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Repetitive Transcranial Magnetic Stimulation for Depression and Posttraumatic Stress Disorder in Veterans With Mild Traumatic Brain Injury

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ABSTRACT

Objectives: Mild traumatic brain injury (mTBI) is a signature injury of military conflicts and is prevalent in veterans with major depressive disorder (MDD) and posttraumatic stress disorder (PTSD). Although therapeutic transcranial magnetic stimulation (TMS) can reduce symptoms of depression and PTSD, whether traumatic brain injury (TBI) affects TMS responsiveness is not yet known. We hypothesized mTBI would be associated with higher pretreatment symptom burden and poorer TMS response.

Materials and Methods: We investigated a registry of veterans ($N = 770$) who received TMS for depression across the US Veterans Affairs system. Of these, 665 (86.4%) had data on TBI and lifetime number of head injuries while 658 had complete data related to depression outcomes. Depression symptoms were assessed using the nine-item Patient Health Questionnaire and PTSD symptoms using the PTSD Checklist for DSM-5. Linear mixed effects models and *t*-tests evaluated whether head injuries predicted symptom severity before treatment, and how TBI status affected clinical TMS outcomes.

Results: Of the 658 veterans included, 337 (50.7%) reported previous mTBI, with a mean of three head injuries (range 1–20). TBI status did not predict depressive symptom severity or TMS-associated changes in depression (all p's > 0.1). TBI status was associated with a modest attenuation of TMS-associated improvement in PTSD (in patients with PTSD Checklist for DSM-5 scores > 33). There was no correlation between the number of head injuries and TMS response ($p > 0.1$).

Conclusions: Contrary to our hypothesis, presence of mTBI did not meaningfully change TMS outcomes. Veterans with mTBI had greater PTSD symptoms, yet neither TBI status nor cumulative head injuries reduced TMS effectiveness. Limitations include those inherent to retrospective registry studies and self-reporting. Although these findings are contrary to our hypotheses, they support the safety and effectiveness of TMS for MDD and PTSD in patients who have comorbid mTBI.

Keywords: Major depression, mild traumatic brain injury, posttraumatic stress disorder, transcranial magnetic stimulation, veterans

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INTRODUCTION

Traumatic brain injury (TBI) is the most common form of brain injury in the world, most of which is mild TBI (mTBI), resulting in an estimated 69 million cases worldwide every year.[1–3] mTBI, also referred to as a concussion, has many causes among the general population, including falls, automobile accidents, sports injuries, and domestic violence.[4–6] However, it is particularly common in service members and veterans, and is considered one of the signature injuries of recent US military conflicts.[7] mTBI is associated with several negative sequelae of physical and mental health. In addition to postconcussive syndromes, exposure to repeated mTBI is implicated in the development of chronic traumatic encephalopathy.[8] From a psychiatric perspective, mTBI is often associated with depression and posttraumatic stress disorder (PTSD),[9] each of which carries additional disability burden and is associated with poorer quality of life.[1,10–12]

Despite the impacts of mTBI on depression and PTSD, there are few available treatments for depression and PTSD in individuals with previous mTBI. Although the US Food and Drug Administration (FDA) has not approved transcranial magnetic stimulation (TMS) in patients with previous mTBI, TMS has been cleared for over a decade for the treatment of pharmacoresistant major depressive disorder (MDD).[13,14] TMS uses rapidly fluctuating magnetic fields to induce electrical currents in targeted brain tissue and to activate specific brain circuits. TMS has a considerable amount of data indicating its safety and tolerability. Recent evidence has led to FDA clearance for the use of TMS in other neuropsychiatric conditions, such as obsessive-compulsive disorder, smoking cessation, and anxious depression,[15] and there is increasing evidence supporting its use to reduce symptoms of PTSD.[16,17,18]

Previous studies have shown mixed clinical outcomes of TMS for depression in patients with a history of mTBI. For example, results from several randomized controlled TMS trials revealed greater decreases in depressive symptoms with active stimulation than with sham,[17,19–21] whereas others found no difference between active and sham TMS in those with mTBI.[22–26] Of note, many of these studies had relatively small sample sizes or were secondary subanalyses from larger studies, which encourages a cautious interpretation of the findings. To date, there have been no randomized controlled studies of TMS for PTSD in patients with mTBI history, although subgroup analyses from one previous study appear to indicate positive outcomes.[17] TMS has more extensively been investigated as a tool to alleviate posttraumatic headache and postconcussive cognitive symptoms after mTBI, with mixed results.[27]

When considering TMS as a treatment for patients with depression and PTSD, there is a rational basis to expect that those patients with mTBI would have poorer outcomes than those of patients without mTBI. Accumulating neuroimaging evidence indicates broad-scale network dysfunction in mTBI, depression, and PTSD.[28] In the cases of depression and PTSD, TMS appears to be able to improve symptoms and modify pathological network function.[29] Although a definitive mechanism(s) of therapeutic response to TMS remains an area of study, TMS likely works by changing localized brain activity in the targeted tissue and inducing a series of polysynaptic or "downstream" changes across multiple neural networks.[30] For example, a small trial comparing active and sham stimulation for depression revealed white-matter improvements localized to the area stimulated by TMS (ie, increased fractional anisotropy values), with a trend toward greater improvements in the active group.[31] Therefore, the integrity of the underlying functional[17,29] and structural[32] anatomy, both of which may be compromised after mTBI, is an important component of a patient's TMS response.

The objective of this study was to investigate the clinical impact of TBI on depression and PTSD baseline symptoms and clinical outcomes in a large registry study of veterans receiving TMS for MDD across the Veterans Affairs (VA) system. Experience of at least one TBI was hypothesized to increase the burden of illness and decrease responsiveness to treatment with TMS. Secondary analyses also explored a "dose-effect," with a greater number of lifetime TBIs hypothesized to create greater burden. Because clinicians may also use off-label TMS parameters, we also explored clinical outcomes restricted to only those veterans who received FDA-cleared protocols.

These data will provide important empirical evidence to help guide future treatment decisions and direct areas of investigation.

MATERIALS AND METHODS

TBI history and symptom rating data were collected from a registry of veterans ($N = 770$) who received TMS for depression at 27 sites across the VA system. The registry is part of a national clinical program evaluation and as such includes any Veteran seeking treatment with TMS. The VA Palo Alto/Stanford Institutional Review Board approved associated procedures. As part of standard VA clinical procedures, TBI status was assessed through self-report, which also inquired about the number of lifetime head injuries. The training for clinicians providing TMS in the VA system recommends excluding patients who have moderate-to-severe TBI based on self-report and/or medical chart review. Thus, only those patients with mTBI (ie, loss of consciousness > 30 minutes, posttraumatic amnesia > 24 hours, and no structural imaging changes) are eligible for TMS treatment. A total of 665 patients (85.3%) reported TBI data. Depressive and PTSD symptoms were assessed at baseline (pretreatment), end point (after an acute course of TMS that typically lasts 30 sessions), and every five treatments throughout TMS using the nine-item patient health questionnaire (PHQ-9[33]) and PTSD Checklist for DSM-5 (PCL-5[34]), respectively. The referral process, TMS procedures, and medication management are described in greater detail in;[16] in brief, medications (and other treatments) were held stable during TMS therapy as part of standard clinical care. Most patients received standard TMS parameters (eg, 10 Hz, to left dorsolateral prefrontal cortex, 120% of motor threshold, 3000 pulses per session for 30 sessions), though different protocols and treatment durations were used for some patients at local discretion.

For primary analyses, TBI was defined as a binary variable (yes/no). To test for differences in clinical burden because of TBI at baseline, *t*-tests were used to evaluate differences in pretreatment PHQ-9 and PCL-5 scores, with TBI as the grouping factor. We examined the effect of TBI status on two outcome measures after a course of TMS treatment, the PHQ-9 and the PCL-5, using linear mixed effects models with a subject random effect and observations at baseline and posttreatment with fixed effects for time (0 = baseline, 1 = end of treatment); TBI status (0 = no, 1 = yes); and a time × TBI interaction. We decided not to use additional time points from the data because this would require assuming a particular trajectory or continued improvement, stabilization, or decline after treatment. Although an accurate assumption can potentially increase power, an inaccurate assumption could yield

misleading results. To aid in the interpretation of any negative results, we report 95% CIs for the mean change during treatment for each group. In this model, the estimate of change, δ, is identical to the coefficient for time for the untreated group. For the treated group, δ is the sum of the time and interaction coefficients. To assess potential confounders, we repeated this model adding variables for age (in years); presence/absence of reported mental health comorbidities; and sex at birth. We fit the same two models separately, with the PHQ-9 score and the PCL-5 score as dependent variables.

Secondary analyses investigated the relationship between number of lifetime reported head injuries and outcomes. Regression analysis was used to investigate whether number of TBI events correlated with either pretreatment morbidity or response to treatment. Analyses on PTSD outcomes were performed in the full cohort (ie, "all comers," regardless of their pretreatment PCL-5 score), and subsequently run separately for individuals who met the symptom-severity criteria for PTSD before treatment (operationally defined as pretreatment PCL-5 score > 33).

RESULTS

TBI Characteristics

Characteristics of the mTBI events of veterans included in this analysis reported are shown in Figure 1. Owing to different numbers of reports across various surveys/questionnaires, reporting below includes the total number of reports included in each analysis. Of the 658 veterans (86% of cohort) with answers to the TBI question, 337 (50.7%) reported previous lifetime mTBI. Age of reported injuries was skewed to lower age ranges (60.6% of reported injuries occurred before the age of 25 years). Of the 321 veterans with mTBI reporting on number of lifetime injuries, there was a mean (SD) of 3.1 lifetime events (3.3) (range 1–20); however, the distribution was left-skewed, with 85% of patients reporting < four lifetime head injuries. The median number of events was two, and 244 of 321 veterans (76%) with mTBI had between one and three reported mTBI events in this study. A total of 225 of 336 veterans (67%) with mTBI reported a loss of consciousness; 49 of 329 (15%) reported some degree of retrograde amnesia; and 145 of 332 (44%) reported anterograde amnesia after their injury. Table 1 provides demographic information.

TMS Treatment Outcomes in the Context of mTBI

Further analyses explored whether mTBI status was associated with TMS treatment outcomes (Fig. 2). We first measured whether mTBI status affected TMS drop-out rates and found mTBI was not associated with increased drop-out rates; veterans without mTBI completed 28.8 sessions of treatment (0.6), compared with 29.8 sessions of treatment (0.66) in veterans with mTBI [n = 491 responses, t(489) = −1.1, p = 0.26]. Within the mTBI group, Spearman correlation did not indicate a statistically significant correlation between the number of head injuries with either pretreatment PHQ-9 (r = 0.013, p = 0.8) or PCL-5 (r = 0.1, p = 0.06).

To analyze the observed effect of TBI status on PHQ-9 after an observed course of TMS treatment, we fit two linear mixed effects models including time, TBI status, and a time × TBI interaction with and without three potential confounders: age, mental health comorbidities (yes/no), and sex at birth. The interaction was not significant in either model, indicating a lack of evidence for a moderating effect of TBI on the effects of TMS treatment on the PHQ-9 score (Fig. 2a). In the nonconfounder model, the interaction p-value was p = 0.88. The estimate [95% CI] for change in the PHQ-9 during treatment in the non-TBI cohort was −7.3 (−8.1, −6.6). In the TBI group, the change was −7.4 (−8.2, −6.6). Results were almost identical in the model with potential confounders (p = 0.93),

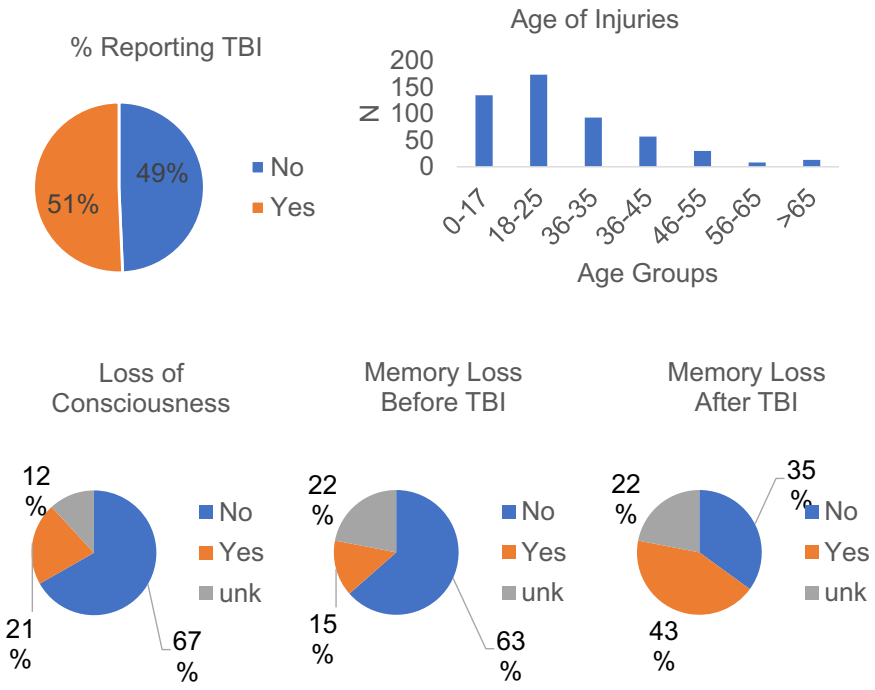

Figure 1. Characteristics of TBI in veterans. In this sample, 51% of the veterans reported TBI (337/665). Age and severity of the injuries shown in the figure. [Color figure can be viewed at www.neuromodulationjournal.org]

Table 1. Demographics.

Variable	No mTBI, n = 321	mTBI, n = 337
Age, mean (SD)	51.18 (14.66)	51.72 (13.45)
Race		
White	230 (70.1%)	266 (78.9%)
Black	53 (16.2%)	28 (8.3%)
Asian*	10 (3%)	20 (6%)
Multiracial	10 (3%)	5 (1.5%)
Other	20 (6.1%)	13 (3.9%)
No response	5 (1.5%)	5 (1.5%)
Biological sex		
Male	250 (76.2%)	283 (84%)
Female	78 (23.8%)	53 (15.7)
No response	–	1 (0.3%)
Gender		
Male	192 (58.5%)	204 (60.5%)
Female	63 (19.2%)	45 (13.4%)
Transgender	3 (0.9%)	3 (0.9%)
Androgynous	1 (0.3%)	2 (0.6%)
Agender	3 (0.9%)	2 (0.6%)
No response	66 (20.1%)	83 (24.6%)
Highest education achieved		
Elementary school	1 (0.3%)	4 (1.2%)
High school or General Educational Degree	50 (15.2%)	23 (6.8%)
Some college, no degree	105 (32%)	107 (31.8%)
Associate degree, vocational program, or certificate	48 (14.6%)	73 (21.7%)
Bachelor's degree	66 (20.1%)	77 (22.8%)
Master's degree	44 (13.4%)	43 (12.8%)
Doctoral degree	12 (3.7%)	8 (24%)
No response	2 (0.6%)	2 (0.6%)
History of suicide attempts		
Yes	125 (38.1%)	127 (37.7%)
No	202 (61.6%)	205 (60.8%)
No response	1 (0.3%)	5 (1.5%)
History of psychiatric hospitalizations		
Yes	186 (56.7%)	176 (45.7)
No	139 (42.4%)	154 (52.2%)
No response	3 (0.9%)	7 (2.1%)
Self-reported comorbidities		
PTSD	158 (48.2%)	214 (63.5%)
Substance use disorder	34 (10.4%)	43 (12.8%)
Alcohol use disorder	46 (14%)	55 (16.3%)
Anxiety spectrum disorders	136 (41.5%)	116 (34.4%)
Obsessive-compulsive disorder	6 (2.7%)	15 (4.5%)
Bipolar disorder	47 (14.3%)	43 (12.8%)

*Asian Indian; American Indian; Native Alaskan; Pacific Islander; Middle Eastern, Southeast Asian, and East Asian.

with the PHQ-9 change estimated as −7.3 (−8.1, −6.5) and −7.4 (−8.2, −6.5) in the untreated and treated groups, respectively (Table 2). Although age ($p < 0.001$) and mental health comorbidities (0.007) were both significant, their presence in the model did not alter the results for TBI. The same is true of sex at birth, which was not significantly associated with PHQ-9 scores ($p = 0.67$). The presence of a TBI was not significantly associated with the PHQ-9 observed at baseline ($p = 0.95$ and $p = 0.69$, respectively).

We repeated the above analysis for the PCL-5 score (Fig. 2b). The interaction term was again not significant in either model without or with the potential confounders ($p = 0.24$ and 0.25, respectively). In the former model, the estimates of change for the PCL-5 score in the non-TBI and TBI groups, respectively, were −14.9 (−17.1, −12.7) and −16.8 (−19.0, −14.6). When we included potential confounders in the model, the estimates were almost identical: −14.7 (−16.9, −12.5) and −16.5 (−18.7, −14.3), respectively (Table 2). Age and mental health comorbidities were both significant at $p < 0.001$, whereas sex at birth was marginally significant ($p = 0.05$), but none of these covariates substantially altered the results for time and TBI. As was the case for the PHQ-9, the presence of a TBI was not significantly associated with baseline PCL-5 scores (includes all participants with a PCL-5 rating) in the model without ($p = 0.99$) or with these potential confounders ($p = 0.82$).

Exploratory post hoc analyses were conducted to assess whether there were differences in response and remission rates between persons with and without mTBI (Table 3). Chi-square analysis indicated no differences between individuals with and without mTBI in response rates [$c^2(1, n = 487) = 2.10$, $p > 0.05$; defined as > 50% reduction in PHQ-9 score] or remission rates [($c^2(1, n = 470) = 2.25$, $p > 0.05$; defined as PHQ-9 < 5]. Additional exploratory analyses were completed to assess whether there were differences in posttreatment PHQ-9 scores based on time since most recent injury. Results indicate there were no differences [$F(7, 434) = 1.96$, $p > 0.05$].

To explore whether observed effects might be more pronounced in those with higher levels of pretreatment PTSD symptoms, follow-up analyses included only veterans with symptomatic or "threshold" level PTSD symptoms (ie, pretreatment PCL-5 score > 33). In these 302 veterans, we observed a significant difference in the change in PCL-5 scores as a function of a history of injury. Veterans without an mTBI showed a greater reduction of 21.9 points (1.5), whereas those with an mTBI showed a reduction of 17 points (1.3) [$t(300) = 2.5$, $p < 0.012$, Cohen's d = 0.29]. There was no relationship between the number of mTBIs and PTSD symptom change (all p's > 0.1). Of note, very few serious adverse events (and only a single seizure) occurred in this cohort,[16] so group comparisons were not performed.

Exploration of Whether mTBI Affects Outcomes When Only Considering On-Label TMS Treatment Protocols

We also explored whether veterans treated with on-label TMS parameters (eg, left-sided TMS using 10 Hz or intermittent theta burst stimulation or 18 Hz dTMS delivered at 120% of motor threshold to the left dorsolateral prefrontal cortex) might show any differences in terms of the impact of mTBI status on treatment outcomes. Examining outcomes only using FDA-cleared protocols (n = 463/665, 69.6%) did not provide any meaningful changes in results. Changes in the PHQ-9 were again unaffected by mTBI status ($n = 336$, $t(334) = 1.24$, $p = 0.22$). mTBI status also did not have a clear impact on PCL-5 changes. When examining all veterans, regardless of the level of pretreatment-PTSD symptom burden, veterans without an mTBI showed a change of 17.8 (1.4), and a change of 14.9 (1.3) was seen in veterans with mTBI [$t(313) = 1.53$, $p = 0.13$, Cohen's d = 0.17]. When analyzing veterans only with "threshold" PTSD (PCL-5 > 33), veterans without an mTBI showed a 22.6-point reduction (1.7) in the PCL-5 whereas veterans with mTBI showed a 17.5-point reduction (1.5) in the PCL-5 [$n = 227$, $t(225) = 2.25$, $p = 0.025$], closely matching what we observed in veterans treated with all forms of clinical TMS. Because of low statistical power, we did not further explore whether mTBI might affect outcomes using off-label protocols.

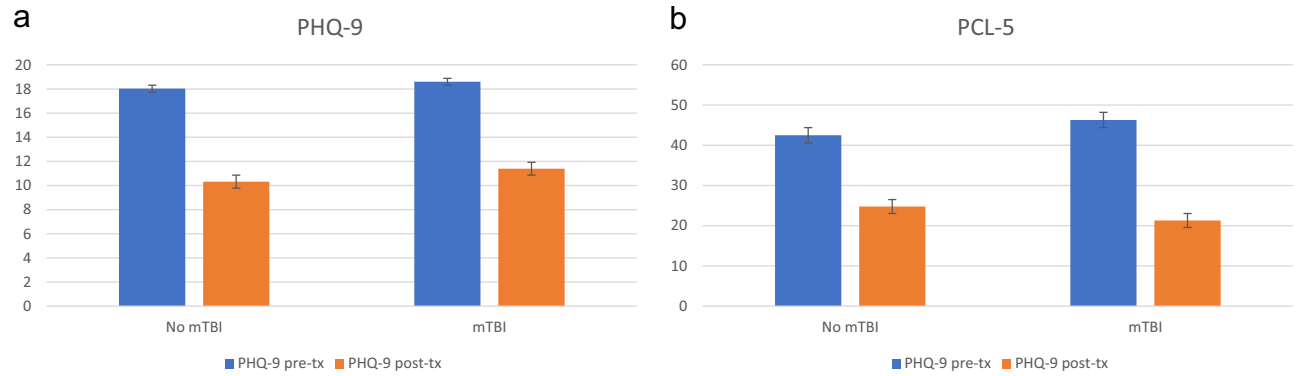

Figure 2. Relationship of mTBI, illness severity and treatment response. a. mTBI is not associated with differences in depressive symptoms. b. mTBI is associated with baseline differences in PTSD symptoms with minimal impact on outcomes. [Color figure can be viewed at www.neuromodulationjournal.org]

DISCUSSION

To our knowledge, this is the largest examination of the possible influence of mTBI on TMS outcomes in patients with depression and PTSD. Counter to our hypothesis, we did not find a meaningful difference in clinical depression symptom severity, attrition, or TMS depression outcomes in the presence of mTBI. Furthermore, similarly to other studies in which 32.1% of individuals with PTSD achieved remission of MDD symptoms, individuals in this analysis with comorbid PTSD were able to benefit from TMS treatment.[35] These data strongly suggest that mTBI with or without PTSD should not be considered a contraindication to clinical TMS for MDD.

Notably, in this data set, veterans with mTBI and PTSD did have slightly more severe PTSD symptoms than did veterans without mTBI before treatment. That stated, the difference between the groups was approximately four points on the PCL-5, which would not be considered clinically meaningful (typically > ten points on the PCL-5 is indicative of a clinically meaningful difference).[36] Previously literature indicated one would expect more severe levels of PTSD symptoms in the context of mTBI, but that was not the case for these veterans.[37] One notable difference is that previous associations between TBI and more severe PTSD symptoms relied on data from service members on active duty, whereas this registry focuses on veterans across a large age range and typically a remote history of mTBI. These veterans likely reflect a patient population with a more long-term condition, in whom the influence of traumatic experiences (and mTBI events) is far more distant.

History of mTBI also showed a modest attenuation of the clinical effectiveness of TMS for veterans with clinically significant PTSD symptoms. Although this was associated with an effect size of Cohen's d = 0.29, the five-point difference on the PCL-5 between the two groups, as noted above, would not be considered clinically meaningful. This provides important guidance for clinicians to frame TMS treatment expectations for patients with mTBI and PTSD. This finding also indicates that further examination of TMS used in this subgroup—patients with threshold PTSD symptoms and comorbid mTBI—may require further consideration. However, another interpretation is that regardless of whether veterans had mTBI, reduction in PTSD symptoms with TMS was statistically significant and clinically meaningful. There were no clear changes in outcomes when examining only on-label protocols, but the small and varied number of other parameters precluded more formal investigation. Other treatment modifications, such as unique coil placement or longer TMS treatment courses, may be important future areas of research for maximizing clinical effectiveness in patients with mTBI history and PTSD.

The fact that mTBI status was not associated with decreased clinical outcomes on depression or PTSD, although counter to our

Table 2. Liner Mixed Effects Model Results.

Variable	Δ	SE	*Z*	*p* Value	95% CI
PHQ-9					
TBI	−7.42	0.41	−18.17	0.000	−8.23, −6.63
No TBI	−7.34	0.40	−18.19	0.000	−8.09, −6.51
Covariates included*					
TBI	−7.42	0.41	−18.17	0.000	−8.23, −6.63
No TBI	−7.34	0.40	−18.19	0.000	−8.09, −6.51
PCL-5					
TBI	−14.9	1.11	−13.40	0.000	−17.1, −12.7
No TBI	−16.8	1.11	−15.02	0.000	−19.0, −14.6
Covariates included*					
TBI	−14.69	1.11	−13.23	0.000	−16.9, −12.5
No TBI	−16.52	1.12	−14.69	0.000	−18.7, −14.3

Number of observations = 1097 with 658 participants for the PHQ-9 and 1069 observations with 643 participants for the PCL-5.
Δ, change in score from pre- to posttreatment.
*Covariates of interest include age, sex at birth, and number of comorbidities.

Table 3. TMS Response and Remission Rates.

Group	Response (*n*, %)	Remission (*n*, %)
No mTBI	96 (19.7%)	52 (11.0%)
mTBI	96 (19.7%)	47 (10.0%)

hypotheses, provides an important and compelling message for patients seeking TMS therapy. These data are also consistent with previous findings that exposure therapy for PTSD can be equally efficacious in patients with and without mTBI.[38] These data also reiterate that TMS is an efficacious treatment for depression and PTSD,[18] and that at least at the population level, mTBI does not negatively influence clinical outcomes. It is possible, however, that a more careful evaluation of different types of mTBI might find more compelling results. For example, one can speculate that patients with frontal mTBI might be less likely to experience a therapeutic benefit from TMS because the stimulation target falls within their area of injury, necessitating individually customized brain stimulation.[39] Furthermore, it is equally possible that TBI severity may also influence clinical response to TMS, which is further complicated given that the safety data on TMS in individuals with moderate-to-severe TBI are limited.

Limitations to this work include those related to large, registry data. This work is collected as part of clinical practice, and as such, there is no sham arm; patients are receiving concurrent care; and no clinician-rated scales are available. That stated, this provides a real-world, naturalistic assessment of the impact of mTBI on clinical TMS outcomes. Another limitation is that TBI was self-reported; although TBI screening and characterization at VA are quite robust when new veterans enter clinical care, data in this report relied upon recollection of earlier events. This issue would be further mitigated by standardized training of TMS providers to deliver TMS to patients with mTBI rather than more severe TBI. Because we did not adjust for the time since service, it is possible that subtle relationships between mTBI and PTSD symptom severity were not identified. Furthermore, as a VA-based analysis, it is not known whether these findings will generalize to non-Veteran patients, although the broad range of head injury across the lifespan should mitigate this concern. Lastly, these analyses were conducted in the absence of brain-based biomarkers or neuroimaging, therefore providing speculative links between potential biological elements and observed findings. Ongoing studies[40] will be able to provide mechanistic insights with more definitive biological data.

CONCLUSIONS

These data indicate that mTBI status has little meaningful effect on TMS outcomes and underscore the real-world effectiveness and safety of therapeutic TMS for PTSD and depression in patients with mTBI. The impact of mTBI on clinical outcomes was nominal at best, and any effects would not be considered clinically meaningful. These outcomes confirm that mTBI should not be considered a contraindication and that therapeutic TMS can be safely recommended for this patient population.

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Authorship Statements

Noah S. Philip, Dhakshin Ramanathan, Michelle R. Madore, and F. Andrew Kozel were responsible for the visualization, investigation, and writing the original draft, in addition to writing, reviewing, and editing the manuscript. McKenna C. Brennan, Bruno Gamboa, and Laura Lazzeroni were responsible for writing, reviewing, and editing the manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.org and at https://doi.org/10.1016/j.neurom.2022.11.015.

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