Comprehensive analysis of the predictors of neurobehavioral symptom reporting in veterans

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Abstract

Objective

This study assessed the strength of military-related concussion-, psychological-, and behavioral-related measures to predict neurobehavioral symptom (NBS) reporting in order to help clarify the extent to which persistent NBS reflect lingering effects of concussion vs other psychological/behavioral factors among veterans.

Methods

Baseline analysis included 351 consecutively enrolled veterans in the Translational Research Center for Traumatic Brain Injury and Stress Disorders longitudinal cohort study. One hundred eighty-six returned for a follow-up evaluation averaging 24 months post baseline. The Neurobehavioral Symptom Inventory (NSI) was used to measure NBS reporting. Predictor variables included diagnosis of military-related mild traumatic brain injury (M-mTBI), psychological measures, including posttraumatic stress disorder, mood, anxiety, and substance abuse disorders, and behavioral measures, including self-reported current pain and sleep impairment. Hierarchical and multivariable regression analyses examined the relationships between the predictor variables and NSI scores. The *k*-fold cross-validation assessed generalizability and validity of the regressions.

Results

Baseline analysis revealed that psychological and behavioral conditions independently accounted for 42.5% of variance in the NSI total score compared to 1.5% for M-mTBI after controlling for psychological and behavioral conditions. Prospective analysis revealed that M-mTBI at baseline did not significantly predict NSI score at follow-up, while psychological and behavioral measures at baseline independently accounted for 24.5% of NSI variance. Posttraumatic stress disorder was the most consistent predictor. Cross-validation analyses supported generalizability of the results.

Conclusions

Psychological and behavioral-related measures are strong predictors of persistent NBS reporting in veterans, while M-mTBI is negligible. NBS more likely reflect influential comorbidities as opposed to brain injury, per se.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); **M-mTBI** = military-related mild traumatic brain injury; **MSVT** = Medical Symptom Validity Test; **mTBI** = mild traumatic brain injury; **NBS** = neurobehavioral symptom; **NSI** = Neurobehavioral Symptom Inventory; **PTSD** = posttraumatic stress disorder; **TBI** = traumatic brain injury; **TRACTS** = Translational Research Center for Traumatic Brain Injury and Stress Disorders; **VA** = Veterans Affairs.

Traumatic brain injury (TBI) is an increasingly common ailment responsible for about 2.8 million total emergency department visits and hospitalizations in the United States in 2013.¹ TBI is also a common consequence of combat experience in the recent military conflicts in Iraq and Afghanistan, affecting between 12% and 23% of returning veterans.^{2,3} Although the vast majority of mild TBIs (mTBIs or concussions) are accompanied by acute changes in cognition and consciousness that are fleeting, there is increasing concern that concussions can be followed by lingering neurobehavioral symptoms (NBS) thought to reflect persistent “postconcussive syndrome.”^{4,5} Common symptoms include dizziness, irritability, headache, and cognitive difficulties in the domains of memory and attention.⁶ The nature and cause of these symptoms is still not well understood, and the claim that they are a direct result of brain injury is controversial.^{7,8}

A major reason for this controversy is that NBS are not specific to mTBI and are common in individuals regardless of their concussion history. Although veterans have a higher prevalence of mTBI than civilians, both populations have a similar prevalence of persistent NBS following mTBI, specifically 21% to 47% of veterans compared to 31% to 53% of civilians.^{2–5,9,10} What’s more, NBS affect about 13% to 25% of veterans and 34% of civilians without history of mTBI.^{4,9,10} One potential explanation for this is the involvement of psychiatric and behavioral conditions. Even when following mTBI, persistent symptoms are significantly correlated with pre- and postinjury psychiatric and behavioral conditions, such as posttraumatic stress disorder (PTSD), anxiety, and depression, illustrating the importance of these issues when assessing and examining NBS.^{9,11–15} Nevertheless, many clinicians and researchers continue to attribute persistent NBS to concussion without fully considering other potential comorbid causal mechanisms.^{16,17}

This veteran-based study was designed to address some of the shortcomings of previous research into the underlying causes of persistent NBS and to provide new insight for clinical applications. The primary aim was to assess the strength of military-related mTBI (M-mTBI), as well as psychological- and behavioral-related measures in predicting NBS reporting in the context of the effects of military deployment. It was hypothesized that psychiatric and behavioral factors would be substantially more powerful predictors of NBS than history of M-mTBI, cross-sectionally and prospectively.

Methods

Participants

Our study sample consisted of veterans and military service members enrolled in the Translational Research Center for TBI and Stress Disorders (TRACTS) longitudinal cohort study¹⁸ investigating TBI and stress-related disorders (current baseline data repository $n = 500$) in post-9/11 veterans. Recruitment and inclusion/exclusion criteria were not based on TBI history or history of any psychiatric or behavioral conditions. Participants’ diagnosis histories ranged from no diagnoses to having multiple comorbid issues. More details regarding participant recruitment, inclusion/exclusion criteria, and institutional oversight are provided in an article by McGlinchey et al.¹⁸

As the figure shows, 481 individuals met the TRACTS inclusion criteria. The current sample was restricted to veterans deployed before the study visit ($n = 457$) and did not include participants who had factors that affect cognitive ($n = 1$), psychiatric ($n = 2$), or neurologic ($n = 2$) function, such as low estimated premorbid IQ, possible psychotic or personality disorder diagnoses, and congenital neurologic irregularities, respectively. We also excluded participants who failed ($n = 31$) or did not complete ($n = 21$) effort/validity measures included in the TRACTS assessment (e.g., Medical Symptom Validity Test [MSVT] scores <85). Participants with a history of moderate or severe TBI were also excluded ($n = 12$), allowing for a focused examination of those with mTBI compared to no TBI history. Furthermore, we excluded individuals who may have exaggerated their reported NBS ($n = 9$) based on the Validity-10 scale, which is embedded in the Neurobehavioral Symptom Inventory (NSI), using the validated cutoff score of 23 or higher.^{6,19} Finally, this study excluded participants who did not complete the behavioral questionnaires ($n = 28$) because of time constraints, resulting in a final sample of 351 veterans included in the baseline analyses.

Among the 351 participants in the baseline sample, 222 returned about 2 years later to repeat all measures, 203 whose data had been fully processed and was available for analysis for this report. For the prospective analysis, we further excluded those who did not complete the NSI ($n = 5$), failed or did not complete the MSVT or Validity-10 effort measures ($n = 8$), had a TBI between baseline and follow-up ($n = 3$), or did not have TBI assessed at follow-up ($n = 1$), resulting in a final sample of 186 veterans for prospective analysis of baseline predictors of follow-up NBS. The participants in these analyses returned for the second assessment an average of 23.9

Figure Exclusion process and final sample sizes for both baseline and follow-up

^aPartial exclusion flags include psychiatric, neurologic, and neuropsychological function, such as low premorbid IQ, possible psychotic or personality disorder diagnoses, and congenital neurologic irregularities, respectively. ^bTwelve to 18 months must have passed since the baseline visit for a participant to be eligible for a follow-up visit. Since data collection is ongoing, not all participants included in the baseline sample are yet eligible for a follow-up. MSVT = Medical Symptom Validity Test; NBS = neurobehavioral symptom; OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OND = Operation New Dawn; TBI = traumatic brain injury; TRACTS = Translational Research Center for Traumatic Brain Injury and Stress Disorders.

(SD = 9) months after their initial evaluation. This is a clinically relevant time period for examining the persistence of NBS over time.^{20,21}

The Veterans Affairs (VA) institutional review board approved the use of human participants for this study. All participants provided written informed consent.

Measures

A doctoral-level psychologist assessed history of TBI (Boston Assessment of TBI–Lifetime version)²² and psychiatric conditions (current PTSD using the Clinician-Administered PTSD Scale for DSM-IV; current mood, anxiety, and substance use disorders using the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-patient Edition). Mild TBI was defined, in accordance with the Department of Defense consensus criteria for TBI severity, as a head injury resulting in loss of consciousness for 0 to 30 minutes, and/or altered mental status for 0 to 24 hours, and/or posttraumatic amnesia for 0 to 1 day.²² These are acute symptoms occurring immediately post injury, not to be confused with longer-term NBS. M-mTBIs include those acquired during military training or deployment through blast exposure or any other means.²² Nonmilitary-related mTBIs include those acquired before or after military training and deployment. On average, participants with a history of M-mTBI experienced their most recent injury 5.7 (SD = 4.4) years before baseline assessment.

Sleep quality during the previous month was assessed using the Pittsburgh Sleep Quality Index, and sleep impairment was defined as a Pittsburgh Sleep Quality Index global score cutoff of >5. Pain was assessed using the short form of the McGill Pain Questionnaire and was defined as current overall pain of mild or greater severity. Embedded effort measures (MSVT, Validity-10) were assessed in the context of an extensive neuropsychological evaluation (not reported here). NBS were assessed via the standard administration and scoring of the NSI.^{6,23} The NSI is a self-report measure consisting of 22 common symptom complaints traditionally associated with concussion, developed to standardize the assessment of “postconcussive” symptoms.⁶ The NSI is considered the gold standard of postconcussive symptom assessment in a wide range of settings, including a number of research studies and clinical use in the field (e.g., VA’s comprehensive secondary evaluation for TBI, the Department of Defense evaluation of long-term effects of mTBI, and the Defense and Veterans Brain Injury Center currently recommends its continued use).²⁴

This battery was administered at baseline and follow-up visits.

Statistical analysis plan

Hierarchical regression analyses assessed the variance in NSI scores explained by M-mTBI and psychological and behavioral variables after accounting for demographic confounders.

Hierarchical regression allows for measurement of the unique predictive value of groups of variables by building sequential linear regression models in which each block of predictors is added in a separate step and the incremental change in explained variance is assessed. NSI total and subscale scores were included as separate dependent variables. Independent variables, which we will refer to as predictors, consisted of current yes/no diagnoses rather than continuous scales to prevent overinflation of explained variance due to overlap between postconcussive and psychiatric/behavioral symptoms. Because our main focus was on M-mTBI, the main analyses did not include nonmilitary-related mTBI as a predictor. However, we performed a sensitivity analysis including a dichotomous indicator of nonmilitary-related mTBI in the variable block containing M-mTBI in order to assess robustness of primary results to the presence or absence of nonmilitary-related mTBI.

In the first hierarchical analysis, demographic characteristics were entered into the model in block 1, M-mTBI was entered in block 2, and all psychiatric and behavioral predictors were entered in block 3. This analysis assessed whether psychiatric and behavioral conditions were associated with variance in NSI beyond that accounted for by M-mTBI and demographic characteristics. In the second analysis, the order in which the variable blocks were entered was switched (i.e., psychiatric/behavioral variables entered in block 2 and M-mTBI entered in block 3), to assess the role of M-mTBI beyond that of psychiatric and behavioral, and demographic variables, in accounting for variance in NSI scores. Each analysis was performed using predictors collected at participants' baseline visit to predict NSI scores collected at the same visit. The analyses were repeated using predictors collected at baseline to predict NSI scores collected at the follow-up visit to assess changes in predictive validity over time ($n = 186$).

To assess potential overfitting in our regression models and confirm the general applicability of our findings, we used the method of k -fold cross-validation with $k = 10$ folds. This procedure is used to create an estimate of the overall prediction error of the model, which can then be used to compute a cross-validated R^2 value.²⁵ The cross-validated R^2 is computed by subtracting the standardized prediction sum of squares from one. The standardized prediction sum of squares is computed as the total sum of squared residuals from the value predicted by the model divided by the total sum of squares. During each of the 10 iterations, a given data point is used either for model fitting or for model testing, but not for both; therefore, the cross-validated measure of R^2 provides a minimally biased estimate of the true predictive performance of the model when applied to new data outside of the original sample.²⁶ However, we report and discuss the traditional R^2 value because of its ease of interpretation as the percentage of explained variance. Setting k equal to 10 folds is recommended to minimize both the variance and the bias of the estimate to the extent possible.²⁵

Finally, we ran multivariable regression models (baseline and follow-up) to examine the individual contribution of the M-mTBI and psychological and behavioral predictors to NSI individual items, subscales, and total score, adjusting for demographics. As a sensitivity analysis, we ran the same multivariable regression models on the subset of participants who had an M-mTBI, replacing the M-mTBI dichotomous indicator with a continuous measure of the time since M-mTBI. All predictors had a variance inflation factor <2.5 , a conservative threshold, indicating that multicollinearity did not pose a problem in the analyses. Missing data were addressed using listwise deletion such that the final samples used in the analysis were not missing values for any variables. The p values were adjusted using the Benjamini and Hochberg method to control for false discovery rate. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Of the 351 participants in the final baseline sample, 43% had experienced at least one M-mTBI (table 1). Current sleep impairment (78%), pain (68%), and PTSD (59%) were highly prevalent. Participants had an average total NSI score of 21 ($SD = 15$) at baseline, with the affective (mean = 8) and cognitive (mean = 5) clusters being the most frequently reported. The longitudinal subsample ($n = 186$) had similar clinical characteristics as the full sample. NSI total score in this subsample was 19 ($SD = 13$) at baseline and 18 ($SD = 13$) at follow-up with affective and cognitive symptoms again being the most prevalently reported at both baseline and follow-up.

Hierarchical regressions (table 2) showed that psychological and behavioral variables accounted for an additional 42.5% of the variance in baseline NSI scores beyond that explained by M-mTBI, whereas M-mTBI accounted for only an additional 1.5% of the variance beyond that explained by psychological and behavioral characteristics. The sensitivity analysis including nonmilitary-related mTBI showed that this finding remained robust. A corresponding tendency was seen in all NSI subscales, with psychological variables accounting for 12.2% to 49.7% of additional variance in baseline NSI subscale scores, while M-mTBI accounted for 0.3% to 1.8% of additional variance. Examination of individual predictors in the final multivariable regression model (table 3) showed that all predictors, with the exception of substance abuse, significantly predicted total NSI scores at baseline. In the individual item and subscale analyses, PTSD was the most consistent predictor at baseline, significantly predicting all subscale scores as well as the vast majority of individual item scores. Pain predicted all subscale scores, while mood disorders, anxiety disorders, and sleep impairment predicted cognitive and affective

Table 1 Demographic and clinical characteristics of veteran sample

	Baseline sample (n = 351)	Military mTBI (n = 151)	No military mTBI (n = 200)	Follow-up sample (n = 186) ^a
Age, y, mean (SD)	32.1 (8.5)	31.5 (7.6)	32.6 (9.0)	32.7 (8.5)
Males, n (%)	320 (91.2)	141 (93.4)	179 (89.5)	164 (88.2)
Race, ^b n (%)				
Black	27 (7.7)	10 (6.7)	17 (8.5)	13 (7.0)
Hispanic	54 (15.4)	21 (13.9)	33 (16.5)	32 (17.2)
White	264 (75.2)	119 (79)	145 (72.5)	138 (74.2)
Other	9 (2.6)	3 (2.0)	6 (3.0)	4 (2.2)
Education, y, mean (SD)	14.0 (2.0)	13.9 (2.0)	14.2 (2.0)	14.1 (2.0)
Service branch, ^b n (%)				
Army	90 (25.6)	46 (30.5)	44 (22)	43 (23.1)
Navy	13 (3.7)	8 (5.3)	5 (2.5)	6 (3.2)
Air Force	16 (4.6)	5 (3.3)	11 (5.5)	10 (5.4)
Marines	71 (20.2)	37 (24.5)	34 (17)	29 (15.6)
National Guard	133 (38.0)	47 (31.1)	86 (43.2)	77 (41.4)
Reserves	44 (12.6)	16 (10.6)	28 (14.1)	27 (14.5)
Military-related mTBI, n (%)	151 (43.0)	NA	NA	71 (38.2)
Time between worst military TBI and baseline visit, y, mean (SD) ^c	NA	5.7 (4.4)	NA	5.4 (3.9)
PTSD, no (%)	206 (58.7)	108 (71.5)	98 (49.0)	110 (59.1)
Mood disorder, n (%)	84 (23.9)	47 (31.1)	37 (18.5)	40 (21.5)
Anxiety disorder, n (%)	72 (20.5)	34 (22.5)	38 (19.0)	34 (18.3)
Sleep impairment, n (%)	272 (77.5)	133 (88.1)	139 (69.5)	135 (72.6)
Pain, n (%)	239 (68.1)	122 (80.8)	117 (58.5)	127 (68.2)
Substance abuse, n (%)	54 (15.4)	27 (17.9)	27 (13.5)	31 (16.7)
Time between baseline and follow-up, mo, mean (SD)	NA	NA	NA	23.9 (8.7)
NSI, mean (SD)				
Total score	20.6 (15.2)	26.2 (15.4)	16.3 (13.6)	18.8 (13.4)
Vestibular subscore (max = 12)	1.4 (1.8)	1.8 (2.0)	1.0 (1.6)	1.1 (1.5)
Somatic subscore (max = 28)	4.4 (4.2)	5.8 (4.7)	3.3 (3.4)	3.9 (3.5)
Cognitive subscore (max = 16)	4.8 (4.2)	6.3 (4.3)	3.8 (3.8)	4.5 (3.8)
Affective subscore (max = 24)	8.3 (6.2)	10.1 (6.2)	6.9 (5.9)	7.7 (5.6)

Abbreviations: mTBI = mild traumatic brain injury; NA = not applicable; NSI = Neurobehavioral Symptom Inventory; PTSD = posttraumatic stress disorder.

^a Values shown were collected at baseline visit.

^b Percentages may not add up to 100 because some participants fall into multiple categories.

^c Only participants who have had at least one military-related mTBI are included in the sample used to compute these values.

subscale scores. M-mTBI was significantly predictive only of somatic and cognitive subscale scores.

Analyses of follow-up data illustrated a similar pattern of results. Hierarchical regressions showed that while baseline psychological and behavioral variables explained an additional

24.5% of the variance in follow-up NSI scores, the additional variance explained by baseline M-mTBI was negligible. For follow-up NSI subscale scores, psychological and behavioral variables at baseline accounted for 6.9% to 25.2% of additional variance beyond baseline M-mTBI, while baseline M-mTBI did not explain significant amounts of additional variance

Table 2 Hierarchical regression models predicting NSI total and subscale scores from mTBI history and psychological/behavioral conditions

Predictor	Total			Vestibular			Somatic			Affective			Cognitive		
	R^2_{adj}	$R^2/\Delta R^2$	p Value	R^2_{adj}	$R^2/\Delta R^2$	p Value	R^2_{adj}	$R^2/\Delta R^2$	p Value	R^2_{adj}	$R^2/\Delta R^2$	p Value	R^2_{adj}	$R^2/\Delta R^2$	p Value
Baseline sample (n = 351)															
1. Age, sex, education	0.0225	0.0309	0.0154	0.0218	0.0302	0.0163	0.0291	0.0374	0.0054	0.0164	0.0249	0.0355	0.0018	0.0103	0.3062
a. Psychological and behavioral conditions associated with variance in NSI scores beyond TBI history															
2a. Military mTBI	0.1255	0.1355/ 0.1046	0.0002	0.0719	0.0825/ 0.0523	0.0002	0.1098	0.1199/ 0.0825	0.0002	0.0778	0.0884/ 0.0635	0.0002	0.0911	0.1015/ 0.0912	0.0002
3a. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.5479	0.5608/ 0.4253	0.0002	0.1812	0.2046/ 0.1221	0.0002	0.3137	0.3333/ 0.2134	0.0002	0.5736	0.5858/ 0.4974	0.0002	0.3936	0.4109/ 0.3094	0.0002
b. TBI history associated with variance in NSI scores beyond psychological and behavioral conditions															
2b. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.5337	0.5457/ 0.5148	0.0002	0.1711	0.1924/ 0.1622	0.0002	0.2974	0.3155/ 0.2781	0.0002	0.5717	0.5827/ 0.5578	0.0002	0.3766	0.3926/ 0.3823	0.0002
3b. Military mTBI	0.5479	0.5608/ 0.0151	0.0011	0.1812	0.2046/ 0.0122	0.0260	0.3137	0.3333/ 0.0178	0.0039	0.5736	0.5858/ 0.0031	0.1216	0.3936	0.4109/ 0.0183	0.0019
Follow up sample (n = 186)															
1. Age, sex, education	0.0146	0.0305	0.1796	0.0017	0.0179	0.4156	0.0329	0.0486	0.0540	0.0079	0.0240	0.2188	−0.004	0.0123	0.5910
a. Psychological and behavioral conditions associated with variance in NSI scores beyond mTBI history															
2a. Military mTBI	0.0496	0.0701/ 0.0396	0.0153	0.0283	0.0493/ 0.0314	0.0321	0.1028	0.1222/ 0.0736	0.0003	0.0171	0.0383/ 0.0143	0.1022	0.0063	0.0278/ 0.0155	0.1515
3a. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.2755	0.3147/ 0.2446	0.0003	0.0678	0.1182/ 0.0689	0.0682	0.2140	0.2565/ 0.1343	0.0003	0.2492	0.2898/ 0.2515	0.0003	0.2090	0.2517/ 0.2239	0.0003
b. mTBI history associated with variance in NSI scores beyond psychological and behavioral conditions															
2b. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.2785	0.3136/ 0.2831	0.0003	0.0631	0.1087/ 0.0908	0.0191	0.2074	0.2460/ 0.1974	0.0003	0.2532	0.2895/ 0.2656	0.0003	0.2135	0.2517/ 0.2394	0.0003
3b. Military mTBI	0.2755	0.3147/ 0.0011	0.6565	0.0678	0.1182/ 0.0096	0.2236	0.2140	0.2565/ 0.0105	0.1737	0.2492	0.2898/ 0.0002	0.8044	0.2090	0.2517/ 0.0000	0.9528

Abbreviations: mTBI = mild traumatic brain injury; NSI = Neurobehavioral Symptom Inventory; PTSD = posttraumatic stress disorder; TBI = traumatic brain injury. The p values were adjusted using the Benjamini and Hochberg method to control for false discovery rate. In the sensitivity analysis including nonmilitary mTBI in baseline analyses of total NSI score, ΔR^2 with the addition of psychological/behavioral conditions (predictor block 3a) was 0.4256 and ΔR^2 with the addition of military and nonmilitary mTBI (predictor block 3b) was 0.0156.

Table 3 Final multiple regression model predicting Neurobehavioral Symptom Inventory total, subscale, and individual items

	mTBI, β	PTSD, β	Mood disorder, β	Anxiety disorder, β	Sleep, β	Pain, β	Substance use, β	Total R^2
Baseline (n = 351)								
Total score	0.13 ^b	0.33 ^b	0.28 ^b	0.12 ^b	0.15 ^b	0.19 ^b	0.01	0.5608
Vestibular factor	0.12	0.18 ^a	0.07	0.03	0.13	0.15 ^a	−0.03	0.2046
Dizzy	0.04	0.15 ^a	0.12	0.04	0.13	0.14 ^a	−0.08	0.1628
Balance loss	0.13	0.14	−0.03	0.01	0.12	0.13	−0.03	0.1358
Uncoordinated	0.13	0.16 ^a	0.07	0.03	0.08	0.12	0.02	0.1594
Somatic factor	0.14 ^a	0.25 ^b	0.10	0.06	0.08	0.23 ^b	0.02	0.3333
Headache	0.14 ^a	0.20 ^b	0.13	0.00	0.08	0.19 ^b	−0.08	0.2361
Nausea	0.01	0.07	0.12	0.11	0.02	0.07	0.09	0.0934
Vision problems	0.09	0.16 ^a	0.05	0.03	0.03	0.16 ^a	−0.02	0.1256
Light sensitivity	0.12	0.17 ^a	0.06	0.01	0.02	0.18 ^b	0.04	0.1582
Noise sensitivity	0.1	0.22 ^b	0.06	0.09	0.09	0.11	0.03	0.1879
Numbness/tingling	0.08	0.13	0.03	0.05	0.09	0.24 ^b	0.05	0.1971
Taste/smell change	0.09	0.18 ^a	0.02	0.00	0.05	0.06	0.02	0.1057
Cognitive factor	0.14 ^b	0.27 ^b	0.23 ^b	0.14 ^b	0.13 ^a	0.13 ^a	0.03	0.4109
Poor concentration	0.11	0.25 ^b	0.17 ^b	0.16 ^b	0.15 ^a	0.08	0.04	0.3268
Forgetfulness	0.16 ^b	0.28 ^b	0.16 ^b	0.06	0.13 ^a	0.15 ^b	0.03	0.3591
Decision-making difficulty	0.10	0.22 ^b	0.26 ^b	0.16 ^b	0.05	0.11	0.02	0.3076
Slow thinking	0.13 ^a	0.19 ^b	0.23 ^b	0.13 ^a	0.11	0.12	0.04	0.3141
Affective factor	0.06	0.32 ^b	0.38 ^b	0.14 ^b	0.16 ^b	0.12 ^a	0.00	0.5858
Fatigue	0.08	0.23 ^b	0.33 ^b	0.06	0.08	0.18 ^b	0.02	0.3957
Sleep difficulty	0.05	0.24 ^b	0.18 ^b	0.09	0.39 ^b	0.08	−0.01	0.4701
Anxiety	0.07	0.33 ^b	0.30 ^b	0.18 ^b	0.09	0.04	−0.01	0.4239
Depression	−0.01	0.19 ^b	0.50 ^b	0.10 ^a	0.02	0.11 ^a	0.01	0.4550
Irritability	0.02	0.38 ^b	0.22 ^b	0.07	0.07	0.06	−0.01	0.3474
Frustrated/overwhelmed	0.07	0.22 ^b	0.34 ^b	0.19 ^b	0.10	0.10	−0.01	0.4205
Appetite change	0.03	0.21 ^b	0.19 ^b	0.02	0.05	0.16 ^a	0.01	0.2107
Hearing difficulty	0.17 ^b	0.17 ^a	0.09	0.03	0.07	0.17 ^b	−0.05	0.2230
Follow-up (n = 186)								
Total score	0.04	0.25 ^b	0.14	0.14	0.21 ^a	0.04	0.05	0.3147
Vestibular factor	0.11	0.14	−0.08	0.12	0.10	0.08	−0.07	0.1182
Dizzy	0.19	0.03	−0.06	0.10	0.11	0.13	−0.09	0.1198
Balance loss	0.09	0.15	−0.06	0.14	0.09	0.06	−0.09	0.1084
Uncoordinated	0.00	0.16	−0.06	0.06	0.05	0.00	0.00	0.0649
Somatic factor	0.12	0.17	0.05	0.04	0.15	0.19 ^a	0.03	0.2565
Headache	0.20 ^a	0.07	0.04	0.04	0.18	0.13	−0.12	0.2006
Nausea	0.12	−0.09	0.07	0.15	0.07	0.10	0.17	0.127

Continued

Table 3 Final multiple regression model predicting Neurobehavioral Symptom Inventory total, subscale, and individual items (continued)

	mTBI, β	PTSD, β	Mood disorder, β	Anxiety disorder, β	Sleep, β	Pain, β	Substance use, β	Total R^2
Vision problems	-0.06	0.05	0.00	-0.04	0.06	0.24 ^a	0.06	0.1044
Light sensitivity	0.10	0.21	0.10	-0.05	0.04	0.19	-0.07	0.1736
Noise sensitivity	-0.02	0.24 ^a	0.08	0.00	0.06	0.10	0.11	0.1673
Numbness/tingling	0.15	0.05	-0.01	0.07	0.11	0.08	0.09	0.11
Taste/smell change	-0.04	0.16	-0.12	0.08	0.15	-0.03	-0.03	0.0903
Cognitive factor	0.00	0.23 ^a	0.10	0.20 ^a	0.21 ^a	-0.05	0.05	0.2517
Poor concentration	0.02	0.19	0.08	0.15	0.25 ^b	-0.03	0.06	0.2298
Forgetfulness	0.08	0.22 ^a	0.03	0.18	0.16	-0.05	-0.01	0.1836
Decision-making difficulty	-0.02	0.20	0.16	0.23 ^b	0.10	-0.04	0.02	0.2025
Slow thinking	-0.07	0.16	0.08	0.14	0.22 ^a	-0.05	0.12	0.1960
Affective factor	-0.02	0.20 ^a	0.25 ^b	0.15	0.19 ^a	-0.03	0.05	0.2898
Fatigue	-0.05	0.19	0.11	0.09	0.23 ^a	-0.03	-0.05	0.1739
Sleep difficulty	0.00	0.12	0.22 ^a	0.08	0.23 ^a	0.05	0.03	0.2428
Anxiety	-0.07	0.18	0.20 ^a	0.16	0.15	-0.01	0.02	0.2019
Depression	0.00	0.09	0.35 ^b	0.11	0.05	-0.04	0.15	0.2564
Irritability	0.02	0.26 ^a	0.17	0.08	0.08	-0.06	0.02	0.1737
Frustrated/overwhelmed	0.04	0.15	0.16	0.20 ^a	0.14	-0.06	0.08	0.1963
Appetite change	-0.06	0.30 ^b	-0.08	-0.05	0.22 ^a	-0.05	0.09	0.2183
Hearing difficulty	0.04	0.11	0.11	-0.03	-0.01	0.14	-0.01	0.1150

Abbreviations: mTBI = mild traumatic brain injury; PTSD = posttraumatic stress disorder.

The β values are adjusted for age, sex, and education. The p values were adjusted using the Benjamini and Hochberg method to control for false discovery rate.

^a $p < 0.05$.

^b $p < 0.01$.

beyond psychological and behavioral variables at baseline for any subscale. Multivariable regressions revealed that only PTSD and sleep impairment at baseline significantly predicted total NSI scores at follow-up. PTSD and sleep impairment also continued to predict follow-up cognitive and affective subscale scores. Furthermore, baseline mood disorder continued to predict affective subscale scores, and baseline pain continued to predict somatic subscale scores at follow-up. Conversely, baseline M-mTBI was not predictive of any subscale and predicted only headaches at the individual item level.

The pattern of results remained the same when we examined these multivariable regression models (table 4) for the subset of participants who had a history of M-mTBI ($n = 150$) and included the duration of time since the worst M-mTBI (mean = 5.4 years, SD = 3.9 years) as a predictor. There were no significant results in the prospective subset of these analyses.

Although the cross-validated estimates of R^2 were slightly lower than the original estimates (tables 4 and 5), the

psychological and behavioral variables continued to have far greater predictive ability compared to M-mTBI history in the cross-validated models ($R^2 = 0.417$ and $R^2 = 0.010$, respectively). The increase in the estimated R^2 value when each new block was entered into the model was very similar in the cross-validated results as in the original results, with the exception of vestibular symptoms at follow-up, which could no longer be accounted for by either psychological variables or TBI history.

Discussion

In our veteran sample, this study clearly demonstrated that psychological and behavioral conditions, especially PTSD diagnosis and sleep impairment, are substantially predictive of long-term NBS, as reported on the NSI. This is remarkably apparent in comparison to the negligible contribution of M-mTBI, which was a minor contributor to NBS reporting at every level. Certainly, if NBS originated from concussion, one would have expected a strong relationship of these symptoms

Table 4 Multiple regression models for subset of participants with history of military mTBI

	Time since mTBI, β	PTSD, β	Mood disorder, β	Anxiety disorder, β	Sleep, β	Pain, β	Substance use, β	Total R^2
Cross-sectional (n = 150)								
Total score	0.00	0.36 ^b	0.30 ^b	0.13	0.14	0.13	-0.07	0.5039
Vestibular factor	0.06	0.12	0.07	-0.01	0.16	0.11	-0.10	0.1748
Dizzy	0.04	0.08	0.13	0.05	0.11	0.09	-0.17	0.1559
Balance loss	0.03	0.13	-0.03	-0.06	0.15	0.11	-0.08	0.1233
Uncoordinated	0.09	0.10	0.06	-0.02	0.14	0.09	0.00	0.1288
Somatic factor	0.00	0.32 ^b	0.11	0.07	0.04	0.14	-0.09	0.2720
Headache	-0.06	0.29 ^a	0.17	0.05	0.08	0.14	-0.14	0.2568
Nausea	0.17	0.10	0.05	0.22	0.01	-0.03	0.08	0.1586
Vision problems	-0.08	0.09	0.13	0.04	-0.01	0.11	-0.10	0.1002
Light sensitivity	-0.04	0.23	0.06	0.03	-0.08	0.14	0.02	0.1578
Noise sensitivity	-0.06	0.23	0.02	0.12	0.10	0.08	-0.08	0.1720
Numbness/tingling	0.05	0.25	0.04	-0.03	0.06	0.15	-0.08	0.1510
Taste/smell change	0.11	0.27	0.02	-0.03	0.01	-0.01	-0.12	0.1261
Cognitive factor	0.03	0.32 ^b	0.22	0.11	0.12	0.10	-0.02	0.3477
Poor concentration	0.03	0.22	0.16	0.20	0.10	0.06	0.03	0.2599
Forgetfulness	0.00	0.38 ^b	0.11	0.01	0.13	0.14	-0.05	0.3215
Decision-making difficulty	0.03	0.27 ^a	0.26 ^a	0.10	0.05	0.05	-0.05	0.2697
Slow thinking	0.05	0.25	0.24 ^a	0.05	0.13	0.10	-0.01	0.2889
Affective factor	-0.02	0.32 ^b	0.43 ^b	0.17	0.15	0.08	-0.02	0.5858
Fatigue	-0.01	0.22	0.40 ^b	-0.01	0.09	0.21	-0.04	0.3967
Sleep difficulty	-0.01	0.32 ^b	0.20	0.11	0.27 ^b	0.11	-0.05	0.4293
Anxiety	0.00	0.32 ^b	0.34 ^b	0.22 ^a	0.12	0.02	0.01	0.4730
Depression	0.02	0.20	0.53 ^b	0.14	0.06	0.00	-0.01	0.4887
Irritability	-0.07	0.28 ^a	0.25 ^a	0.13	0.09	0.00	0.06	0.3222
Frustrated/overwhelmed	-0.04	0.18	0.36 ^b	0.22 ^a	0.09	0.03	-0.04	0.3592
Appetite change	-0.11	0.21	0.22	0.07	0.07	0.09	-0.06	0.1991
Hearing difficulty	0.00	0.20	0.07	0.03	0.09	0.16	-0.18	0.1732
Longitudinal (n = 70)								
Total score	-0.01	0.28	0.04	0.03	0.19	-0.06	-0.08	0.3271
Vestibular factor	-0.28	0.00	-0.14	0.08	0.10	0.11	-0.15	0.2001
Dizzy	-0.25	-0.09	-0.16	0.10	0.12	0.09	-0.12	0.2034
Balance loss	-0.27	0.10	-0.18	0.06	0.07	0.09	-0.14	0.1681
Uncoordinated	-0.18	0.02	0.01	0.05	0.05	0.11	-0.12	0.1221
Somatic factor	0.04	0.25	-0.08	-0.09	0.06	0.10	-0.06	0.3427
Headache	0.06	0.10	-0.03	0.11	0.13	-0.01	-0.28	0.2170
Nausea	-0.12	-0.06	-0.05	-0.06	0.00	0.22	0.21	0.1803

Continued

Table 4 Multiple regression models for subset of participants with history of military mTBI (*continued*)

	Time since mTBI, β	PTSD, β	Mood disorder, β	Anxiety disorder, β	Sleep, β	Pain, β	Substance use, β	Total R^2
Vision problems	0.10	0.15	-0.12	-0.09	0.05	0.02	0.01	0.2507
Light sensitivity	0.09	0.19	0.07	-0.18	-0.03	0.04	-0.12	0.2052
Noise sensitivity	-0.02	0.28	-0.09	-0.16	0.05	-0.01	0.09	0.3470
Numbness/tingling	-0.07	0.22	-0.07	-0.13	-0.03	0.17	0.04	0.1298
Taste/smell change	0.17	0.12	-0.18	0.22	0.11	0.01	-0.08	0.1542
Cognitive factor	0.03	0.26	0.00	0.07	0.22	-0.17	-0.04	0.2814
Poor concentration	0.02	0.17	0.01	0.10	0.18	-0.06	0.09	0.1678
Forgetfulness	0.01	0.25	-0.01	0.10	0.18	-0.17	-0.12	0.1694
Decision-making difficulty	0.02	0.33	0.09	0.03	0.08	-0.29	-0.21	0.4030
Slow thinking	0.05	0.14	-0.08	-0.01	0.32	-0.06	0.08	0.2745
Affective factor	0.00	0.17	0.20	0.10	0.15	-0.07	-0.05	0.2219
Fatigue	-0.02	0.07	0.02	-0.10	0.15	0.01	-0.21	0.1170
Sleep difficulty	0.03	0.03	0.24	0.10	0.27	0.09	-0.07	0.2268
Anxiety	0.00	0.13	0.16	0.16	0.15	-0.15	-0.06	0.2242
Depression	0.14	0.23	0.31	-0.01	0.06	-0.11	0.06	0.2762
Irritability	-0.08	0.24	0.08	0.06	-0.05	-0.11	-0.05	0.1603
Frustrated/ overwhelmed	-0.10	0.11	0.06	0.19	0.04	-0.07	0.07	0.1545
Appetite change	-0.06	0.30	-0.06	-0.09	0.19	-0.13	0.00	0.2165
Hearing difficulty	0.13	0.19	0.10	-0.06	0.09	-0.12	-0.06	0.1906

Abbreviations: mTBI = mild traumatic brain injury; PTSD = posttraumatic stress disorder.

The β values are adjusted for age, sex, and education. The p values were adjusted using the Benjamini and Hochberg method to control for false discovery rate. There were missing data on time since injury for one participant of the 151 with history of mTBI.

^a $p < 0.05$.

^b $p < 0.01$.

to M-mTBI diagnosis, as opposed to psychiatric and behavioral issues. These results are consistent with previous studies showing that NBS are not uniquely related to mTBI, but are substantially predicted by and/or correlated with psychological and behavioral-related issues.^{11–15} Furthermore, our comprehensive prospective assessment confirmed the baseline findings. Cross-validation supported the validity of the results, and although definitive generalizability of this study to the veteran population cannot be verified through cross-validation, previous work using the TRACTS database has been remarkably consistent with epidemiologic studies.^{27–29} Collectively, these findings have critical implications on how clinicians conceptualize and attempt to manage long-term NBS.

It appears probable that long-term “postconcussive” NBS may not be the direct consequence of the concussion itself, but rather are reflections of co-occurring psychological or behavioral conditions. Concussion may be indirectly associated

with NBS through psychological and behavioral conditions as mediators; however, it is also possible that these symptoms were initiated or exacerbated by the, often traumatic, circumstances surrounding the concussion (e.g., blast exposure, motor vehicle accident), instead of the concussion itself. Speculatively, if long-term postconcussive NBS are not caused by brain damage due to physical injury, then NBS are potentially more treatable than previously believed, if attributed to the correct etiology.

Hence, treatment should be focused on the multiple psychological and behavioral comorbidities in a holistic approach, as opposed to a compartmentalized management of symptoms.^{17,30,31} The specific sources of NBS vary among individuals, but iatrogenesis, misattribution, and expectation seem to have large roles in the development of persistent symptoms. Repeated cognitive or neurologic reexamination from multiple practitioners, without communication between their differentiated specialties (e.g., emergency department,

Table 5 The *k*-fold (*k* = 10) cross-validation of hierarchical regression models

NSI measure	Block entered	<i>R</i> ²	<i>k</i> -Fold CV <i>R</i> ^{2a}
Baseline (n = 351)			
Total	1. Age, sex, education	0.0309	0.00903
	2. mTBI	0.1355	0.11157
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.5608	0.52859
	1. Age, sex, education	0.0309	0.01064
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.5457	0.51547
	3. mTBI	0.5608	0.5254
Vestibular	1. Age, sex, education	0.0302	0.00331
	2. mTBI	0.0825	0.04639
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.2046	0.15038
	1. Age, sex, education	0.0302	0.00573
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.1924	0.14282
	3. mTBI	0.2046	0.14418
Somatic	1. Age, sex, education	0.0374	0.01489
	2. mTBI	0.1199	0.09779
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.3333	0.28169
	1. Age, sex, education	0.0374	0.00426
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.3155	0.26554
	3. mTBI	0.3333	0.28187
Affective	1. Age, sex, education	0.0249	0.00899
	2. mTBI	0.0884	0.05974
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.5858	0.55572
	1. Age, sex, education	0.0249	−0.00131
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.5827	0.5521
	3. mTBI	0.5858	0.55285
Cognitive	1. Age, sex, education	0.0103	−0.01078
	2. mTBI	0.1015	0.07483
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.4109	0.36921
	1. Age, sex, education	0.0103	−0.02054
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.3926	0.35723
	3. mTBI	0.4109	0.37289
Follow-up (n = 186)			
Total	1. Age, sex, education	0.0305	−0.0188

Continued

Table 5 The *k*-fold (*k* = 10) cross-validation of hierarchical regression models (*continued*)

NSI measure	Block entered	<i>R</i> ²	<i>k</i> -Fold CV <i>R</i> ^{2a}
	2. mTBI	0.0701	0.01313
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.3147	0.20295
	1. Age, sex, education	0.0305	−0.0062
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.3136	0.22247
	3. mTBI	0.3147	0.21103
Vestibular	1. Age, sex, education	0.0179	−0.0406
	2. mTBI	0.0493	−0.03242
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.1182	−0.03678
	1. Age, sex, education	0.0179	−0.0286
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.1087	0.00744
	3. mTBI	0.1182	−0.00625
Somatic	1. Age, sex, education	0.0486	−0.01049
	2. mTBI	0.1222	0.06359
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.2565	0.12087
	1. Age, sex, education	0.0486	−0.00544
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.246	0.13778
	3. mTBI	0.2565	0.13611
Affective	1. Age, sex, education	0.024	−0.0492
	2. mTBI	0.0383	−0.04787
	3. PTSD, anxiety, depression, pain, sleep	0.2898	0.17463
	1. Age, sex, education	0.024	−0.01891
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.2895	0.21114
	3. mTBI	0.2898	0.19683
Cognitive	1. Age, sex, education	0.0123	−0.02762
	2. mTBI	0.0278	−0.02369
	3. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.2517	0.1372
	1. Age, sex, education	0.0123	−0.04415
	2. PTSD, anxiety, depression, pain, sleep impairment, substance use	0.2517	0.13914
	3. mTBI	0.2517	0.12823

Abbreviations: CV = cross-validation; mTBI = mild traumatic brain injury; NSI = Neurobehavioral Symptom Inventory; PTSD = posttraumatic stress disorder.
^a A negative value of the cross-validated *R*² occurs when the sum of squared prediction errors of the model exceeds the total sum of squares, indicating a poor-fitting model.

primary care, neurology, physical medicine), may reinforce the misattribution of symptoms to mTBI or increase patients' self-perception of impairment.^{16,17,32} For instance, practitioners associating NBS with possible permanent brain damage in a patient or diagnosing him/her with "post-concussive syndrome" may negatively inform the patient's perception of their injury, the source of their issues, and the possibility of recovery.^{16,32,33}

The substantial role of psychological and behavioral issues supports the targeting of cognitive and behavioral factors for potential treatment of persistent NBS.³³ Psychotherapeutic treatments, such as cognitive behavior therapy, should be considered because they address cognitive biases, misattributions, and comorbid issues, increasing quality of life and decreasing symptom burden in patients affected by long-term NBS.^{31,33–35}

This study had several limitations. As mentioned, direct or indirect causality cannot be determined through these analyses. Because of the nature of NBS, use of self-report data was necessary. As such, there may have been bias introduced by a number of factors, including misattribution and social desirability bias. Objective measures from semi-structured clinical interviews, the Clinician-Administered PTSD Scale and Boston Assessment of TBI–Lifetime, were used to assess PTSD symptomatology and TBI information, respectively, and these too were self-report and subject to shortcomings. In addition, there was overlap between the symptoms examined by the psychiatric and behavioral measures and those assessed on the NSI. To minimize overinflation of explained variance caused by this overlap, current yes/no diagnoses of psychiatric and behavioral issues were used. Our sample had a higher prevalence of M-mTBI and PTSD diagnoses than seen in previous studies,^{2,3} likely because of self-selection bias in enrolling in the TRACTS longitudinal cohort study. Not all participants in our cross-sectional sample had follow-up data, creating the potential for selection bias caused by differential loss to follow-up; however, rates of M-mTBI history and all psychological and behavioral predictors were highly similar across cross-sectional and longitudinal samples. Although our exclusion criteria based on effort and validity measures (MSVT and Validity-10 scale) limited our sample, it reduced the risk of untruthful reporting or exaggeration of symptoms and allowed us to more accurately assess the associations among NBS reporting, M-mTBI, and psychological/behavioral conditions.^{36,37}

This long-term (>1 year) prospective, longitudinal study of NBS effectively assesses and accounts for the common comorbidities associated with mTBI. The methodology used allowed for a detailed and well-controlled assessment of the contributors to NBS reporting, supporting and substantially extending previous findings in the field. Our comprehensive prospective analyses demonstrated the strength of these predictive relationships and the validity of the relationships

over an extended time. Findings were consistent with previous longitudinal research with military and civilian samples showing that, although mTBI was a noteworthy factor during the initial assessment, it was not a meaningful contributor after accounting for psychological/behavioral factors at least 3 months post assessment. In contrast, PTSD and psychological factors considerably influenced NBS reporting at all time points assessed.^{11,12,21,38} PTSD is a logical driving force behind reported NBS because PTSD is associated with cognitive deficits regardless of concussion history and many "postconcussive" symptoms present similarly to the hyperarousal dimension of PTSD symptoms.^{11,13,39}

The results of the cross-validation procedure confirm the validity of the regressions. Findings from this study are likely generalizable to the veteran population from which the sample was drawn. While this was a veteran sample, the data were wholly consistent with the extant civilian literature.^{4,5,9,11,12,14}

It is undeniable that NBS cannot be directly attributed to mTBI alone. Rather, PTSD and sleep disturbance appear to be influential factors in developing NBS in the veteran population. This was true for the sample as a whole, as well as when the analyses were restricted to only those veterans who experienced an M-mTBI. The NSI and other similar measures should be considered general measures of symptom burden and should not be used as a measure of "postconcussive symptoms." These data suggest that clinicians should be cautious about providing patients with the possibly iatrogenic diagnosis of "postconcussive syndrome" and should focus treatment on behavioral symptoms, such as sleep disorder and chronic pain, as well as the potential psychiatric comorbidities that are likely to be prevalent in these patients. Our data also imply that M-mTBI may have an indirect relationship with NBS through PTSD and other psychological factors, and this will be evaluated in future work.

Author contributions

Ryan J. Andrews: study concept and design, acquisition, analysis and interpretation of data, drafting and critical revision of manuscript. Jennifer R. Fonda: study design, analysis and interpretation of data, critical revision of manuscript. Laura K. Levin: study design, analysis and interpretation of data, critical revision of manuscript. Regina E. McGlinchey: study concept and design, acquisition and interpretation of data, critical revision of manuscript, study supervision. William P. Milberg: study concept and design, acquisition and interpretation of data, critical revision of manuscript, study supervision.

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