to its relative rarity, and its highly variable clinical manifestations that can mirror psychiatric disorders and neurological conditions such as stroke (2). The FTD diagnostic process is further complicated by the phenotypic heterogeneity of FTD, which encompasses many distinct behaviors, affective changes, and movement and speech difficulties. NLP provides an appropriate framework to capture these complex patterns, because NLP tools can glean valuable information about subtle features buried within a large corpus of clinical text, far beyond the simple presence/absence encodings typically found in health systems data. Future work may benefit from the use of NLP phenotyping pipelines trained on FTD-specific text features.

To facilitate clinical intuition, raw NLP ontologies extracted from text were organized into validated RDoC domains. RDoC domains were then clustered into a low dimensional space to enable visualization and the identification of three distinct phenotypes (Low, Moderate, and High distress). This analysis revealed a continuum of distress within and across FTD variants, with some diagnosed FTD cases showing surprisingly low levels of symptom distress, although the majority were in the Moderate to High groups. This approach demonstrates how unstructured clinical text can

TABLE 4 Percentage incidence of demographic and clinical characteristics criteria by each phenotype group.

	Low distress $N = 149$	Moderate distress $N = 632$	High distress $N = 132$	*p*-value
FTD	8.05%	14.71%	71.97%	<0.001
Total behavioral symptoms	8.9%	40%	67.3%	<0.001
Demographic characteristics				
Age	59.6 (9.8)	54.4 (10.6)	53.5 (10.4)	<0.001
Female	12.08%	9.97%	8.33%	>0.05
Race				
White	75.16%	71.83%	71.96%	>0.05
Hispanic	14.76%	8.38%	12.12%	0.006
Black	8.05%	18.35%	15.15%	0.008
Education				
College or more	58.33%	39.76%	34.37%	>0.05
Clinical characteristics				
Physical				
Any TBI	12.8%	50.6%	66.7%	<0.0001
Cardiac	10.7%	11.6%	25%	<0.0001
HBP	34.2%	43.4%	44.7%	0.10
Lung disease	9.4%	10.4%	12.1%	0.75
OSA	32.2%	35%	44.7%	0.06
Insomnia	15.4%	35%	44.7%	<0.0001
Obesity	31.5%	33.7%	48.5%	0.002
Stroke	3.4%	7.1%	18.2%	<0.001
Headache	18.8%	38.8%	59.8%	<0.001
Seizures	1.3%	5.1%	18.2%	<0.001
Psychological				
schizophrenia	0.0%	1.09%	5.3%	0.0004
Anxiety	15.4%	42.69%	56.8%	0.0001
Bipolar	3.4%	16.9%	34.8%	0.0001
Depression	24.8%	60.9%	75.8%	<0.001
PTSD	18.8%	60.8%	72%	<0.001
Overdose	1.3%	5.1%	18.2%	<0.001
Substance abuse disorder	10.7%	36.9%	49.2%	<0.001
Alcohol abuse	9.4%	31%	38.6%	<0.0001
Suicide	0.0%	9.0%	25.8%	<0.0001

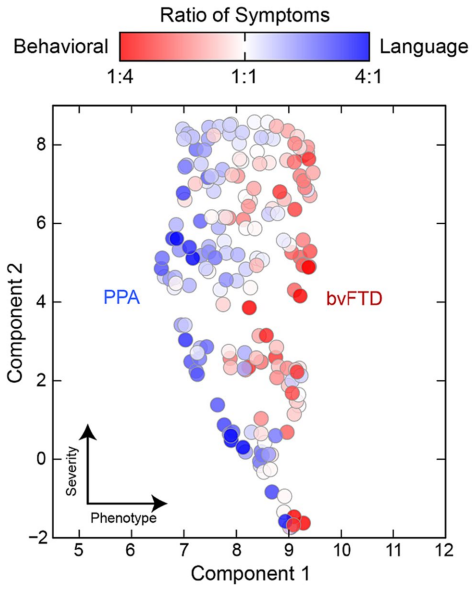

FIGURE 5
UMAP dimensional reduction of RDoC domains for the FTD+ group only ($n = 200$). To identify FTD variants, individuals were color coded by the relative ratio of behavioral (red) to language (blue) related concepts in their clinical notes. Colored clusters indicate individuals presenting with distinct behavioral and language variants and symptomology.

be used to assess the heterogeneity of neurological disease. Future work could include an in-depth temporal analysis to better understand how time from diagnosis influences our current model of symptom distress and how different phenotypes progress through the disease over time.

A comparison of the FTD group and matched controls revealed large differences in the incidence of multiple comorbidities. Prior work has found links between military related TBI and PTSD and FTD (22). The strong associations with specific comorbidities and FTD found in this study reinforce these connections. These findings have implications for identification and care, as these individuals present with a degree medical complexity that demands detailed and appropriate treatment strategies. Additionally, The FTD group exhibited significantly higher rates of overdose, depression, bipolar disorder, schizophrenia, suicidal ideation/attempt, stroke/CVD, cardiac issues, and seizures. FTD is associated with a higher burden of psychiatric and neurological comorbidities which may contribute to the complexity of its clinical presentation as demonstrated by the high prevalence of comorbidities identified among those with FTD. Thus, the broader clinical context is crucial when evaluating individuals for FTD, as the presence of these comorbidities may influence disease progression and treatment efficacy. A limitation of the interpretation of this data is a lack of review of the validity of psychiatric diagnosis associated with the FTD cases. For example, a patient could be misdiagnosed with bipolar disorder early on in the disease process, but then be diagnosed with FTD after consultation with experts and progression over time. It could be helpful for clinicians to continue to consider FTD as a rule out early on in the diagnostic stages, given the large overlap of FTD with psychiatric presentations.

Overall, those with FTD had higher risk of suicidal ideation and overdose as compared to controls and this could be an important factor when trying to decide on early intervention approaches and psychoeducation for clinicians and/or caregivers in the future studies. Additionally, the FTD cases in this study had the features of emotional liability and interpersonal trauma one might see in psychiatric disorders but this was often coupled with an impulsivity that could be associated with the high rates of overdose and interpersonal conflict. This is consistent with the current studies regarding FTD in the general

population (23, 24). Future studies looking at the effectiveness of therapeutic and pharmacological approaches aimed at mitigating this impulsivity could help to inform treatment options across phenotypes in the future (24). Our NLP approach is limited in being able to differentiate between apathy and impulsivity, or even to consistently identify apathy, because it is reliant on clinical bias in reporting while note taking, but it can identify these concepts generally across a large population which could help to aid future studies.

From chart review and verified with NLP analysis across cases, FTD cases had significantly higher incidence of interpersonal trauma as compared to control, although controls in this population also had incidences of interpersonal trauma. For the cases that were chart reviewed, this interpersonal trauma was related to high reports of distress, substance use, and suicidal ideation. This is consistent with work done by Takeda et al. and Massimo et al. showing the impact of FTD on caregivers and the impact of FTD on relationships (25, 26). Our work is novel in that we were able to identify these issues from a large-scale NLP approach and validate these findings within our specific population. Future work could include studies evaluating the effectiveness of targeting therapeutic approaches aimed at helping people with FTD and their caregivers manage these interpersonal relationships and the difficulty of dealing with the relationship issues that arise given the stress of the disease could help in treatment of this disease.

In our statistical evaluation of symptoms over time since diagnosis, symptoms seemed to increase over time (Figure 3C). It is unclear, however, if this is due to lack of effective treatment or progression of the disease. Either way, taking the current literature as a whole, managing impulsivity and supporting patients in improving interpersonal relationships across the disease progression and across the lifespan, could be key in making a clinical impact on the experience of distress in this patient population.

Cumulative symptom severity across all domains distinguished FTD subtypes in important ways that may compliment the typical classification of FTD by variant. Our study explored the existence of distinct subtypes within the FTD population based on symptom presentation. By performing dimensional reduction of RDoC domains for the FTD group and creating two indices for Behavioral and Language variant, we assessed the variability in symptom profiles among veterans with FTD and were able to identify a unique subtype with distinct symptom profiles. Our result shows that phenotyping approaches may help to further elucidate the relationship between FTD symptom distress and disease progression, enabling more accurate prognoses. Future work could also explore whether an NLP tool for assessing overall dementia symptom severity could serve as a rapid heuristic for population level disease progression. Automated NLP screening of distress could also be useful for validating or extending existing tools such as the Frontotemporal dementia Rating Scale, FRS in large populations (27). This study highlights how clinical phenotyping and clustering approaches may offer opportunities to better understand rare and heterogeneous diseases and improve early detection and clinical care for individuals living with dementia.

Limitation

This study, focused on identifying the clinical phenotypes of Frontotemporal Dementia (FTD) among post-9/11 era veterans, holds several limitations. The generalizability of results is restricted given the specific study demographic, while the retrospective design could introduce bias due to the potential for incomplete historical medical records. The study relies on ICD-10 codes for identifying FTD cases. The number of FTD cases is relatively small ($n = 200$), which might limit the statistical power of the study.

Conclusion

This study demonstrated the potential of NLP and phenotyping approaches to enhance the classification of FTD subtypes, considering cumulative symptom severity alongside the traditional variant-based classification. By leveraging NLP and validated domains, valuable insights into distress levels, comorbidities, and interpersonal relationships in FTD patients were gained. The findings revealed that FTD exhibits a continuum of severity and symptom distress, both within and across variants, with distress levels often co-occurring with other conditions. This highlights the importance of sensitivity to overall symptom distress in diagnosing FTD and suggests that incorporating NLP and phenotyping methods could aid in early detection strategies for FTD, ultimately contributing to improved patient outcomes.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: these data sets are part of the VA medical record system. Requests to access these datasets should be directed to maryjo.pugh@hsc.utah.edu.

Ethics statement

The studies involving humans were approved by University of Utah and the Veterans Administration in Salt Lake City, Utah. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

SP: Conceptualization, Methodology, Writing – review & editing, Data curation, Formal analysis, Visualization. JM: Conceptualization, Methodology, Writing – review & editing, Investigation, Project administration, Supervision, Writing – original draft. EK: Formal analysis, Visualization, Writing – review & editing. LC: Data curation, Software, Writing – review & editing. SK: Data curation, Methodology, Writing – review & editing. HS: Conceptualization, Funding acquisition, Methodology, Writing – review & editing. TC: Data curation, Writing – review & editing. DT: Writing – review & editing. RR: Writing – review & editing. MP: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1270688/full#supplementary-material

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Conceptualizing care partners' burden, stress, and support for reintegrating Veterans: a mixed methods study

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Background: People who support Veterans as they transition from their military service into civilian life may be at an increased risk of psychological distress. Existing studies focus primarily on paid family caregivers, but few studies include spouses and informal non-family "care partners." We sought to identify key challenges faced by care partners of Veterans with invisible injuries.

Methods: Semi-structured interviews were conducted with 36 individuals involved in supporting a recently separated US military Veteran enrolled in a 2-year longitudinal study. CPs completed validated measures on perceived stress, caregiving burden, quality of their relationship, life satisfaction, and flourishing. Independent *t*-tests were used to compare cases in these groups on caregiving burden, quality of their relationship, life satisfaction, and flourishing. Care partners were categorized as reporting high and low levels of stress. Exemplar cases were used to demonstrate divergences in the experiences of CPs with different levels of stress over time.

Results: Care partners reported shifts in self-perception that occurred from supporting a Veteran, emphasizing how they helped Veterans navigate health systems and the processes of disclosing health and personal information in civilian contexts. Exemplar cases with high and low burdens demonstrated divergent experiences in self-perception, managing multi-faceted strain, and coping with stress over time. Case studies of specific care partners illustrate how multi-faceted strain shifted over time and is affected by additional burdens from childcare, financial responsibilities, or lack of education on mental health issues.

Conclusions: Findings suggest the unique needs of individuals who support military Veterans with invisible injuries, highlighting variations and diachronic elements of caregiving. This sample is younger than the typical caregiver sample with implications for how best to support unpaid care partners caring for Veterans in the early to mid-period of their use of VA and civilian health services.

KEYWORDS

military Veterans, caregiver burden, caregiving, mixed methods, health services, veteran reintegration

Introduction

Since 2001, there has been increased focus on the "invisible wounds of war," which refers to mental health issues and cognitive impairments resulting from military service in the twenty-first century (1). Longer deployments as well as advances in combat medicine (2), have led a significant proportion of returning soldiers to report high levels of psychological and physical distress (3), and difficulties in reintegrating into civilian society (4–6). Compared to past eras, there is greater emphasis on diagnosing Post Traumatic Stress Disorder (PTSD), traumatic brain injuries, and depressive symptoms in post-9/11 Veterans. However, the effects of these conditions are still poorly understood compared to injuries categorized as physical wounds. The medical costs for invisible conditions alone are ~$2–3 billion per year (7), and families bear a significant "private burden" of uncompensated costs related to service-connected disabilities (8).

The effects of caregiving by family members are well-established in medical literature but are largely based on geriatric populations (9). Caregivers for military and Veteran populations are more likely to be younger, have dependents, and face longer periods of care for individuals with higher disability burdens (10). For Veterans enrolled in health care with the US Department of Veterans Affairs (VA), studies have suggested that caregivers who support Veterans have higher depression and burden compared to civilian counterparts and more financial strain over time (11). This mirrors wider findings that caregiving can lead to negative impacts on the health, wellbeing, economic security, and careers of family caregivers (12–14).

Within the literature on people who are caregivers for Veterans, studies tend to focus on caregivers for military servicemembers (15, 16), enrollees in the paid VA caregiver program (17), or caregivers who support patients with a specific diagnostic condition (e.g., cancer, diabetes, etc.). Abraham et al. have demonstrated less visible forms of "emotional work" of Veteran caregivers (18), while others have examined how caregivers enrolled in VA support programs perceive their uncompensated work (19). In the wake of the two million US troops that were deployed to Iraq and Afghanistan, researchers called for more treatments focused on Veterans and their whole support system. These include family-centered interventions that account for caregiver burden and deal with psychological distress experienced by Veterans and their families (20), with greater attention paid to the early period of post-deployment adjustment (21) and the effects on spouses and children (22).

Caregivers of Veterans, specifically Veterans with invisible injuries, have unique sets of needs (23). Due to the complex nature of invisible injuries, these Veterans' care requires increased effort from caregivers (22) and associated burden (24). Previous research revealed that family and social resources available for caregivers of Veterans aid in mitigating their overall psychological distress (25). Studies have demonstrated the unique consequences of PTSD on family functioning, such as emotional numbing and withdrawal (26), how spouses are often responsible for maintaining normalcy (27), and lower levels of life satisfaction (28). Many Veteran caregivers' needs, such as emotional support, understanding Veterans' benefits, locating Veteran services, and more, go unfulfilled (16).

Research partnerships in recent years have been developed to establish a clear research agenda for US military and Veteran caregivers based on existing studies from RAND and efforts from the Elizabeth Dole Foundation (29). Extant studies tend to focus on paid caregivers in the VHA Program of Comprehensive Assistance for Family Caregivers (PCAFC), leaving gaps in knowledge about unpaid caregivers and Veterans who are not enrolled in VHA health care.

Direct engagement with military and Veteran caregivers has contributed to the development of the "Military and Veteran Caregiver Experience Map," a conceptual model designating stages in caregivers' "journeys" (30). More recent research has focused on suicidal ideation among military caregivers (31) and on evaluating existing programs, such as a study showing that a VA caregiver program was effective in reducing anxiety, depression, caregiver burden, and overall stress (32).

In this study, we adopted the term "care partner," (CP) which aligns with recent calls for an inclusive approach to caregiving that recognizes the wide range of activities and roles individuals may perform in support of those they care for (33, 34). In addition to spouses, this term enabled us to recruit friends, siblings, parents, or others who might be nominated by Veteran study participants. Although CPs play a significant role in the reintegration processes of post-9/11 Veterans with invisible injuries, less is known about how they subjectively view the burden and stress of caregiving, as well as how it impacts their wellbeing. More specifically, we build on an existing conceptual definition of burden (35) to incorporate the distinct perspectives of CPs for military Veterans. This conceptualization of caregiver burden incorporates the following three attributes: self-perception (perceived negative and positive feelings or aspects related to the caregiving role), multifaceted strain (multiple types of strain associated with caregiving, such as health problems, psychological stress, social isolation, or financial problems), and time (change in caregiving burden over time). Incorporating temporality from repeated interviews and analysis of personal history aligns with a life course perspective attentive to continuity and provides context to change in caregivers' experiences (36, 37) and shifts common in Veterans' lives (38). We adopt a mixed methods approach to understand why some caregivers report greater strain and burden and how their narratives diverge.

This study examines the role that informal CPs play in the lives of military Veterans with invisible injuries (mental or cognitive health conditions) in the early phase of their adjustment to civilian life. We do so by using a mixture of quantitative and qualitative methods to offer a more comprehensive view of caregiving and discover potential ways to assist Veteran CPs. The specific aims are to (1) examine associations between CP characteristics and outcomes (flourishing, stress, burden); (2) to describe CP perspectives on how they support the Veteran in their life; and (3) through mixed method analysis, to understand patterns of convergence or divergence between CPs reporting high and low levels of burden.

Methods

Design

We adopted a mixed methods approach to offer breadth and depth of understanding beyond what qualitative or quantitative methods would allow alone (39). Specifically, our mixed method design was an explanatory unidirectional approach (40) where questionnaire data merged with qualitative findings from thematic analysis and in-depth case study analysis. Interview data was reported using a qualitative descriptive design with narratives (41). The study was approved by the Indiana University Institutional Review Board and VA Research and Development Committee.

Participants

This study included a sample of CPs participating in a 2-year longitudinal study that examined community reintegration among military Veterans with an invisible injury (42), which includes clinical diagnosis of post-traumatic stress disorder, depression, anxiety, traumatic brain injury, or other mental or cognitive health condition and their care partners. As reported elsewhere, 91% of these Veteran participants had a disability rating (43). A CP is defined by the Veteran as someone who supports him/her in an area considered important to reintegration (family/social life, school, work, rehabilitation, etc.), typically a family member, partner, friend, or neighbor (33). Following the baseline visit, Veterans were encouraged to nominate an individual who currently supports their adjustment to civilian life. Nominated individuals were contacted via phone to describe the study and inquire about their interest in study participation. Of the 75 Veterans, 48 nominated a CP, which led to a convenience sample of 36 CPs enrolled in the study.

Procedures

Before collecting any data, a member of the research team discussed the study aims with CPs and obtained consent and HIPAA authorization. Data collection included a mix of quantitative and qualitative data. The qualitative data collection involved semi-structured open-ended interviews. CPs received a $25 gift card for each assessment. The quantitative data collection included demographic information and self-administered close-ended questionnaires.

Semi-structured interviews

Following a semi-structured interview guide, CPs were asked about their role in supporting the Veterans and how the Veteran's reintegration impacts their own health and wellbeing. Specific topics that were covered included the CP's role in the Veteran's transition experience, family or social issues, financial/economic issues, and their perceptions on the overall reintegration experience. CPs were interviewed at baseline, 12 months, and 24 months and each interview lasted 60–90 min. Interviews were conducted individually and were either face-to-face in a private room or virtually by phone or videoconferencing, depending upon participant preference and in accordance with protocols adopted during the COVID-19 pandemic period. The digitally recorded interviews were transcribed verbatim, checked for accuracy by listening to the tapes and comparing them with the transcripts, and de-identified.

Measures

Caregiving burden

The Zarit Burden Interview (ZBI) assesses the perceived burden of caregiving (i.e., the extent to which caregiving causes stress, and interferes with the caregiver's health and other relationships or responsibilities). This 12-item questionnaire includes a 5-point Likert scale (0 = Never, 4 = Nearly always). Summed scores range from 0 to 48, such that a higher perceived burden is indicated by higher scores (44). The cutoff between low and high burden has been reported as 12 (45), 13 (46), and 19 (47). A high burden was defined as 13 points and higher for this study. Studies have suggested that the caregiving burden is multi-dimensional, including role strain (how caregiving conflicts with other roles) and personal strain (individualized stress) (48, 49).

Perceived stress

The Perceived Stress Scale (PSS) is a 10-item measure that assesses stress on a 0 (Never) to 4 (Very Often) scale (50). Items include "In the last month, how often have you felt that you were unable to control the important things in your life?" and "In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?" Scores range from 0 to 40 where normative scores are 12.1 (SD = 5.9) for men and 13.7 (SD = 6.6) for women. For this study, high stress was operationalized as a score of 14 or higher.

Flourishing

The "Flourishing measure" includes six domains that contribute to sustained wellbeing (51) and has been validated in a cross-cultural study (52). The Flourishing measure includes the following six domains: happiness, health (mental and physical), meaning and purpose, character, social relationships, and financial stability, an enabler to the other five domains. The response set ranges from 1 (Strongly disagree) to 7 (Strongly agree). The Secure Flourishing Index (SFI) is an average of all 12 items, where higher scores indicate higher levels of flourishing.

Life satisfaction

The Satisfaction with Life Scale (SWLS) assesses an individual's quality of life as they experience and evaluate it. When completing the SWLS, respondents indicate the extent to which they agree or disagree with five items (1 = Extremely dissatisfied, 7 = Highly satisfied) (53). The SWLS has good validity and temporal stability (54). Scores are summed for the five items. Extreme dissatisfaction is operationalized as a score in the 5–9 range, neutral satisfaction is a score of 20, and extreme satisfaction is a score in the 31–35 range.

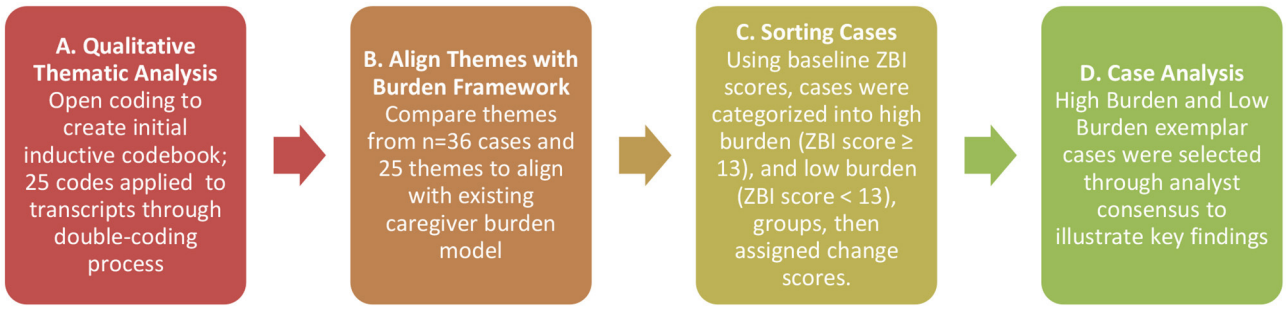

FIGURE 1
Data analysis process.

Quality of relationship

The Quality of Relationship Scale assesses the CP's relationship with the Veteran, which is adapted from the mutual communal relationship scale (55–57). This scale has 10 items with responses that range from 1 (Never) to 4 (Always), with five questions focused on the giving aspect and five questions on the receiving aspects of the relationship (58).

Caregiver resources

A list of 14 resources available to CPs was included to determine the extent to which CPs access these resources. Based on previous studies (59), this list of resources included informal sources of information, religious networks, health care, mental health care, wellness activities, financial support, case management, and support groups. Respondents indicated whether they had used the resource and the extent to which it was helpful (1 = "Not at all," 2 = "Somewhat," 3 = "Very").

Data analysis procedures

The overall mixed methods approach is described in Figure 1. First, a qualitative thematic analysis combined with matrix analysis (60) was undertaken to develop cross-cutting patterns from interviews with CPs. Three coders independently read interview transcripts in "open coding," where each analyst inductively identified relevant excerpts with a provisional label (61). Analytic memos were written regularly during open coding to connect emergent content related to community reintegration. Case summaries were compared using a data matrix to further identify themes and achieve data saturation. A codebook was developed and refined until a shared understanding was achieved. Next, at least two team members independently coded each transcript; pairs met in person to review the double-coded transcripts and resolve discrepancies through consensus. Qualitative data was coded and analyzed using NVivo (62). Subsequently, themes were aligned with concepts from the caregiver burden model (i.e., self-perception, multi-faceted strain, disclosure, navigation, resources, needs, and strategies).

Consistent with the study aims, cases were sorted using baseline ZBI scores. Cases were categorized into high burden (ZBI score ≥ 13, 10/34, 29.4%) and low burden (ZBI score < 13, 24/34, 70.6%) groups for focused analysis of interview transcripts according to their baseline burden score. Combining 12-month scores for burden with baseline burden scores, cases were categorized as staying high (4/27, 14.8%), low (17/27, 63.0%), shifting from high to low burden (4/27, 14.8%), or low to high burden (2/27, 7.4%). Seven CPs did not complete surveys at 12 months.

For the quantitative measures, descriptive statistics (e.g., mean, frequencies) were calculated to characterize the sample in terms of demographic variables and psychosocial outcomes. To examine associations between CP characteristics and outcomes, Pearson correlations were calculated among PSS, SFI, SWLS, Zarit Burden, and Quality of Relationship Scale scores. Additionally, to compare CPs reporting high burden with those reporting low burden, independent *t*-tests were used to compare these groups on PSS, SFI, SWLS, and Quality of Relationship Scale scores. To account for multiple comparisons increasing the possibility of a Type I error, a False Discovery rate adjustment was made (63).

In the next stage of analysis, baseline ZBI scores were used to categorize cases into high-burden (ZBI score ≥ 13, 10/34, 29.4%) and low-burden (ZBI score < 13, 24/34, 70.6%) groups. Combining 12-month scores for burden with baseline burden scores, cases were categorized as staying high (4/27, 14.8%), low (17/27, 63.0%), shifting from high to low burden (4/27, 14.8%), or low to high burden (2/27, 7.4%). Seven CPs did not complete surveys at 12 months. In the last phase of analysis, we selected exemplar cases that illustrated cross-cutting findings and changes in burden over time.

Results

Sample characteristics

Of the 36 CPs, a majority were women (72.2%) and married or partners (72.2%) to the Veteran for whom they provided care (see Table 1). Consequently, most CPs lived with the Veteran (63.9%) and, on average, had known the Veteran for a considerable length of time, mean = 15.1 years (SD = 10.0, range = 0.8, 34). Only 11.1% of CPs had been caregiving for the Veteran for less than a year, while 52.8% had been a caregiver for more than 5 years.

TABLE 1 Aim 2 care partner participant characteristics ($n = 36$).

Age (years), Mean (SD)	38.3 (11.3)
Gender (female), *n* (%)	26 (72.2%)
Race/Ethnicity, *n* (%)	
Black/African American	4 (11.1%)
White/Caucasian	28 (77.8%)
Asian	3 (8.3%)
American Indian or Alaskan Native	1 (2.8%)
Hispanic/Latino	2 (5.6%)
Served in the military (past or current), *n* (%)	13 (36.1%)
Employment, *n* (%)	
Full time (35 h/wk or more)	22 (61.1%)
Part time (<35 h/wk)	3 (8.3%)
Retired/Unemployed/Student/Homemaker	11 (30.6%)
Financial, *n* (%)	
Comfortable	28 (77.8%)
Just enough to make ends meet	7 (19.4%)
Not enough to make ends meet	0 (0%)
Prefer to not say	1 (2.8%)
Relationship to Veteran, *n* (%)	
Spouse or partner	26 (72.2%)
Parent	1 (2.8%)
Sibling	1 (2.8%)
Child	2 (5.6%)
Other non-relative (ex-spouse, friend, mentor, etc.)	7 (19.4%)
Lives with Veteran, *n* (%)	23 (63.9%)
Time providing regular care to Veteran, *n* (%)	
<1 year	4 (11.1%)
1 year to <3 years	5 (13.9%)
3–5 years	4 (11.1%)
>5 years	19 (52.8%)
Unsure	4 (11.1%)

Also, 58.3% of CPs were parents or guardians to a child under the age of 18 years. Over a third (36.%) reported military service. One respondent reported participation as a paid caregiver in the VHA PCAFC.

Associations among caregiver burden, stress, flourishing, life satisfaction, and relationship quality

As expected, burden was significantly positively correlated to perceived stress ($r = 0.50$, $p = 0.003$). Additionally, burden was significantly inversely related to secure flourishing ($r = -0.60$, $p < 0.001$) and relationship quality ($r = -0.45$, $p = 0.008$). Though an inverse trend between burden and life satisfaction was observed, this correlation was non-significant ($r = -0.26$, $p = 0.14$).

Descriptive statistics are shown in Table 2 for survey measures completed by CPs. As expected, CPs with high burden had significantly higher stress ($p = 0.02$), lower secure flourishing ($p = 0.02$), and marginally significantly lower life satisfaction ($p = 0.08$) and relationship quality ($p = 0.06$).

As shown in Table 3, CPs did not access many of the resources available. The most frequently accessed resources were a religious or spiritual network and informal information sources, such as websites and articles. In contrast, formal, structured programs and resources, such as loans, support groups, case managers, caregiving training, and stipends, were rarely accessed.

Qualitative themes relevant to care partner burden

Based on the themes and case descriptions that follow, Figure 2 depicts how burden was conceptualized in this study. The diagram retains the dynamic relationship between self-perception, multi-faceted strain, and change over time but adds factors that increase or decrease the burdens that are specific to CPs to Veterans.

Self-perception

CPs expressed a wide range of feelings and perceptions associated with their caregiving role. Negative emotions named included stress, anger, overwhelmed, frustrated, tired, or drained. For example, P4032 stated, "I feel like I run around like a chicken with my head cut off. So as a spouse, I feel like it's very overwhelming;" P4004 explained, "So yeah, I get stressed out. Do I know everything about what to do about everything all of the time? Absolutely not."

However, CPs described their own qualities that were helpful in managing their caregiver role. These qualities included being adaptable, understanding the military experience, accepting their situation, being solution-focused, staying calm, and being a positive, caring person. As an example of adaptability being an asset, P4021 described, "I'm used to being flexible… it was always important to me for my husband to be happy with whatever job he's working for after the military, so if that meant we need to move a certain city, that's okay. I work in healthcare, so it's not as hard for me to find jobs." Similarly, another CP relied on her acceptance and adaptability for managing the caregiver role. P4017 stated, "It's not a pity thing… When you sign on and you know that this is a lifestyle, you are choosing, and the choice was made that our marriage and we know that like his Marine Corps job is what's going to drive. And we were in that together. So but as a result, that means that I am not going to have a career… There is a lot of fluidity, and you have to be willing to just go with the flow and let his stuff drive it and not yours, if that makes sense." P4006 described herself as a "fixer" meaning she will "try to figure out well, how can we fix this? Well, how can we make it better?" She viewed this as a strength in her role as a caregiver. Similarly, P4038 described herself as "a person that loves to take care of people" and "the bubbly, cheery,

TABLE 2 Descriptive statistics of baseline survey measures assessed in the care partner sample by burden level.

Measure	Full sample ($n = 34$) Mean (SD)	Low burden ($n = 24$) Mean (SD)	High burden ($n = 10$) Mean (SD)
Burden	9.29 (7.23)	5.46 (3.40)	18.50 (5.38)
Stress (PSS)	13.15 (6.26)	11.38 (6.02)	17.40 (4.74)
Secure flourishing (SFI)	7.88 (1.14)	8.23 (0.87)	7.04 (1.31)
Life satisfaction (SWLS)	5.32 (1.16)	5.56 (1.20)	4.78 (0.90)
Relationship quality	3.16 (0.53)	3.28 (0.44)	2.88 (0.63)

High burden = 13 and higher.

TABLE 3 Frequency of care partner resources accessed and perceived as helpful ($n = 35$).

Resource	Accessed resource (n, %)	Helpful (n, %)
A religious or spiritual network	14 (40.0%)	14 (100.0%)
Informal sources of information (i.e., magazine articles, websites such as WebMD, and informational pamphlets)	14 (40.0%)	13 (92.9%)
Structured wellness activities for yourself (i.e., classes or group activities on exercise, yoga/meditation, and healthy eating)	13 (37.1%)	12 (92.3%)
Health care resources for yourself (i.e., doctors' appointments, visits to health care facilities)	9 (25.7%)	7 (77.8%)
Psychological counseling from a trained healthcare professional for yourself (i.e., psychologist, psychiatrist, and social worker)	7 (20.0%)	6 (85.7%)
Some other resource	7 (20.0%)	7 (100.0%)
A helping hand (i.e., loans, donations, legal guidance, or housing assistance other than VA stipends or payments)	4 (11.4%)	4 (100.0%)
A referral service for finding programs to help you with your challenges helping you care for the Veteran	3 (8.6%)	3 (100.0%)
Structured support groups such as online or in-person support groups for caregivers	3 (8.6%)	3 (100.0%)
An advocate or case manager; someone to try to coordinate help for the Veteran	3 (8.6%)	3 (100.0%)
Structured education or training (i.e., in-person classes, one-on-one training, online modules, or printed workbooks to inform you about caregiving)	1 (2.9%)	1 (100.0%)
A monthly stipend or payment from the VA in exchange for the care you provide	1 (2.9%)	1 (100.0%)
Respite care/someone who provided care to the Veteran while you did other things	1 (2.9%)	0 (0.0%)
A call-in help number for family members/friends of Veterans like yourself	1 (2.9%)	1 (100.0%)

Respondents indicating that a resource was "Somewhat" or "Very" helpful was categorized as "Helpful."

happy-go-lucky person. Day in and day out, will find the positive in everything."

Multiple responsibilities and roles

As noted by Liu et al. (30), CPs manage caregiving responsibilities alongside their other social roles. CPs reported that they helped their Veteran with daily medications, medical appointments, physical safety (i.e., falling), emotional support, and meals. One CP described monitoring her husband's mood and providing support when he appeared to need it. P4006 stated, "So at this point, that's what I really feel like that my role is really just to make sure that he has a loving support at home and that he knows that he's accepted no matter what and… recognize that oh okay, something is a little off… Either he's not communicating, or he seems a little withdrawn and then just trying to gently talk to him about are you just tired." Similarly, when asked "Are you like worried about him?" P4012 responded, "It's kind, it's almost like a motherly worried. Because I can tell that he's anxious and that he's feeling that anxiety." P4011 described her caregiving stress in the following way: "It can be a very, very tiring struggle sometimes to help everybody and make sure that he is still okay and still on the schedule that he needs or making it to the appointment or remembering to eat." In addition to monitoring emotional changes, CPs reported that Veterans had angry outbursts that were hard to manage. P4020 explained: "I'm trying to keep him calm. You know… It's upsetting because he'll get angry and be upset more, which can cause the kids to get upset. Yeah, it's stressful." Some of these CPs primarily managed household finances, daily household decisions, and household moves, or were the only driver in the household. For example, P4003 stated "So I take care of all of the financial stuff at our house." Similarly, P4011 explained, "And I'm like the stick in the middle that controls everything (laughter). Yes. Very much so. I kind of rule everything, and I didn't like to take that spot, but I do pretty good at it (laughter)."

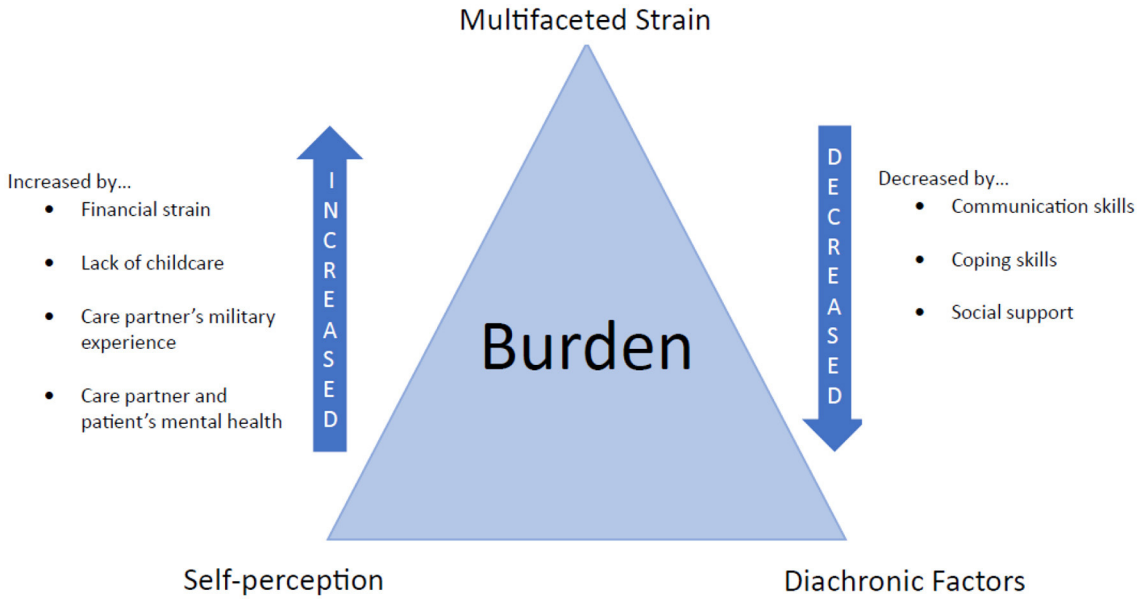

FIGURE 2
Diagram of components of care partner burden.

Monitoring disclosure and aiding in navigation

CPs played a crucial role in supporting help-seeking behavior, including encouraging Veterans to disclose information with appropriate timing and context. P4016 explained how her husband "was so closed off" that he did not respond to initial mental health outreach, but that her presence at therapy appointments was beneficial: "I was able to kind of explain certain situations… that he maybe he didn't even realize was happening."

CPs describe how they helped Veterans navigate through challenges related to accessing health services, scheduling appointments, and paying for health services. One CP expressed how it "was easier to navigate with two brains than one" (P4013). This CP emphasized caring for his spouse: "No, it's not a burden. I'm not even stressed either, because of the way I deal with stress, which is another thing that she is mad about, how I'm different from her on that aspect."

P4025, a CP with high self-reported stress, described in detail attempts to help:

> "I'd come home and say so when's your appointment? Oh, I couldn't do that. And so I would be encouraging and say, okay, want me to call? No, I can do it. I'll do it tomorrow. And it took the initial phone call took 5 or 6 days and then the initial appointment, there was a lot of anxiety leading up to the appointment, and the day of the appointment, there's anxiety, and so it's, which the cultural stuff?"

This CP explained the importance of persistent monitoring coupled with empathy about the Veteran's anxiety about attending scheduled appointments. Other CPs discussed how they witnessed "getting the runaround" (P4011) when trying to access services; P4004 explained that it was necessary to reach out to the Patient Advocate for assistance.

Resources, needs, and strategies

In terms of resources that would aid CPs, respondents discussed a range of needs and strategies that they used. Several CPs suggested that focused courses or workshops delivered after military separation occurs would be beneficial with specific courses dedicated to CPs supporting Veterans. Topics that were suggested included communication skills, awareness of mental health issues, and support in navigating the VA healthcare system. P4020 suggested a coupled-focused course: "No, nobody ever contacted me and said this is what PTSD looks like—like I think that it should be mandatory for couples to go through classes before deployments and after deployments, and you know." Other CPs expressed the need for consistency when it comes to health care services and courses to understand VA benefits, including disability and insurance from a CP perspective. P4002 proposed presentations about supporting a Veteran be held at local community centers to aid in caring efforts.

Table 3 summarizes which types of resources CPs found useful. The most accessed resources, structured wellness activities, informal information sources, and participation in spiritual or religious networks, were reported to be helpful.

Exemplary cases

The following offer exemplar cases that illustrate high and low burdens. To demonstrate within-case changes, we likewise offer

cases that remained as either high or low burden or changed their burden-level at 12 months.

High-burden cases

Among CPs reporting high levels of burden, P4019 was a spousal CP who himself served nearly three decades in the Navy and has a 70% service-connected disability. He left service prior to his wife, which was when they "reversed roles" and he was the primary caretaker of their children while she was deployed. He supported his wife primarily through cooking and cleaning but expressed how he wished he could provide more support for his wife but that they have communication issues. This CP scored higher for "role strain" than for "personal strain," which converges with evidence from his interviews.

P4009 was also a Veteran who served in the Air Force for 6 years. Her husband struggled with mental health (depression, PTSD), which was a major stressor in their relationship. As a result, she felt "almost like a single parent," caring for their four children while working as a mental health professional. This CP was categorized as having a high burden at baseline and at 12 months. She described stress from coping with the volatility of her spouse's mood, explaining how he "shuts off" and "self-isolates" from her and their children, leaving her feeling less hope for the future.

P4026 was a case where at baseline, the CP was struggling to support his girlfriend due to her own challenges with civilian reintegration, PTSD, and migraines. The CP was also a Veteran but had a smoother transition into higher education following his military service. The couple temporarily separated when the Veteran decided to move to a new state, but the CP changed his mind and moved in with her in her new residence. Though the CP had a high burden at baseline, at 12 months, the CP was categorized as low burden and had higher scores for flourishing.

Low burden cases

Reporting low burden, P4004 was the sole CP who had been in the VA's "Program of Comprehensive Assistance for Family Caregivers" (PCAFC) for 5 years. This CP quit her job in oral hygiene to become a full-time caregiver to her husband, a Veteran who was medically discharged and had memory problems, several physical issues, and PTSD. P4004 navigates VHA health services, taking him to multiple weekly appointments, as well as managing medication and paperwork. Despite some lost earnings from her prior career, she reported low levels of stress and burden and a good quality of life.

P4020 had four children and had been married to the Veteran for 14 years. She had witnessed significant physical (back and shoulder pain) and mental health changes (increased anger and isolation) after his first combat deployment. Like P4004, P4020 assisted with her husband's medical care and engaged in couples counseling. P4020 remained a low-burden case at baseline and 12 months. Despite being the sole support for him outside of the mental health care team, she had a strong social network, including family, friends, and coworkers, and engages in self-care through meditation, traveling, and receiving massages.

Discussion

In this study, we draw on self-reported caregiver burden in addition to interviews spaced 12 months apart to capture the experiences of CPs of US military Veterans. The objective was to use a mixed methods approach to categorize 36 CPs into discernible groups through a conceptual framework that posits three aspects of burden: multi-faceted strain, self-perception, and change over time. We demonstrated how CPs were categorized as high or low burden initially, but also how some cases shifted categories based on changing circumstances and factors exacerbating or diminishing personal strain. A life course perspective developed for military households can address the unique challenges of managing civilian-military cultural issues, the strain of emotional dysregulation among recently separated Veterans, and intertwined physical and mental health conditions (38, 64). These findings offer longitudinal evidence that supports the broader framework promoted by the Dole Foundation's caregiver journey map (30). In particular, our findings reinforce how the process of self-identifying as a caregiver can be a gradual process, followed by critical points where burden and wellbeing may fluctuate.

Drawing on an existing conceptual model for caregiver burden (35), we closely examine specific cases to identify antecedents and consequences of CP burden that are specific to providing support for military Veterans. Existing studies tend to focus on either the potentially positive aspects of caregiving or emphasize the emotional distress (65) but are less likely to describe financial strain or the opportunity costs of caregiving (66). This sample was notable for its relatively small use of available resources; a single CP was enrolled in a formal caregiver program, and CPs reported little training or preparation for support tasks. CPs in this study described how they supported Veterans who were dealing with emotional dysregulation. Likewise, CPs play an integral role in monitoring how their partners interact with civilians in stressful environments, often shielding them from potentially challenging spaces or repairing conversations where Veterans encountered communication problems with civilians.

In contrast to the preponderance of caregiving studies with older participants, these findings highlight the disruptions that occur for those in the early adult stage (ages 17–45), as they shift careers, manage childcare responsibilities, and transition from military service. CPs discussed balancing support for their partner alongside caring for children and pursuing their own career. Consistent with other studies (67), spousal caregivers reported a lack of confidence in their ability to support their partners and also described difficulties with intimacy. Male spouses in particular reported more issues with role strain—that is, feeling unsure or inadequate in their ability to support their spouse. Multi-faceted strain in the context of the challenges of early adulthood reinforces the importance of a life course perspective (31, 32).

Limitations of these findings should be noted. CPs were recruited based on being nominated by a participating Veteran, which likely limited the heterogeneity of the sample. Most participating Veterans were male, whereas 72% of CPs were female, and most had been caring for the Veterans for more than 5 years. More research is needed to better understand how findings might apply across different sociodemographic groups. The study

included multiple data collection points which offered a window into how CPs changed over a 12-month period.

Conclusion

Few studies have examined how the experiences of unpaid caregivers support military Veterans with invisible injuries such as post-traumatic stress disorder and traumatic brain injuries. Findings suggest the unique needs of individuals who support military Veterans with invisible injuries, highlighting variations and diachronic elements of caregiving. Distinguishing between the experiences of CPs who report high and low burden offers insight into how unpaid caregivers are affected by childcare, financial responsibilities, or incomplete knowledge of appropriate mental health care.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Indiana University IRB and Roudebush VA Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. MF: Conceptualization, Investigation, Resources, Visualization, Writing – original draft, Writing – review & editing, Project administration. AM: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. LD: Data curation, Writing – review & editing. A-ND: Writing – review & editing. DN: Writing – review & editing. KS: Writing – review & editing. GT: Funding acquisition, Conceptualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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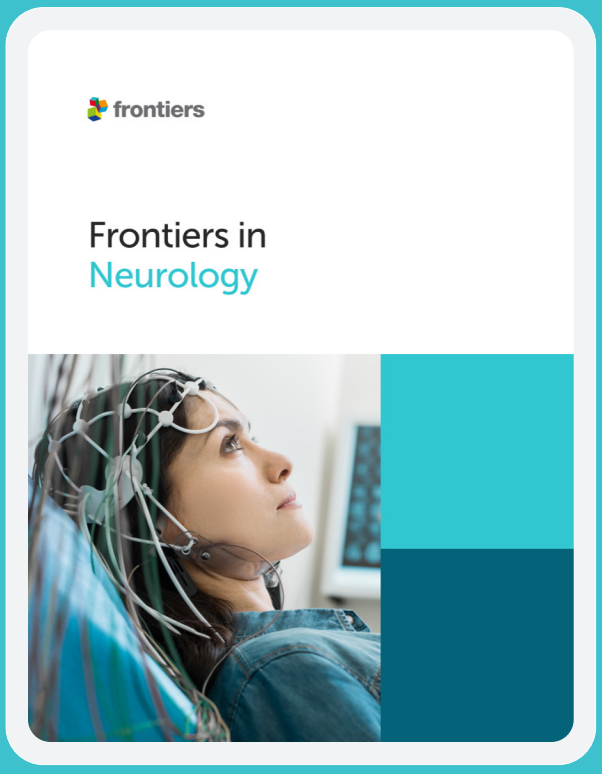

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