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Cognitive symptoms in veterans with migraine or traumatic brain injury: A Million Veteran Program study

Matthew S. Herbert PhD[1,2,3] | Victoria C. Merritt PhD[1,2,3] | Niloofar Afari PhD[1,2,3] | Million Veteran Program | Marianna Gasperi PhD[1,2,3,4,5,6]

[1]VA San Diego Healthcare System, San Diego, California, USA

[2]VA Center of Excellence for Stress and Mental Health, San Diego, California, USA

[3]Department of Psychiatry, University of California, La Jolla, California, USA

[4]Research Service, Veterans Affairs Puget Sound Health Care System, Seattle, Washington, USA

[5]Northwest Network Mental Illness, Research, Education, and Clinical Center (MIRECC), Seattle, Washington, USA

[6]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington, USA

Correspondence
Marianna Gasperi, Research Service, Veterans Affairs Puget Sound Health Care System, 1959 NE Pacific Street, Box 356560, Seattle, WA 98195-6560, USA.
Email: mgasperi@uw.edu

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Abstract

Objective: To examine the spectrum and severity of cognitive symptoms in veterans with migraine, traumatic brain injury (TBI), or both; and to evaluate the extent to which psychiatric conditions contribute to the relationship of migraine and TBI with cognitive symptoms.

Background: Migraine contributes significantly to global disability, with veterans facing additional burdens due to high comorbidity of TBI and psychiatric conditions. Understanding the intersection of these conditions is crucial for improving veterans' health-care outcomes.

Methods: This observational study used self-reported data from 338,217 veterans enrolled in the Million Veteran Program (MVP) to assess cognitive symptoms using the Medical Outcomes Study Cognitive Functioning Scale Revised (MOS-Cog-R) and psychiatric conditions in veterans with migraine only, TBI only, both, or neither.

Results: Of the participants, 30,080/338,217 (8.9%) veterans reported migraine, 31,906/338,217 (9.4%) reported TBI, and 7828/338,217 (2.3%) reported both migraine and TBI. Veterans with only migraine or only TBI reported similar levels of cognitive symptoms ($M = 74.19$, standard deviation [SD] = 25.18; $M = 73.87$, SD = 24.98, respectively), which were substantially higher than veterans without these conditions ($M = 62.52$, SD = 27.90). Veterans with both conditions reported the most cognitive symptoms ($M = 83.01$, SD = 22.13) and psychiatric conditions (depression = 5041/7828 [64.4%], anxiety = 3735/7828 [47.7%], post-traumatic stress disorder = 4243/7828 [54.2%]). The association of migraine and TBI with cognitive symptoms persisted beyond the influence of psychiatric conditions ($B = -2.20$, standard error = −0.36, $p < 0.001$).

Conclusion: Veterans with migraine reported cognitive challenges analogous to veterans with TBI, indicating a need for careful attention to cognitive symptoms in veterans with migraine. Further, the associations of migraine and TBI with cognitive symptoms

Abbreviations: cIRB, central institutional review board; MOS-Cog-R, Medical Outcomes Study Cognitive Functioning Scale Revised; MVP, Million Veteran Program; PTSD, post-traumatic stress disorder; TBI, traumatic brain injury; VA, Veterans Affairs.

in veterans were not explained by psychiatric conditions. These findings encourage future research to elucidate the association between self-reported and objective cognitive symptoms and to identify factors, including environmental exposure and genetic influences, contributing to cognitive impairment to optimize the assessment and treatment of veterans with migraine.

Plain Language Summary

We studied how migraine and traumatic brain injuries (TBIs) affect cognitive abilities, like thinking and memory. We found that veterans with either migraine or TBIs had similar cognitive difficulties; however, problems with thinking and memory were worse for veterans with both conditions, regardless of whether they also had a mental health condition like anxiety, depression, or post-traumatic stress disorder. This study highlights the importance of closely monitoring cognitive symptoms in veterans with migraine and brain injuries, and calls for further research to understand this relationship better.

KEYWORDS
cognitive function, migraine headache, Million Veteran Program, post-traumatic stress disorder, traumatic brain injury

INTRODUCTION

Migraine, recognized as the second leading cause of disability globally, is a complex neurological disorder characterized by moderate-to-severe headaches, nausea, and heightened sensitivity to light and sound.[1] Beyond these physical symptoms, patients with migraine often experience cognitive disturbances that are transient yet debilitating.[2] The cognitive symptoms associated with migraine attacks, such as "brain fog,"[3] difficulty focusing, and temporary memory difficulties, can greatly impact the quality of life of those who experience them.[4,5] Although clinical studies show diminished cognitive performance during migraine episodes, there is less consistent evidence for long-term cognitive impairment associated with migraine.[2,6] Nonetheless, recent emphasis has been placed on cognitive impairment as a pressing concern among those who experience migraine.[2]

In military veterans, the relationship between cognitive symptoms and migraine is complicated by the high prevalence of comorbid traumatic brain injury (TBI).[7] TBI is independently linked to cognitive symptoms, making it challenging to isolate the specific cognitive effect of migraine in veterans with a history of TBI.[8,9] Indeed, a common sequela of TBI is post-traumatic headache, which can have a migraine-like presentation.[10] Current data suggest that post-traumatic headaches and migraine are distinct disorders but that a history of migraine may increase the risk of experiencing more severe post-traumatic headache.[11] Furthermore, the high rates of psychiatric comorbidities in veterans—including depression, anxiety, and post-traumatic stress disorder (PTSD), which are commonly associated with both migraine and post-traumatic headache—are likely contributing factors to the cognitive symptoms observed in these conditions.[11,12]

For many veterans, managing the physical and cognitive symptoms of migraine attacks, alongside the consequences of TBI, can be overwhelming. This combination can impact daily functioning, particularly in the context of past military service and exposure to traumatic events.[7,13,14] Recognizing and addressing cognitive symptoms linked to migraine, which can often go undetected, is critical for enhancing diagnosis, treatment, and quality of life.[15–17] Improved understanding of how migraine attacks intersect with cognitive symptoms and TBI in veterans can lead to better outcomes, reducing the overall burden of these conditions.

Using data from the Veterans Affairs (VA) Million Veteran Program (MVP), the aims of this study were to (1) examine the spectrum and severity of self-reported cognitive symptoms in veterans with migraine only, TBI only, migraine and TBI together, and neither condition; and (2) evaluate the extent to which common psychiatric comorbidities contribute to the relationship of migraine and TBI with cognitive symptoms. MVP provides comprehensive data from a nationwide sample of veterans and is thus an ideal data source for carrying out the present research. We hypothesized that veterans with migraine only would report significant cognitive symptoms and that veterans with both migraine and TBI would report the most pronounced cognitive symptoms.

METHODS

Participants

The current observational study data came from MVP, a national research project to determine how genetic traits, health habits, and environmental factors affect veterans' health and illness. The design and recruitment procedures of MVP have been documented in detail previously.[18] Written informed consent was obtained on the day of

the MVP study visit. The MVP protocol was approved by the VA Central Institutional Review Board (cIRB) in 2010, and study enrollment began in 2011. The VA cIRB (under project "MVP033") and the Research and Development Committee at VA San Diego Healthcare System and at VA Puget Sound Health Care System approved the current project. Veterans were included in the present study if they had complete data (outcome variables of interest) on the Baseline Survey, Lifestyle Survey, and sociodemographic information in data release v21. Of the 819,417 veterans enrolled in MVP through September 30, 2020, 481,200 participants were excluded due to incomplete survey data, resulting in an analytic sample of 338,217 (41.3%).

Measures

All data were derived from the MVP Baseline Survey and MVP Lifestyle Survey. Veterans were asked to complete the MVP Baseline Survey at the time of enrollment, and the Lifestyle Survey was given after the study enrollment visit.[18] Briefly, the MVP Baseline Survey was developed to collect demographics, family pedigree, health status, lifestyle habits, military experience, medical history, family history of specific illnesses, and physical features. The MVP Lifestyle Survey contains questions from validated instruments in domains selected to provide information on sleep and exercise habits, environmental exposures, dietary habits, and well-being.[18]

Sociodemographic characteristics

Age at MVP enrollment, gender, race, ethnicity, marital status, the highest level of education completed, and household income were obtained from the MVP Baseline Survey. Because veteran enrollment is ongoing, the age and symptoms reported by veterans reflect their individual conditions at the time of survey completion.

Migraine, TBI, and psychiatric diagnoses

As part of the MVP Baseline Survey, participants were provided a list of health conditions from various health domains, including psychiatric and neurological conditions. Participants were instructed, "Please tell us if you have been diagnosed with the following conditions," followed by the list of conditions. All self-reported health conditions evaluated on the MVP Baseline Survey were classified as binary variables, with participants indicating a given condition's presence or absence (i.e., yes vs. no) *across their lifetime*. The diagnoses of migraine, TBI, concussion or loss of consciousness, depression, anxiety, and PTSD were derived from these data. "TBI" and "concussion or loss of consciousness" were collapsed into a single variable, indicating the presence of *either* condition or the lack of both.

Cognitive symptoms

Cognitive symptoms over the previous month were assessed using the Medical Outcomes Study Cognitive Functioning Scale Revised (MOS-Cog-R)[19] from the MVP Lifestyle Survey. The MOS-Cog-R is a self-report questionnaire assessing the frequency of six cognitive domains, including reasoning, concentration, confusion, forgetfulness, attention, and reaction speed. Individuals are asked, "How much of the time during the past month…" followed by a description of the symptom. Participants indicated on a scale from 1 ("all of the time") to 6 ("none of the time") how often they had trouble with each task. The MOS-Cog-R total score (range = 6–36) yielded a single score across symptoms and was transformed to the MOS-Cog-R 100 (MOStotal-6/30*100; range 0–100), with higher scores indicating better cognitive function. Individual domain scores were also evaluated (range = 1–6). The psychometric properties of the MOS-Cog-R have been previously evaluated in a representative sample of > 2000 US adults, which demonstrated good reliability and discriminant validity.[19]

Statistical analysis

All analyses were conducted in R Studio.[20] The sample size was based on available data. Descriptive statistics characterized the sample across sociodemographic and health variables using mean and standard deviation or frequency and percentage, as indicated. Pearson's chi-squared test and Kruskal–Wallis rank sum test were used to evaluate differences between individuals with and without migraine and TBI history. Individuals were categorized into four groups: (1) individuals who had a history of both migraine and TBI ("Both"), (2) individuals who had only TBI history and no migraine history ("TBI Only"), (3) individuals with a history of migraine and no history of TBI ("Migraine Only"), and (4) individuals with neither a history of migraine nor TBI ("Neither").

To address aim 1, the average MOS-Cog-R-100 and domain scores were compared across the four groups using the Kruskal–Wallis test for omnibus differences, Dunn's test,[21] and Cliff's delta[22] for effect size calculations of differences between groups. Cliff's delta test effect size (δ) interpretation used small (0.11), medium (0.28), and large (0.43) levels.[23] To address aim 2, linear regression (ordinary least squares, variables entered using standard forced entry), adjusted for depression, anxiety, PTSD, age, and sex, was used to evaluate the contribution of migraine, TBI, and psychiatric conditions to the total MOS-Cog-R-100 score (Model 1), as well as the interaction between migraine and TBI (Model 2). Data were analyzed from January 2023 to April 2023. No statistical power calculation was conducted prior to the study due to the large sample size based on available data. We evaluated key linear regression assumptions. Linearity was assessed using scatter plots, and the independence of residuals was checked with the Durbin–Watson statistic. We visually inspected homoscedasticity using residual versus fitted value plots and applied robust standard errors to mitigate any detected heteroscedasticity.

Multicollinearity was evaluated through variance inflation factors for each predictor, and influential outliers were identified using Cook's distance. Given our large sample size, the central limit theorem supported the assumption of normality. We utilized a two-tailed testing approach to determine the significance of the regression coefficients. Statistical significance was set to $p < 0.001$.

RESULTS

In this observational study of 338,217 veterans, 30,080 (8.9%) reported a history of migraine diagnosis, 31,906 (9.4%) reported TBI, and 7828 (2.3%) reported both migraine and TBI, at rates consistent with previous reports.[24,25] A significant association was observed between the history of migraine and a report of TBI, $\chi^2(1, N = 10{,}634)$, $p < 0.001$. For analyses, individuals were assigned to migraine only ($n = 22{,}252$), TBI only ($n = 24{,}078$), both TBI and migraine ($n = 7828$), and neither ($n = 284{,}059$) groups. Table 1 presents the sociodemographic characteristics of the overall sample and by the different migraine/TBI groups. The overall sample was predominantly men (92.1%) identifying as White (85.8%), with a mean age of 67.2 (11.8) years. A small minority of the sample identified as Hispanic/LatinX (6.3%); more than half had some college education or higher (77.1%), annual income below $65,000 (68.6%), and self-reported their marital status as "married/civil union/cohabitating" (63.2%). The group with both migraine and TBI was younger ($M = 65.3$ years), mostly men (81.2%), and largely White (82.9%). Veterans with both migraine and TBI had the highest levels of education (85.0%, some college or higher); the lowest rate of married/civil union/cohabitating (59.7%); and reported the highest levels of depression (64.4%), anxiety (47.7%), and PTSD (54.2%; Table 1).

Figure 1 shows the proportion of veterans in the four groups who reported experiencing cognitive symptoms across the six domains of the MOS-Cog-R. Individuals with a history of both migraine and TBI reported the highest prevalence of cognitive problems in all domains, with rates ranging from 76.1% for confusion to 90.5% for forgetfulness. In contrast, individuals who reported having neither migraine nor TBI had the lowest prevalence of cognitive problems, with rates ranging from 32.0% for confusion to 63.7% for forgetfulness. Table 2 shows the average MOS-Cog-R scores across the four

TABLE 1 Sociodemographic characteristics for overall sample and by self-reported migraine and TBI group.

Characteristic	Total sample[a]	Neither	Migraine only	TBI only	Both	p[b]
Total participants, no (%)	338,217 (100%)	284,059 (84.0%)	22,252 (6.6%)	24,078 (7.1%)	7828 (2.3%)	
Age, mean (SD)	67.2 (11.8)	68.1 (11.4)	60.3 (12.5)	65.8 (11.6)	58.5 (12.5)	<0.001
Gender						<0.001
Men	311,448 (92.1%)	266,375 (93.8%)	16,244 (73.0%)	22,470 (93.3%)	6359 (81.2%)	
Women	26,769 (7.9%)	17,684 (6.2%)	6008 (27.0%)	1608 (6.7%)	1469 (18.8%)	
Race (% migraine prevalence)						<0.001
African American (11.5%)	34,666 (10.2%)	29,287 (10.3%)	3219 (14.5%)	1389 (5.8%)	771 (9.8%)	
White (8.3%)	290,121 (85.8%)	244,200 (86.0%)	17,791 (80.0%)	21,639 (89.9%)	6491 (82.9%)	
Another race (13.4%)[c]	13,430 (4.0%)	10,572 (3.7%)	1242 (5.6%)	1050 (4.4%)	566 (7.2%)	
Hispanic or LatinX (11.8%)	21,408 (6.3%)	17,440 (6.1%)	1808 (8.1%)	1445 (6.0%)	715 (9.1%)	<0.001
Highest degree						<0.001
<High school	10,262 (3.1%)	9246 (3.3%)	437 (2.0%)	444 (1.9%)	135 (1.7%)	
High school diploma/GED	69,672 (20.9%)	61,526 (22.0%)	3260 (14.8%)	3873 (16.3%)	1013 (13.1%)	
Some college–bachelor's	205,415 (61.6%)	169,848 (60.6%)	14,685 (66.9%)	15,483 (65.2%)	5399 (69.8%)	
Master's or higher	48,331 (14.5%)	39,621 (14.1%)	3582 (16.3%)	3942 (16.6%)	1186 (15.3%)	
Married/civil union/cohabitating	213,680 (63.2%)	180,184 (63.4%)	13,607 (61.1%)	15,216 (63.2%)	4673 (59.7%)	<0.001
Annual household income						<0.001
≤$60,000	207,177 (68.6%)	175,233 (69.1%)	12,864 (64.4%)	14,264 (66.2%)	4816 (68.5%)	
$60,000–$99,999	60,758 (20.1%)	50,316 (19.8%)	4424 (22.2%)	4603 (21.4%)	1415 (20.1%)	
≥$100,000	34,170 (11.3%)	28,032 (11.1%)	2673 (13.4%)	2664 (12.4%)	801 (11.4%)	
Depression	84,121 (24.9%)	58,529 (20.6%)	10,488 (47.1%)	10,063 (41.8%)	5041 (64.4%)	<0.001
Anxiety	49,906 (14.8%)	32,926 (11.6%)	6879 (30.9%)	6366 (26.4%)	3735 (47.7%)	<0.001
PTSD	56,461 (16.7%)	37,681 (13.3%)	6727 (30.2%)	7810 (32.4%)	4243 (54.2%)	<0.001

Abbreviations: PTSD, post-traumatic stress disorder; SD, standard deviation; TBI, traumatic brain injury.

[a]Mean (SD) or *N* (%).

[b]*T*-test for means or two sample tests of proportions.

[c]Includes American Indian or Alaska Native, Asian, Native Hawaiian or Pacific Islander, and all other races not listed.

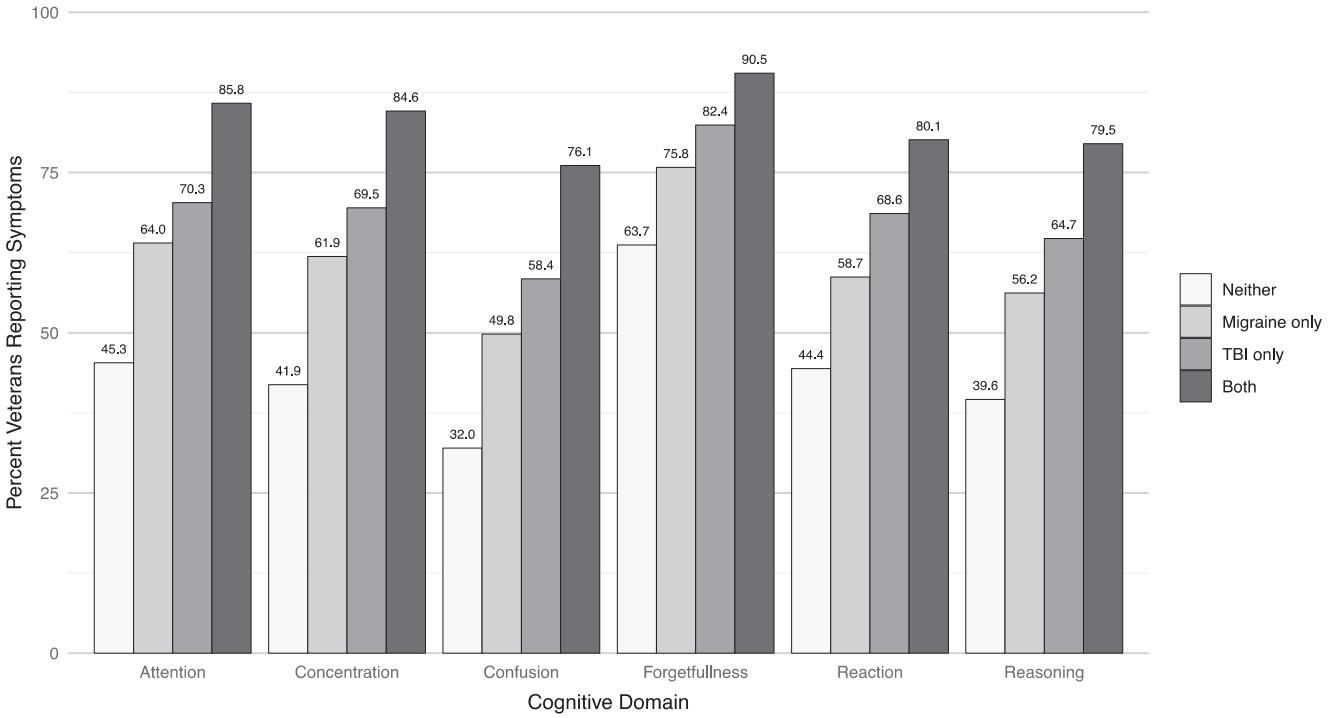

FIGURE 1 Cognitive symptom endorsement in veterans reporting history of migraine, TBI, or both migraine and TBI. This graph illustrates the percentage of veterans reporting symptoms in each of six cognitive MOS-Cog-R domains: attention, concentration, confusion, forgetfulness, reaction, and reasoning. The participants are categorized into four groups based on their self-reported history: veterans with neither migraine nor TBI, with migraine only, with TBI only, and with both migraine and TBI. MOS-Cog-R, Medical Outcomes Study Cognitive Functioning Scale Revised; TBI, traumatic brain injury.

TABLE 2 Average MOS-Cog-R scale scores in the past month across self-reported migraine and TBI groups in 338,217 veterans.

		Migraine and TBI status				
	Total sample[a]	Neither	Migraine only	TBI only	Both	
	338,217 (100%)	284,059 (84.0%)	22,252 (6.6%)	24,078 (7.1%)	7828 (2.3%)	*Omnibus* p_1
Reasoning	5.2 (1.3)	5.2 (1.3)	4.8 (1.4)	4.8 (1.4)	4.3 (1.5)	<0.001
Concentration	5.1 (1.3)	5.2 (1.3)	4.7 (1.4)	4.7 (1.4)	4.1 (1.6)	<0.001
Confusion	5.3 (1.3)	5.4 (1.2)	4.9 (1.4)	4.9 (1.4)	4.4 (1.6)	<0.001
Forgetfulness	4.7 (1.3)	4.8 (1.3)	4.3 (1.5)	4.3 (1.4)	3.7 (1.6)	<0.001
Attention	5.0 (1.3)	5.1 (1.3)	4.6 (1.5)	4.6 (1.5)	4.0 (1.6)	<0.001
Reaction	5.1 (1.3)	5.2 (1.2)	4.8 (1.4)	4.8 (1.4)	4.2 (1.6)	<0.001
MOS-Cog-R-100	81.3 (23.1)	83.0 (22.1)	74.2 (25.2)	73.9 (25.0)	62.5 (27.9)	<0.001

Note: Mean (SD) from raw scores, with higher scores reflecting better cognitive functioning.

Abbreviations: MOS-Cog-R, Medical Outcomes Study Cognitive Functioning Scale Revised; SD, standard deviation; TBI, traumatic brain injury.

[a]Kruskal–Wallis test.

groups, and Table 3 provides the effect sizes for the pairwise comparisons on the MOS-Cog-R scores. All omnibus group differences were significant at $p < 0.001$, with more severe symptom scores in those with both migraine and TBI, followed by veterans in groups with one condition only, and the least severe symptom scores in the group with neither migraine nor TBI. Pairwise comparisons showed differences across most groups. When comparing veterans with both conditions (migraine and TBI) to those with neither condition, the effect sizes were medium to large. In comparisons between groups with only one condition (either TBI or migraine) to groups with both or neither condition, the effect sizes were smaller, ranging from small to medium, showing fewer cognitive symptoms when only one condition was present. Direct comparisons between the "TBI only" and "migraine only" groups revealed no significant differences in attention, concentration, confusion, and reasoning. Where significant differences were observed, the effect sizes were minimal, showing

TABLE 3 Effect sizes and 95% CI for pairwise comparisons by migraine and TBI groups.

	Both versus TBI	Both versus migraine	Both versus neither	TBI versus migraine	TBI versus neither	Migraine versus neither
n	31,906	30,080	291,887	46,330	308,137	306,311
Reasoning	−0.19 (−0.21 to −0.18)*	−0.20 (−0.19 to −0.21)*	−0.36 (−0.37 to −0.35)*	−0.01 (−0.02 to 0.00)	−0.18 (−0.19 to −0.17)*	−0.17 (−0.16 to −0.18)*
Concentration	−0.23 (−0.25 to −0.21)*	−0.21 (−0.24 to −0.22)*	−0.42 (−0.43 to −0.41)*	0.00 (−0.00 to 0.02)	−0.21 (−0.22 to −0.20)*	−0.21 (−0.22 to −0.20)*
Confusion	−0.22 (−0.23 to −0.20)*	−0.22 (−0.23 to −0.21)*	−0.39 (−0.40 to −0.38)*	−0.00 (−0.01 to 0.01)	−0.18 (−0.19 to −0.17)*	−0.18 (−0.19 to −0.17)*
Forgetfulness	−0.23 (−0.24 to −0.21)*	−0.23 (−0.24 to −0.22)*	−0.41 (−0.42 to −0.40)*	−0.03 (−0.04 to −0.02)*	−0.23 (−0.24 to −0.22)*	−0.19 (−0.20 to −0.18)*
Attention	−0.23 (−0.25 to −0.22)*	−0.21 (−0.24 to −0.23)*	−0.43 (−0.42 to −0.44)*	0.00 (−0.01 to 0.02)	−0.20 (−0.22 to−0.21)*	-0.21 (−0.22 to −0.20)*
Reaction	−0.19 (−0.20 to −0.18)*	−0.20 (−0.22 to −0.21)*	−0.36 (−0.37 to −0.35)*	−0.03 (−0.04 to −0.02)*	−0.19 (−0.20 to −0.18)*	−0.16 (−0.15 to −0.17)*
MOS-Cog-R-100	−0.25 (−0.24 to −0.26)*	−0.26 (−0.25 to −0.27)*	−0.47 (−0.46 to −0.48)*	−0.02 (−0.03 to −0.02)*	−0.26 (−0.25 to −0.27)*	−0.23 (−0.22 to −0.24)*

Note: Cliff's delta used for effect size calculation; small ≥ 0.11, medium ≥ 0.28, large ≥ 0.43.

Abbreviations: CI, confidence interval; MOS-Cog-R, Medical Outcomes Study Cognitive Functioning Scale Revised; TBI, traumatic brain injury.

*$p < 0.001$.

TABLE 4 Linear regression models with and without interaction, predicting MOS-Cog-R-100 score.

	MOS-Cog-R-100 score			
	Main effects		Interaction	
Model	*B* (SE)	std. Beta (CI)	*B* (SE)	std. Beta (CI)
Constant	84.55* (0.25)	0.35 (0.34 to 0.37)	84.48* (0.25)	0.35 (0.34 to 0.36)
Migraine	−3.56* (−0.15)	−0.15 (−0.17 to −0.14)	−3.06* (−0.16)	−0.13 (−0.15 to −0.12)
TBI	−4.48* (−0.14)	−0.19 (−0.21 to −0.18)	−4.02* (−0.15)	−0.17 (−0.19 to −0.16)
Anxiety	−7.18* (−0.14)	−0.31 (−0.32 to −0.30)	−7.17* (−0.14)	−0.31 (−0.32 to −0.30)
Depression	−10.50* (−0.11)	−0.45 (−0.46 to −0.45)	−10.51* (−0.11)	−0.46 (−0.46 to −0.45)
PTSD	−8.90* (−0.13)	−0.39 (−0.40 to −0.37)	−8.89* (−0.13)	−0.38 (−0.40 to −0.37)
Gender	−2.46* (−0.14)	−0.11 (−0.12 to −0.09)	−2.42* (−0.14)	−0.10 (−0.12 to −0.09)
Age	0.07* (0.00)	0.04 (0.03 to 0.04)	0.07 * (0.00)	0.04 (0.03 to 0.04)
Interaction			−2.20* (−0.36)	−0.10 (−0.13 to −0.07)

Note: Reference category for migraine, TBI, anxiety, depression, and PTSD was lack of endorsement or "no"; reference category for sex was female; main effects model: $R^2 = 0.16$, $F(7, 331{,}991) = 8745.64$, $p < 0.001$; interaction model: $R^2 = 0.16$, $F(8, 331{,}990) = 7659.68$, $p < 0.001$.

Abbreviations: CI, confidence interval; MOS-Cog-R, Medical Outcomes Study Cognitive Functioning Scale Revised; PTSD, post-traumatic stress disorder; SE, standard error; TBI, traumatic brain injury.

*$p < 0.001$.

negligible differences between veterans in these two groups across reported cognitive symptoms of forgetfulness and reaction time.

Table 4 presents the results from linear regression analyses designed to predict cognitive symptoms, as measured by the MOS-Cog-R-100 score in veterans. Two models were evaluated: the main effects model (Model 1) and the interaction model (Model 2), which included the interaction of migraine and TBI. Both models included anxiety, depression, PTSD, gender, and age as additional predictors. In Model 1, both migraine ($\beta = -0.15$) and TBI ($\beta = -0.19$) were significant independent predictors of increased cognitive symptoms even with controlling for psychiatric conditions, suggesting a moderate negative association with cognitive scores. History of lifetime psychiatric conditions was also a significant independent predictor, with depression exhibiting the largest negative association ($\beta = -0.45$), followed by PTSD and anxiety. In Model 2, the interaction term between migraine and TBI was significant ($\beta = -0.10$), indicating that the co-occurrence of migraine and TBI was additionally negatively related to cognitive symptoms beyond the individual

associations of migraine and TBI alone, highlighting the interplay among migraine, TBI, and cognitive outcomes in veterans.

DISCUSSION

This study evaluated veterans' self-reported cognitive symptoms in relation to history of migraine and TBI, aiming to determine their overlap and to explore how these conditions, both individually and combined, are associated with self-reported cognitive symptoms in a large and nationally representative sample of veterans. Within the full sample ($N = 338{,}217$), approximately 9% of veterans reported having been diagnosed with migraine, 9% reported having been diagnosed with TBI, and 2% reported having been diagnosed with both migraine and TBI. Results showed that cognitive symptoms were highest in veterans with both migraine and TBI. Additionally, veterans with migraine only and TBI only self-reported more severe cognitive symptoms than veterans without these conditions, but the groups had comparable symptom profiles to one other. Furthermore, migraine and TBI history were independently associated with cognitive symptoms, and these relationships were not fully explained by psychiatric comorbidities. The interaction of migraine and TBI was an additional significant predictor of cognitive symptoms, highlighting an important intersection between these two conditions. In sum, this study demonstrates the need to consider both TBI and cognitive symptoms in veterans with migraine and underscores the compounded cognitive challenges faced by those with coexisting migraine and TBI.

The prevalence of veterans self-reporting lifetime migraine diagnosis in the current study was higher than the 5.3% prevalence reported by a recent study examining migraine diagnosis among 11 years of electronic health record data in 10.8 million veterans receiving care in the Veterans Health Administration.[26] The prevalence of TBI in veterans varies considerably across service eras,[27] with the rates among post-9/11 veterans estimated to be as high as 17.5% for mild TBI and 3.0% for moderate to severe TBI.[28] The current study, evaluating veterans of all service eras, reported a lower TBI prevalence, which may reflect the relatively older average age of MVP-enrolled veterans.[29] Efforts to estimate the co-occurrence of migraine and TBI have been limited, with most studies examining headaches in the context of TBI and vice versa rather than establishing epidemiological comorbidity.[30,31] Given the large and nationally representative sample of MVP, our findings reflect reasonable estimates of lifetime self-reported prevalence of migraine, TBI, and their comorbidity. Our group's previous research corroborated the agreement between the self-report migraine data used here and electronic health record data.[24] Nonetheless, differences in prevalence rates from those reported previously highlight potential differences in diagnostic criteria, reporting methods (e.g., self-reported, physician diagnosed, cut-off on a clinical assessment), population characteristics, and context (e.g., specialty clinic versus general public). Additional research is needed to understand better the prevalence estimates of these conditions across different methods and groups and to determine if cognitive symptoms differ based on self-reported versus physician-diagnosed migraine or TBI.

Our results showing greater cognitive symptoms in veterans with migraine only versus those without migraine align with existing literature on self-reported cognitive symptoms.[6] In contrast, objective cognitive functioning (i.e., cognitive functioning assessed via neuropsychological testing) in the context of migraine has revealed less consistent findings. A 2012 review found deficits in memory, attention, and information processing speed among individuals with migraine.[5] Notably, these associations were driven by studies conducted in neurological care facilities which may not generalize to more general community samples. A 2022 review revealed differences between migraine and non-migraine groups in general cognitive function and language but no differences in visuospatial functioning, attention, executive functioning, or memory.[2] Given the transient nature of migraine-related cognitive symptoms,[32] individuals with migraine may achieve normal scores on objective neuropsychological evaluations while still experiencing subjectively significant cognitive challenges. Our findings highlight the need for additional research to better understand both subjective and objective cognition in those with migraine.

Our study makes a unique contribution to the migraine and TBI literature by contrasting subjective cognitive symptoms between veterans with migraine only and TBI only and provides a more nuanced understanding of self-reported cognitive symptoms in veterans with these conditions. To our knowledge, this is one of a handful of studies that have specifically examined differences in cognitive symptoms between veterans with migraine and TBI history.[15,31] Although we detected significant differences in forgetfulness, reaction speed, and overall cognitive symptoms between veterans with migraine only versus TBI only, the effect sizes were very small, suggesting similar cognitive dysfunction across these two distinct groups. These findings extend the scant previous literature on cognitive symptoms in migraine and TBI, which had significant shortcomings, such as the use of primarily clinical populations, small sample sizes, and groups with only one disorder.[2,33] For example, prior work demonstrated significantly greater cognitive impairment in persons with mild TBI ($n = 20$) versus migraine ($n = 20$); however, in addition to the small sample size, having comorbid migraine was not an exclusion criterion in the TBI group, which may have impacted findings.[34] In contrast, our findings indicate that in a large and representative sample of veterans, those with a history of migraine reported a similarly severe level of subjective cognitive symptoms to those with TBI. The finding that veterans exclusively with migraine reported cognitive symptoms of a magnitude comparable to those with only TBI is novel and important. This contributes to a growing understanding of the consequences of migraine and TBI and underscores the need for a nuanced understanding of cognitive symptoms in these separate but equally debilitating conditions.

There was a significant association between migraine and TBI in veterans, and experiencing both conditions was associated with greater cognitive symptoms relative to either condition alone. Self-reported PTSD, anxiety, and depression were associated with being in migraine only, TBI only, and both groups, with the highest

psychiatric symptomology reported in veterans with both migraine and TBI. The independent association between migraine and TBI with cognitive symptoms persisted even when controlling for PTSD, anxiety, and depression. Further, the interaction of migraine and TBI was also associated with worse cognitive symptoms. Together, these results suggest the associations of migraine and TBI with cognitive symptoms are not merely additive, as individuals with both migraine and TBI showed worse cognitive symptoms than would be predicted based on the separate associations of each condition alone and were not explained by common comorbid psychiatric conditions. It is possible other variables not measured in this study, including non-headache chronic pain conditions and insomnia, which are common in both migraine and TBI, could account for the cognitive symptoms in this comorbid group.[35–38]

While this study provides valuable insights, several limitations should be acknowledged. Using data from a single source (the MVP) may limit generalizability due to potential biases of the sample, including demographic and clinical characteristics. Additionally, the observational framework constrained our ability to ascertain causative relationships. Our findings encourage future longitudinal studies to elucidate causative relationships among migraine, TBI, and cognitive symptoms among veterans. The self-report data used in this study are potentially susceptible to recall bias and inaccuracies. For instance, veterans who self-reported migraine may actually have post-traumatic headaches with migraine features; additional research with more formal diagnostics is warranted to ensure the separation of these distinct conditions with overlapping symptomology. However, it is also worth noting that self-report data may capture cognitive symptoms that might go unnoticed in neuropsychological assessments conducted outside of active migraine episodes or in individuals not typically referred for such evaluations. Nonetheless, these findings should be replicated in veterans using gold-standard strategies for determining migraine, TBI, and psychiatric diagnoses. Due to data availability, our sample included less than half of MVP enrollees. Sociodemographic characteristics (e.g., age, gender, education, income) and MOS-Cog-R scores, however, are consistent with the overall MVP sample, as detailed in a recent study,[29] suggesting that our sample is representative of the larger study. Last, the study did not account for all factors that might influence cognitive function, such as comorbid physical health conditions, lifestyle factors, and genetic predisposition. Our findings pave the way for further research into the multiple factors affecting cognitive function in veterans. Understanding the biological markers, genetics, and lifestyle factors contributing to individual conditions and their overlap promises to provide valuable insights, potentially contributing to improved approaches to diagnosis and treatment.[39]

CONCLUSION

The findings from this investigation provide crucial insights into the complex interplay of migraine, TBI, and subjective cognitive symptoms among veterans. The novel findings that migraine alone is associated with cognitive symptoms as frequent as those experienced by veterans with TBI and the interaction effects of migraine and TBI emphasize the importance of comprehensive assessments, including self-report and tailored interventions in the veteran and general population. Future efforts should aim to evaluate causal relationships through longitudinal research; explore the role of other potential contributing factors, including chronic pain and sleep; and examine the genetic and lifestyle factors influencing these conditions.

AUTHOR CONTRIBUTIONS

Matthew S. Herbert: Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Victoria C. Merritt:** Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Niloofar Afari:** Conceptualization; supervision; writing – original draft; writing – review and editing. **Marianna Gasperi:** Conceptualization; data curation; formal analysis; funding acquisition; methodology; project administration; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Matthew S. Herbert, **Victoria C. Merritt**, **Niloofar Afari**, **Million Veteran Program**, and **Marianna Gasperi** declare no conflicts of interest.

REFERENCES

1. Steiner T, Stovner L, Jensen R, Uluduz D, Katsarava Z. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD 2019. *J Headache Pain*. 2020;21:137.
2. Gu L, Wang Y, Shu H. Association between migraine and cognitive impairment. *J Headache Pain*. 2022;23(1):1-18.
3. McWhirter L, Smyth H, Hoeritzauer I, Couturier A, Stone J, Carson AJ. What is brain fog? *J Neurol Neurosurg Psychiatry*. 2023;94(4):321-325.
4. Vuralli D, Ayata C, Bolay H. Cognitive dysfunction and migraine. *J Headache Pain*. 2018;19(1):109. doi:10.1186/s10194-018-0933-4
5. Araújo CM, Barbosa IG, Lemos SMA, Domingues RB, Teixeira AL. Cognitive impairment in migraine: a systematic review. *Dement Neuropsychol*. 2012;6:74-79.

6. Gil-Gouveia R, Oliveira AG, Martins IP. Subjective cognitive symptoms during a migraine attack: a prospective study of a clinic-based sample. *Pain Physician*. 2016;19(1):E137-E150.
7. McGeary DD, Resick PA, Penzien DB, et al. Cognitive behavioral therapy for veterans with comorbid posttraumatic headache and posttraumatic stress disorder symptoms: a randomized clinical trial. *JAMA Neurol*. 2022;79(8):746-757.
8. McInnes K, Friesen CL, MacKenzie DE, Westwood DA, Boe SG. Mild traumatic brain injury (mTBI) and chronic cognitive impairment: a scoping review. *PLoS ONE*. 2017;12(4):e0174847.
9. Tsai Y-C, Liu C-J, Huang H-C, et al. A meta-analysis of dynamic prevalence of cognitive deficits in the acute, subacute, and chronic phases after traumatic brain injury. *J Neurosci Nurs*. 2021;53(2):63-68.
10. Lew HL, Lin P-H, Fuh J-L, Wang S-J, Clark DJ, Walker WC. Characteristics and treatment of headache after traumatic brain injury: a focused review. *Am J Phys Med Rehabil*. 2006;85(7):619-627.
11. Lambru G, Benemei S, Andreou AP, et al. Position paper on post-traumatic headache: the relationship between head trauma, stress disorder, and migraine. *Pain Ther*. 2021;10:1-13.
12. Afari N, Harder LH, Madra NJ, et al. PTSD, combat injury, and headache in veterans returning from Iraq/Afghanistan. *Headache*. 2009;49(9):1267-1276.
13. Balba NM, Elliott JE, Weymann KB, et al. Increased sleep disturbances and pain in veterans with comorbid traumatic brain injury and posttraumatic stress disorder. *J Clin Sleep Med*. 2018;14(11):1865-1878.
14. Shahidi B, Bursch RW, Carmel JS, et al. Greater severity and functional impact of post-traumatic headache in veterans with comorbid neck pain following traumatic brain injury. *Mil Med*. 2021;186(11–12):1207-1214.
15. Begasse de Dhaem O, Robbins MS. Cognitive impairment in primary and secondary headache disorders. *Curr Pain Headache Rep*. 2022;26(5):391-404.
16. Devianne J, Mawet J, Hugon J, Roos C, Paquet C. Is there a link between headache and cognitive disorders? A systematic review. *Rev Neurol (Paris)*. 2022;178(4):285-290.
17. Steiner TJ, Terwindt GM, Katsarava Z, et al. Migraine-attributed burden, impact and disability, and migraine-impacted quality of life: expert consensus on definitions from a Delphi process. *Cephalalgia*. 2022;42(13):1387-1396.
18. Gaziano JM, Concato J, Brophy M, et al. Million Veteran Program: a mega-biobank to study genetic influences on health and disease. *J Clin Epidemiol*. 2016;70:214-223. doi:10.1016/j.jclinepi.2015.09.016
19. Yarlas A, White M, Bjorner J. The development and validation of a revised version of the medical outcomes study cognitive functioning scale (Mos-cog-R). *Value Health*. 2013;16(3):A33-A34.
20. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2018.
21. Dunn OJ. Multiple comparisons using rank sums. *Dent Tech*. 1964;6(3):241-252.
22. Cliff N. Dominance statistics: ordinal analyses to answer ordinal questions. *Psychol Bull*. 1993;114(3):494-509.
23. Vargha A, Delaney HD. A critique and improvement of the CL common language effect size statistics of McGraw and Wong. *J Educ Behav Stat*. 2000;25(2):101-132.
24. Gasperi M, Schuster NM, Franklin B, Nievergelt CM, Stein MB, Afari N. Migraine prevalence, environmental risk, and comorbidities in male and female veterans. *JAMA Netw Open*. 2024;7(5):e2411428.
25. Merritt VC, Crocker LD, Sakamoto MS, Chanfreau-Coffinier C, Delano-Wood L, Program MV. Psychiatric symptoms influence social support in VA Million Veteran Program enrollees screening positive for traumatic brain injury. *Soc Sci Med*. 2022;312:115372.
26. Seng EK, Fenton BT, Wang K, et al. Frequency, demographics, comorbidities, and health care utilization by veterans with migraine: a VA nationwide cohort study. *Neurology*. 2022;99(18):e1979-e1992.
27. Lindberg MA, Moy Martin EM, Marion DW. Military traumatic brain injury: the history, impact, and future. *J Neurotrauma*. 2022;39(17–18):1133-1145.
28. Howard JT, Stewart IJ, Amuan M, Janak JC, Pugh MJ. Association of traumatic brain injury with mortality among military veterans serving after September 11, 2001. *JAMA Netw Open*. 2022;5(2):e2148150.
29. Nguyen X-MT, Whitbourne SB, Li Y, et al. Data resource profile: self-reported data in the Million Veteran Program: survey development and insights from the first 850 736 participants. *Int J Epidemiol*. 2023;52(1):e1-e17.
30. Lucas S, Hoffman JM, Bell KR, Dikmen S. A prospective study of prevalence and characterization of headache following mild traumatic brain injury. *Cephalalgia*. 2014;34(2):93-102.
31. Ishii R, Schwedt TJ, Trivedi M, et al. Mild traumatic brain injury affects the features of migraine. *J Headache Pain*. 2021;22:1-15.
32. Gil-Gouveia R, Martins IP. Clinical description of attack-related cognitive symptoms in migraine: a systematic review. *Cephalalgia*. 2018;38(7):1335-1350.
33. Ashina H, Al-Khazali HM, Iljazi A, et al. Psychiatric and cognitive comorbidities of persistent post-traumatic headache attributed to mild traumatic brain injury. *J Headache Pain*. 2021;22(1):1-10.
34. Bell BD, Primeau M, Sweet JJ, Lofland KR. Neuropsychological functioning in migraine headache, nonheadache chronic pain, and mild traumatic brain injury patients. *Arch Clin Neuropsychol*. 1999;14(4):389-399.
35. Henningsen P, Hausteiner-Wiehle C, Häuser W. Migraine in the context of chronic primary pain, chronic overlapping pain disorders, and functional somatic disorders: a narrative review. *Headache*. 2022;62(10):1272-1280.
36. Tiseo C, Vacca A, Felbush A, et al. Migraine and sleep disorders: a systematic review. *J Headache Pain*. 2020;21:1-13.
37. Montgomery MC, Baylan S, Gardani M. Prevalence of insomnia and insomnia symptoms following mild-traumatic brain injury: a systematic review and meta-analysis. *Sleep Med Rev*. 2022;61:101563.
38. Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA*. 2008;300(6):711-719.
39. Schur EA, Noonan C, Buchwald D, Goldberg J, Afari N. A twin study of depression and migraine: evidence for a shared genetic vulnerability. *Headache*. 2009;49(10):1493-1502.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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