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ARTICLE

Late contributions of repetitive head impacts and TBI to depression symptoms and cognition

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Abstract

Objective

To test the hypothesis that repetitive head impacts (RHIs), like those from contact sport play and traumatic brain injury (TBI) have long-term neuropsychiatric and cognitive consequences, we compared middle-age and older adult participants who reported a history of RHI and/or TBI with those without this history on measures of depression and cognition.

Methods

This cross-sectional study included 13,323 individuals (mean age, 61.95; 72.5% female) from the Brain Health Registry who completed online assessments, including the Ohio State University TBI Identification Method, the Geriatric Depression Scale (GDS-15), and the CogState Brief Battery and Lumos Labs NeuroCognitive Performance Tests. Inverse propensity-weighted linear regressions accounting for age, sex, race/ethnicity, and education tested the effects of RHI and TBI compared to a non-RHI/TBI group.

Results

A total of 725 participants reported RHI exposure (mostly contact sport play and abuse) and 7,277 reported TBI (n = 2,604 with loss of consciousness [LOC]). RHI (β, 1.24; 95% CI, 0.36–2.12), TBI without LOC (β, 0.43; 95% CI, 0.31–0.54), and TBI with LOC (β, 0.75; 95% CI, 0.59–0.91) corresponded to higher GDS-15 scores. While TBI with LOC had the most neuropsychological associations, TBI without LOC had a negative effect on CogState Identification (β, 0.004; 95% CI, 0.001–0.01) and CogState One Back Test (β, 0.004; 95% CI, 0.0002–0.01). RHI predicted worse CogState One Back Test scores (β, 0.02; 95% CI, −0.01 to 0.05). There were RHI × TBI interaction effects on several neuropsychological subtests, and participants who had a history of both RHI and TBI with LOC had the greatest depression symptoms and worse cognition.

Conclusions

RHI and TBI independently contributed to worse mid- to later-life neuropsychiatric and cognitive functioning.

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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

AD = Alzheimer disease; **ADRD** = Alzheimer disease–related dementias; **BHR** = Brain Health Registry; **CBB** = CogState Brief Battery; **CI** = confidence interval; **DET** = detection; **FMS** = Forward Memory Span; **GDS-15** = 15-item Geriatric Depression Scale; **GNG** = Go/No-Go; **IDN** = identification; **LOC** = loss of consciousness; **NCPT** = NeuroCognitive Performance Tests; **OCL** = one card learning; **ONB** = one-back test; **OSU TBI-ID** = Ohio State University TBI Identification Method; **RHI** = repetitive head impact; **RMS** = Reverse Memory Span; **TBI** = traumatic brain injury; **TMTB** = Trail-Making Test Part B; **UCSF** = University of California, San Francisco.

Exposure to repetitive head impacts (RHIs), such as those incurred from contact/collision sports, military service, domestic violence, and other sources, is associated with long-term neuropsychiatric and cognitive disorders.[1–4] These RHIs have been linked with the development of neurodegenerative diseases, including chronic traumatic encephalopathy,[5–9] as well as other types of neuropathologies (e.g., cerebrovascular disease).[10] It is hypothesized that RHIs lead to increased opportunity for recurrent traumatic brain injuries (TBIs), either symptomatic concussions or, more frequently, asymptomatic subconcussions, to initiate pathophysiologic processes that affect later-life neuropsychiatric and cognitive functioning. Subconcussions, or head impacts that cause neuronal injury but do not result in immediate symptoms, play a prominent role in this relationship.[11,12] It remains uncertain if exposure to RHI is an independent risk factor for neuropsychiatric and cognitive disorders due to limitations of previous studies. These include small sample sizes, focus on male American football players, lack of appropriate "control" groups, and reliance on retrospective reports to assess clinical status.[3]

There has also been lack of consideration of the role of TBI in those exposed to RHI. Recurrent symptomatic concussions and asymptomatic subconcussions might mediate the relationship between RHI and long-term neuropsychiatric and cognitive dysfunction. Alternatively, TBIs such as moderate to severe TBIs (e.g., falls, motor vehicle accidents) might have independent or synergistic effects. The broad literature on TBI and dementia has similarly failed to account for exposure to RHI, potentially contributing to the inconsistent reports on the association between TBI and Alzheimer disease (AD) and AD-related dementias (ADRD).[13–23] Overall, isolated examination of the late effects of RHI and TBI is problematic due to their association with each other and their unique effects on neuropsychiatric and cognitive functioning.

This study investigated the contributions of RHI (e.g., from contact sport participation, abuse, and military service) and history of TBI (with and without loss of consciousness [LOC]) on symptoms of depression and cognitive functioning. We leveraged the Internet-based Brain Health Registry (BHR)[24] and analyzed the data from 13,323 individuals (≥40 years) who completed self-report measures of RHI exposure and TBI, as well as self-report measures of depressive symptomatology and computerized neuropsychological tests. We hypothesized that RHI and TBI would have independent and interactive effects on depression symptoms and cognitive function.

Methods

Participants and design

A detailed overview of the BHR (brainhealthregistry.org/) is provided elsewhere.[24–26] The BHR was launched by the University of California, San Francisco (UCSF) in April 2014 as an Internet-based registry for the recruitment, screening, and longitudinal monitoring of cognition and functioning of individuals interested in participating in research on AD/ADRD across the United States. The only eligibility criterion is being 18 years or older. Participants are recruited through BHR-owned sources (e.g., website, social media), paid venues (e.g., online advertising, postal mail/email), and from publicity and word of mouth. Approximately 60,000 participants across the United States are enrolled in the BHR.[24] To participate, individuals visit the BHR website, create a username and password, sign online consent, and complete a series of online assessments including demographic and health questionnaires, medical and neurologic histories, subjective cognitive complaint measures, 2 depression scales, and computerized neuropsychological tests. Participants are asked to complete the online assessments every 6 months. All online assessments are completed voluntarily, without supervision, and not all participants complete all measures.

Standard protocol approvals, registrations, and patient consents

All participants signed online consent forms. Study protocols of the BHR are approved by the UCSF Institutional Review Board.

Measures

History of RHIs and TBI

A modified online version of the Ohio State University TBI Identification Method (OSU TBI-ID)[27] was added to the BHR in August 2015 to determine history of exposure to RHI and TBI. Exposure to RHI was considered to be present if the participant answered yes to the question "Have you ever had a period of time in which you experienced multiple, repeated impacts to your head (e.g., history of abuse, contact sports, military duty)?" Participants reported the cause of the RHI by selecting from one of the following options: abuse, contact sports, military duty, and other. Multiple causes can be selected. A history of TBI was determined if the participant endorsed having had a TBI on any 1 of the 5 questions from the OSU TBI-ID. If at least one is endorsed, the participant is prompted

to answer the question, "Were you knocked out or did you lose consciousness?" If they respond affirmatively, participants report the duration of LOC (<30 minutes, 30 minutes to 24 hours, >24 hours). We examined 3 groups based on TBI history: those who had no history of TBI (TBI−), those with a history of TBI but no LOC (TBI+ without LOC), and those with a history of TBI with LOC (TBI+ with LOC). Mild TBI was defined as TBI+ without LOC or TBI+ with LOC <30 minutes. Moderate to severe TBI was defined as LOC ≥30 minutes.[28]

Symptoms of depression

The 15-item Geriatric Depression Scale (GDS-15)[29] assessed symptoms of depression. The GDS-15 was part of the BHR platform at its launch in 2014. It includes 15 yes/no items that evaluate the presence of depressive symptoms. The items are summed to obtain a total score that ranges from 0 to 15. Higher scores indicate worse depression symptom severity.

Neuropsychological assessment

Participants complete online computerized neuropsychological test batteries, including (1) CogState Brief Battery (CBB)[30] and (2) Lumos Labs NeuroCognitive Performance Tests (NCPT).[31] The CBB and NCPT were part of the BHR platform at its launch in April 2014. The specific outcome variables used in this study are summarized below.

CogState Brief Battery

The CBB is a well-validated computerized neuropsychological test battery.[30] Scores on the CBB corresponded with self-reported diagnoses of AD in 6,463 participants from the BHR.[25] The CBB consists of 4 tests that draw on playing-card stimuli.[25,30] Outcome variables from the CBB include (1) detection (DET) speed (reaction time for correct responses in milliseconds normalized using a log 10 transformation); (2) identification (IDN) speed (reaction time for correct responses in milliseconds normalized using a log 10 transformation); (3) one card learning (OCL) accuracy (proportion of correct responses, normalized using an arcsine transformation); and (4) one-back test (ONB) speed (reaction time for correct responses normalized using a log 10 transformation). Higher scores reflect worse performance for DET, IDN, and ONB, whereas lower scores are worse for OCL. These subtests assess psychomotor function, attention, visual learning, and working memory.

Lumos Labs NCPT

The NCPT is a brief, Internet-based cognitive assessment platform that has been reported to be reliable and valid in an unsupervised setting.[31] The NCPT subtests and outcome variables used for this study include (1) Go/No-Go (GNG; average reaction time in milliseconds); (2) Trail-Making Test Part B (TMTB; time to completion in milliseconds); and (3) Forward and Reverse Memory Span (FMS and RMS, respectively; total number of correct trials for forward and reverse, separately). Higher values indicate worse performance for GNG and TMTB, and lower scores are worse for NCPT FMS and NCPT RMS. These subtests assess attention, working memory, processing speed, and executive function.

Statistical analyses

A flow chart on the derivation of the sample and rationale for participant inclusion and exclusion is provided in figure 1. This cross-sectional study included 13,323 individuals who were ≥40 years from the BHR using the time point at which there was available neuropsychological data and corresponding data for RHI and TBI. Participants <40 were excluded to permit inferences on mid- to later-life depression symptoms and cognitive functioning and to minimize inclusion of individuals with active exposure to RHI.

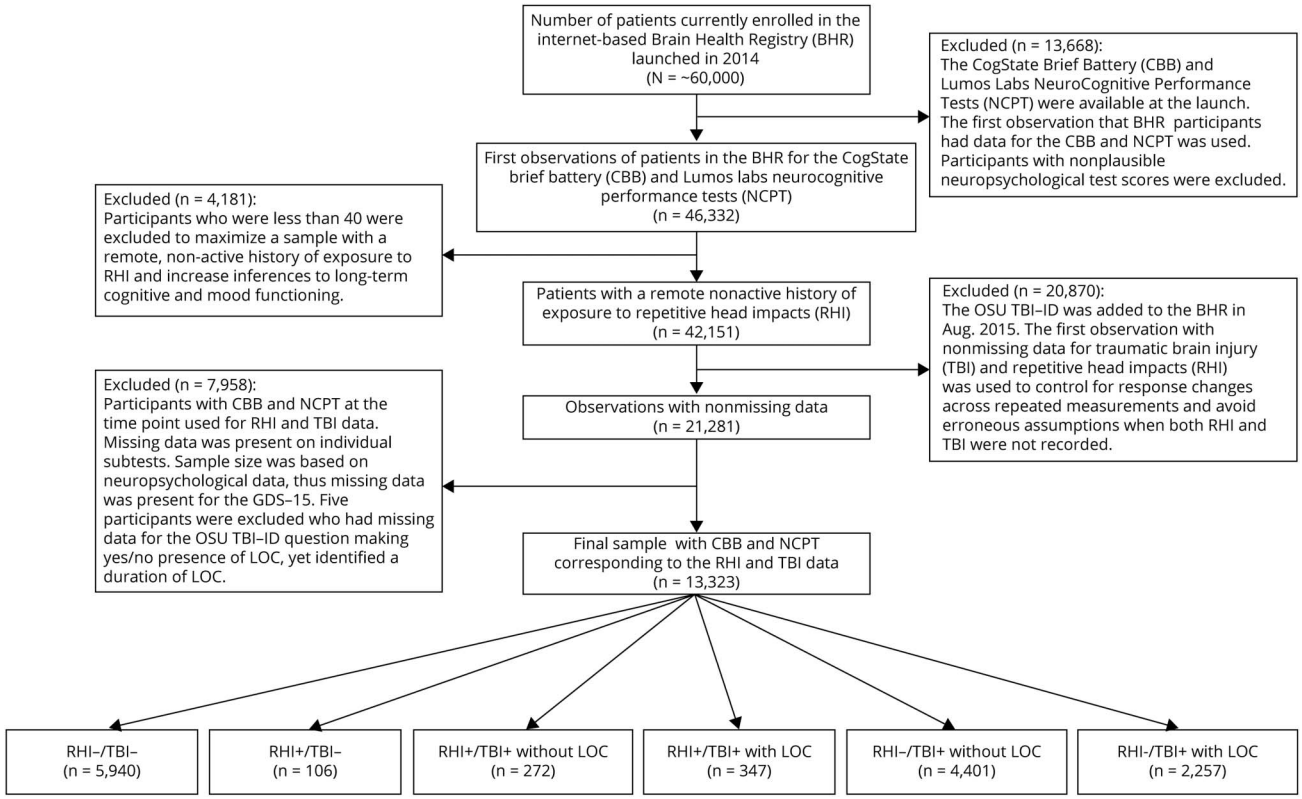
All analyses were performed using R version 3.4.3 and the level of statistical significance was set at $p < 0.05$. Inverse propensity weighted linear regressions were used to examine the independent effects of RHI+, TBI+ without LOC, and TBI+ with LOC, as well as the interaction effects between RHI+ and TBI+ (RHI+ × TBI without LOC, RHI+ × TBI with LOC) on the GDS-15, CBB subtests (DET, IDN, OCL, ONB), and the NCPT subtests (GNG, TMTB, FMS, RMS). The referent group for all models was RHI−/TBI−, or the unexposed group. Propensity score methods accounted for possible confounding from age, sex, race/ethnicity (Caucasian, African American, Latino, Asian, more than one race, and other), and education (high school or less, some college, 2-year college degree, 4-year college degree, advanced degree). To calculate the propensity score, a multinomial logistic regression first determined the probability of having a history of RHI and/or TBI based on an individual's age, sex, race/ethnicity, and education level.[32] This estimated probability represented the propensity score. To optimize equal distribution of age, sex, race/ethnicity, and education across RHI and TBI groupings, each individual's propensity score was weighted using the following formula: $\frac{1}{PS_i}$, where PS_i is the probability that the individual (i) belongs to the RHI and TBI group given the model parameters and their age, sex, race/ethnicity, and education. This inverse weighted propensity score[33] served as the covariate in a multivariable linear regression model. Compared to conventional covariate adjustment, propensity score methods can reduce potential for overfitting models.[34] Bootstrap analysis was performed on 1,000 replicates to account for the unequal group sizes and accurately estimate the standard error of the coefficients from the inverse propensity weighted linear regressions. In so doing, bootstrap analyses also reduce type I error.

Student t tests with Sidak correction for multiple comparisons were conducted to compare the means of the 6 different exposure group combinations: RHI−/TBI−, RHI−/TBI+ without LOC, RHI−/TBI+ with LOC, RHI+/TBI−, RHI+/TBI+ without LOC, and RHI+/TBI+ with LOC.

Data availability

Data from the BHR are available upon request and with the completion of a data use agreement.

Figure 1 Sample size derivation flow diagram



GDS-15 = 15-item Geriatric Depression Scale; LOC = loss of consciousness; OSU TBI-ID = Ohio State University TBI Identification Method.

Results

Sample characteristics

Demographic characteristics and sample sizes are shown in table 1 and figure 1. Of the 13,323 participants, 725 identified being exposed to RHI (see table 2 for breakdown by cause of RHI). Note that 31 participants reported multiple causes and 42 participants had missing data for cause of RHI. Of the 2,604 participants who reported a TBI+ with LOC, 1,953 reported LOC <30 minutes and 436 reported LOC ≥30 minutes; 215 participants had missing data for duration. Given a majority of the research on exposure to RHI has been among male samples, it is important to indicate that 322 of the 725 (44.4%) exposed to RHI and 5,116 of the 7,277 (70.3%) who reported a TBI history were female. However, those who reported a history of contact sport play and abuse were predominantly male and female, respectively (table 2).

RHI+ and TBI+ history: depression symptoms

Table 3 provides an overall summary of the model statistics. Of the total sample, 16.4% (n = 2,160 of the 13,168 who completed the GDS-15) of participants reported clinically meaningful symptoms of depression on the GDS-15 (score >5). These rates are similar to those reported among community-dwelling older adults.[35] Compared to the unexposed group, those who reported a TBI+ with LOC had 0.75 (95% confidence interval [CI], 0.59–0.91) higher scores on the GDS-15, on average, compared to the unexposed group. Those who reported a TBI+ without LOC had 0.43 (95% CI, 0.31–0.54) higher scores on the GDS-15.

The largest effects on the GDS-15 were observed for RHI: those who reported a history of RHI had 1.24 (95% CI, 0.36–2.12) higher scores on the GDS-15 compared to the unexposed group. There was not a statistically significant interaction effect between RHI+ and TBI+ on the GDS-15 (figure 2).

Student *t* test with Sidak correction for multiple comparisons compared the means of the 6 RHI/TBI groups on the GDS-15 (figure 3). There was a dose–response-like pattern between the degree of exposure to RHI/TBI and GDS-15 scores: the unexposed group had the lowest GDS-15 scores and the scores subsequently increased as exposure to RHI was introduced and TBI severity increased; the effects were greatest for the RHI+/TBI+ with LOC compared to all other groups (table 4).

RHI+ and TBI+ history: cognitive function

Compared to those unexposed, those who reported a TBI+ with LOC had statistically significant worse performance on the CBB IDN, CBB OCL, and the CBB ONB. TBI+ with LOC also corresponded to 9.57 (95% CI, 5.17, 13.98) and 1,834.71 (95% CI, 243.59, 3,425.84) milliseconds slower on the NCPT GNG and TMTB, respectively, compared to the unexposed group. TBI+ without LOC was

Table 1 Sample demographic characteristics

Demographic characteristics	Total sample	RHI+/TBI−	RHI+/TBI+ without LOC	RHI+/TBI+ with LOC	RHI−/TBI+ without LOC	RHI−/TBI+ with LOC	RHI−/TBI−
N	13,323	106	272	347	4,401	2,257	5,940
Age	61.95 (9.37)	60.75 (9.92)	60.36 (9.44)	59.85 (8.91)	61.53 (9.23)	61.76 (9.30)	62.56 (9.47)
Sex, female	9,657 (72.5)	36 (34.0)	121 (44.5)	165 (47.6)	3,290 (74.8)	1,540 (68.2)	4,505 (75.8)
Race/ethnicity, Caucasian only/non-Latino	11,808 (88.6)	86 (81.1)	216 (79.4)	295 (85.0)	3,935 (89.4)	2,034 (90.1)	5,242 (88.2)
Education							
High school/GED or less	564 (4.2)	4 (3.8)	18 (6.6)	17 (4.9)	176 (4.0)	97 (4.3)	252 (4.3)
Some college, no degree	1,843 (13.8)	17 (16.0)	44 (16.2)	76 (21.9)	628 (14.3)	359 (15.9)	719 (12.1)
2-year college degree	979 (7.3)	4 (3.8)	23 (8.5)	31 (8.9)	368 (8.4)	166 (7.4)	387 (6.5)
4-year college degree	4,321 (32.4)	33 (31.1)	85 (31.3)	104 (30.0)	1,466 (33.3)	698 (30.9)	1,935 (32.6)
Advanced degree	5,616 (42.2)	48 (45.3)	102 (37.5)	119 (34.3)	1,763 (40.1)	937 (41.5)	2,647 (44.5)

Abbreviations: *GED* = General Equivalency Development; LOC = loss of consciousness; RHI = repetitive head impact; TBI = traumatic brain injury.
Values are mean (SD) or n (%). Race/ethnicity categories for the present study included Caucasian, African American, Asian, Latino, more than one race, and other.

associated with worse performance on the CBB IDN and CBB ONB.

Compared to the unexposed group, those who reported a history of RHI had worse performance on the CBB ONB subtest. There was a statistically significant interaction effect between RHI+ and TBI+ with LOC on the NCPT RMS and NCPT TMTB. There was also an interaction effect between RHI+ and TBI+ without LOC on OCL. For each, the presence of both RHI and TBI+ had a synergistic, negative effect on neuropsychological test performance (table 3 and figures 2 and 3).

Table 2 Sample demographic characteristics across the different causes of exposure to repetitive head impacts

Demographic characteristics	Contact sport play	Abuse	Military duty
N	311	205	30
Age, y	60.48 (9.51)	59.16 (8.36)	64.93 (11.75)
Sex, female	38 (12.2)	187 (91.2)	3 (10.0)
Race/ethnicity, Caucasian only/non-Latino	271 (87.1)	150 (73.2)	23 (76.7)
Education			
High school/GED or less	4 (1.3)	22 (10.8)	0
Some college, no degree	40 (12.9)	59 (28.8)	4 (13.3)
2-year college degree	17 (5.5)	25 (12.2)	6 (20.0)
4-year college degree	101 (32.5)	56 (27.3)	8 (26.7)
Advanced degree	149 (47.9)	43 (20.9)	12 (40.0)

Abbreviation: GED = General Equivalency Development.
Values are mean (SD) or n (%). A total of 106 participants reported other causes and 31 participants reported multiple causes. Forty-two participants had missing data for cause of repetitive head impact exposure. Race/ethnicity categories for the present study included Caucasian, African American, Asian, Latino, more than one race, and other.

Student *t* test with Sidak correction for multiple comparisons compared the means of the 6 RHI/TBI groups on each of the neuropsychological subtests, as shown in figures 2 and 3. There was a consistent statistically significant finding for worse neuropsychological test performance for the RHI+/TBI+ with LOC compared to each of the RHI− groups (table 4). Although there were no consistent statistically significant differences between the other RHI+ (i.e., RHI+/TBI without LOC, RHI+/TBI−) and RHI− groups, there was a pattern for worse neuropsychological test performance among the RHI+ groups compared to the RHI− groups.

Regarding differences between the RHI+ groups, there was only a significant difference for TMTB: the RHI+/TBI+ with LOC group had worse test performance compared to the RHI+/TBI− group (mean difference 13,295.08, 95% CI, −22,700.88, −3,889.28), but not when compared to the RHI+/TBI+ without LOC group (mean difference −8,048.11, 95% CI, −16,715.85, 619.62). Differences between the RHI− groups were present for the IDN and GNG. For IDN, RHI− groups that had TBI+ with (mean difference −0.01, 95% CI, −0.01, 0.002) and without LOC (mean difference −0.004, 95% CI, −0.01, −0.0002) had worse test performance compared to the RHI−/TBI− group. For GNG, the RHI−/TBI+ with LOC group had worse performance

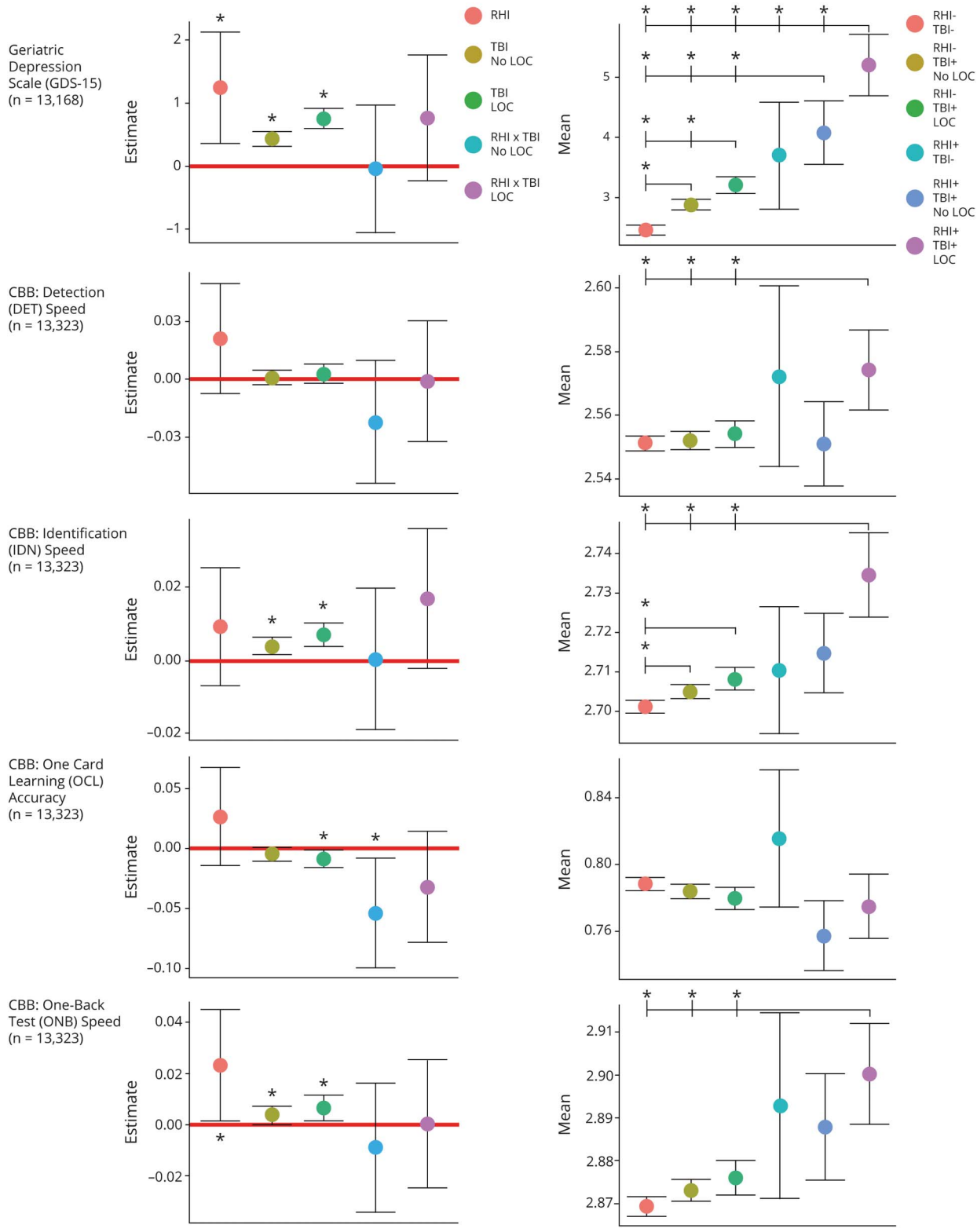
Table 3 Main effects of repetitive head impacts (RHIs) and traumatic brain injury (TBI) on mid- to later-life reported symptoms of depression and neuropsychological test performance compared to the reference unexposed RHI−/TBI− group: summary of inverse propensity weighted linear regressions

	RHI+			TBI+ without LOC			TBI+ with LOC			RHI+ × TBI without LOC			RHI+ × TBI with LOC		
	β (95% CI)	*t*	*p* Value	β (95% CI)	*t*	*p* Value	β (95% CI)	*t*	*p* Value	β (95% CI)	*t*	*p* Value	β (95% CI)	*t*	*p* Value
GDS	1.24 (0.36 to 2.12)	2.75	<0.01	0.43 (0.31 to 0.54)	7.37	<0.01	0.75 (0.59 to 0.91)	9.30	<0.01	−0.04 (−1.05 to 0.97)	−0.08	0.93	0.76 (−0.24 to 1.76)	1.50	0.13
DET	0.02 (−0.01 to 0.05)	1.45	0.15	0.001 (−0.003 to 0.05)	0.49	0.62	0.003 (−0.002 to 0.01)	1.16	0.25	−0.02 (−0.05 to 0.01)	−1.37	0.17	−0.001 (−0.03 to 0.03)	−0.06	0.95
IDN	0.009 (−0.01 to 0.03)	1.13	0.36	0.004 (0.001 to 0.01)	3.13	<0.01	0.01 (0.004 to 0.01)	4.23	<0.01	0.001 (−0.02 to 0.02)	0.05	0.96	0.02 (−0.002 to 0.04)	1.74	0.08
OCL	0.03 (−0.01 to 0.07)	1.29	0.20	−0.004 (−0.01 to 0.001)	−1.51	0.13	−0.01 (−0.02 to -0.001)	−2.21	0.03	−0.05 (−0.10 to -0.01)	−2.29	0.02	−0.03 (−0.08 to 0.01)	−1.35	0.18
ONB	0.02 (0.002 to 0.05)	2.11	0.04	0.004 (0.0002 to 0.01)	2.05	0.04	0.01 (0.002 to 0.01)	2.78	0.01	−0.01 (−0.03 to 0.02)	−0.67	0.50	0.001 (-0.02 to 0.03)	0.05	0.96
GNG	1.15 (−19.71 to 22.02)	0.11	0.91	2.38 (−0.97 to 5.73)	1.39	0.16	9.57 (5.17 to 13.98)	4.26	<0.01	−2.14 (−26.75 to 22.48)	−0.17	0.86	13.97 (−10.40 to 38.34)	1.12	0.26
TMTB	−2,951.44 (−7,238.64 to 1335.76)	−1.35	0.18	−117.30 (−1,249.60 to 1,015.00	−0.20	0.84	1,834.71 (243.59 to 3,425.84)	2.26	0.02	5,364.26 (−323.56 to 11,052.08)	1.85	0.06	11,460.36 (4,940.83 to 17,979.90)	3.45	<0.01
RMS	0.16 (−0.20 to 0.51)	0.87	0.38	0.01 (−0.05 to 0.06)	0.28	0.78	0.02 (−0.04 to 0.09)	0.66	0.51	−0.12 (−0.52 to 0.28)	−0.59	0.56	−0.48 (−0.88 to -0.09)	−2.42	0.02
FMS	0.11 (−0.21 to 0.43)	0.67	0.50	−0.02 (−0.07 to 0.02)	−1.00	0.32	−0.02 (−0.07 to 0.04)	−0.54	0.59	−0.14 (−0.50 to 0.22)	−0.78	0.43	−0.35 (−0.70 to 0.002)	−1.95	0.05

Abbreviations: CI = confidence interval; DET = detection; FMS = Forward Memory Span; GDS-15 = 15-item Geriatric Depression Scale; GNG = Go/No-Go; IDN = identification; LOC = loss of consciousness; OCL = one card learning; ONB = one-back test; RMS = Reverse Memory Span; TMTB = Trail-Making Test Part B.

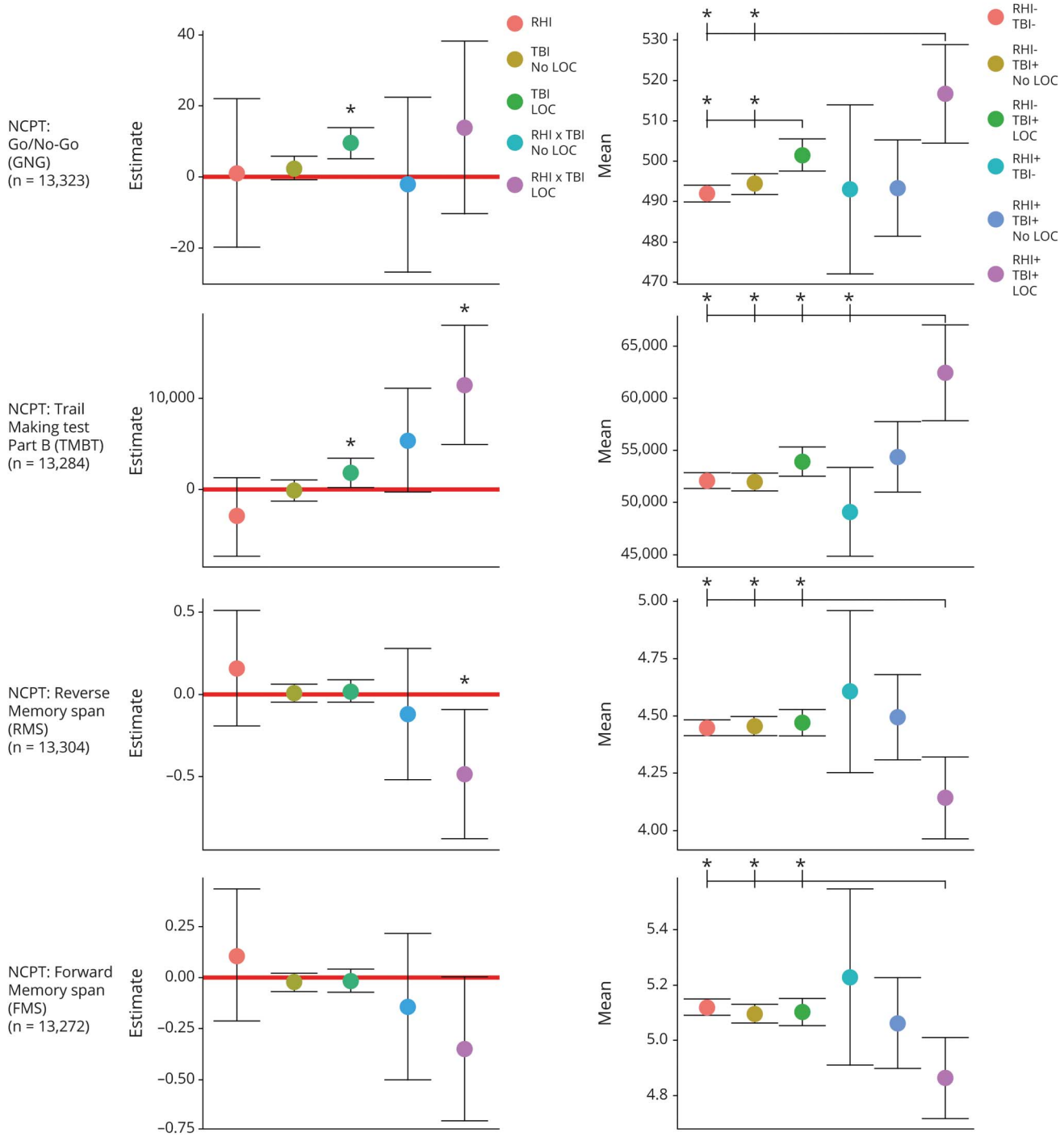
An inverse propensity weighted linear regression examined the main effects of RHI, TBI+ without LOC, and TBI+ with LOC, as well as the interaction between RHI and TBI+ (with and without LOC) on each outcome. The referent group was the participants who did not report a history of RHI or TBI (n = 5,940). Propensity score procedures accounted for confounding between the RHI and TBI groups for age, sex, race/ethnicity, and education. DET, IDN, and ONB estimates are reaction time for correct responses in milliseconds normalized using a log 10 transformation, OCL is proportion of correct responses normalized using an arcsine transformation. GNG is average reaction time in milliseconds, TMTB is time to completion in milliseconds, and RMS and FMS are total number of correct trials. Higher scores are worse for DET, IDN, ONB, GNG, and TMTB, whereas lower scores are worse for OCL and RMS and FMS. Higher scores on the GDS-15 reflect greater depression symptoms. $p < 0.05$ is statistically significant. Sample size: n = 13,323 for DET, IDN, ONB, OCL, and GNG; due to missing data, n = 13,272 for FMS; n = 13,304 for RMS; n = 13,284 for TMTB; and n = 13,168 for GDS-15.

Figure 2 The effects of repetitive head impacts (RHIs) and traumatic brain injury (TBI) on the (GDS-15) and the CogState Brief Battery (CBB)



Left figures show the statistically significant results of the inverse propensity weighted linear regressions that compared individuals who reported a history of RHI and TBI with and without loss of consciousness (LOC) to those with no RHI or TBI history (RHI−/TBI−) on reported symptoms of depression and neuropsychological test performance. The inverse propensity score accounted for age, sex, race/ethnicity, and education. Error bars are 95% confidence intervals (CIs). *p* Values only shown for statistically significant effects following bootstrap analysis performed on 1,000 replicates. Right figures show the means and 95% CIs for the 6 RHI and TBI groups. The y-axis for IDN, DET, and ONB represents reaction time for correct responses in milliseconds normalized using a log 10 transformation. The y-axis for OCL is proportion of correct responses, normalized using an arcsine transformation. Higher scores reflect worse performance for IDN, DET, and ONB, whereas lower scores are worse for OCL. Higher scores on the Geriatric Depression Scale 15-item version reflect greater reported symptoms of depression. DET = detection.

Figure 3 The effects of repetitive head impacts (RHIs) and traumatic brain injury (TBI) on the Lumos Labs Neurocognitive Performance Tests (NCPT)



Left figures show the statistically significant results of the inverse propensity weighted linear regressions that compared individuals who reported a history of RHI and TBI with and without loss of consciousness (LOC) to those with no RHI or TBI history (RHI−/TBI−) on neuropsychological test performance. The inverse propensity score accounted for age, sex, race/ethnicity, and education. Error bars are 95% confidence intervals (CIs). *p* Values only shown for statistically significant effects following bootstrap analysis performed on 1,000 replicates. Right figures show the means and 95% CIs for the 6 RHI and TBI groups. The y-axis for GNG is average reaction time in milliseconds and TMTB is time to completion in milliseconds, all raw scores. Higher values indicate worse performance for GNG and TMTB, whereas lower scores are worse for Reverse and Forward Memory Span (y-axis is total number of correct trials).

relative to both the RHI−/TBI+ without LOC (mean difference −7.20, 95% CI, −14.18, −0.21) and the RHI−/TBI− (mean difference −9.57, 95% CI, −16.16, −2.98) groups (figures 2 and 3).

Post hoc analyses: interactions with demographic factors

Post hoc multivariable linear regression analyses showed no statistically significant interactions between the demographic

Table 4 Mean differences in computerized depression symptoms and neuropsychological test scores between repetitive head impact (RHI)+/traumatic brain injury (TBI)+ with loss of consciousness (LOC) compared to the RHI− groups

	RHI−/TBI+ without LOC			RHI−/TBI+ with LOC			RHI−/TBI−		
	Mean difference (95% CI)	*t*	*p* Value	Mean difference (95% CI)	*t*	*p* Value	Mean difference (95% CI)	*t*	*p* Value
GDS-15	−2.32 (−3.11 to −1.54)	−8.70	<0.01	−2.00 (−2.80 to −1.20)	−7.34	<0.01	−2.75 (−3.52 to −1.98)	−10.47	<0.01
DET	−0.02 (−0.04 to −0.003)	−3.38	0.01	−0.02 (−0.04 to −0.001)	−3.03	0.04	−0.02 (−0.04 to −0.003	−3.55	<0.01
IDN	−0.03 (−0.05 to −0.01)	−5.37	<0.01	−0.03 (−0.04 to −0.01)	−4.73	<0.01	−0.03 (−0.05 to −0.02)	−6.02	<0.01
OCL	0.01 (−0.02 to 0.04)	0.87	0.99	0.005 (−0.03 to 0.04)	0.47	1.00	0.01 (−0.02 to 0.04)	1.34	0.95
ONB	−0.03 (−0.05 to −0.01)	−4.40	<0.01	−0.02 (−0.04 to −0.01)	−3.84	<0.01	−0.03 (−0.05 to −0.01)	−5.03	<0.01
GNG	−22.32 (−41.09 to −3.55)	−3.49	<0.01	−15.13 (−34.27 to 4.02)	−2.32	0.27	−24.70 (−43.29 to −6.11)	−3.89	<0.01
TMTB	−10,460.94 (−17,384.20 to −3,537.67)	−4.43	<0.01	−8,508.93 (−15,784.73 to −1,233.12)	−3.43	<0.01	−10,343.64 (−17,330.06 to −3,357.21))	−4.34	<0.01
RMS	0.31 (0.04 to 0.59)	3.35	0.01	0.33 (0.05 to 0.61)	3.41	<0.01	0.30 (0.03 to 0.58)	3.29	0.01
FMS	0.23 (0.01 to 0.45)	3.07	0.03	0.24 (0.01 to 0.47)	3.02	0.04	0.26 (0.03 to 0.48)	3.35	0.01

Abbreviations: CI = confidence interval; DET = detection; FMS = Forward Memory Span; GDS-15 = 15-item Geriatric Depression Scale; GNG = Go/No-Go; IDN = identification; OCL = one card learning; ONB = one-back test; RMS = Reverse Memory Span; TMTB = Trail-Making Test Part B.

Student *t* test with Sidak correction for multiple comparisons (presented *p* values are Sidak adjusted) were conducted to compare the means of the 6 different exposure group combinations: RHI−/TBI−, RHI−/TBI+ without LOC, RHI−/TBI+ with LOC, RHI+/TBI−, RHI+/TBI+ without LOC, and RHI+/TBI+ with LOC. There was a consistent finding for greater depression symptoms and worse neuropsychological test performance for the RHI+/TBI+ with LOC compared to each of the RHI− groups. Thus the table shows mean differences between each of the RHI− groups compared to the RHI+/TBI+ with LOC group. For the GDS-15, the RHI+/TBI+ with LOC had effects compared to all other groups and the above is only relative to the RHI− groups given it was the prominent finding for depression symptoms and neuropsychological test scores.

DET, IDN, and ONB estimates are reaction time for correct responses in milliseconds normalized using a log 10 transformation, OCL is proportion of correct responses normalized using an arcsine transformation. GNG is average reaction time in milliseconds, TMTB is time to completion in milliseconds, and RMS and FMS is total number of correct trials. Higher scores are worse for DET, IDN, ONB, GNG, and TMTB, whereas lower scores are worse for OCL, RMS, and FMS. Higher scores on the GDS-15 reflect greater depression symptoms. $p < 0.05$ is statistically significant. Sample size: n = 13,323 for DET, IDN, ONB, OCL, and GNG; due to missing data, n = 13,272 for FMS; n = 13,304 for RMS; n = 13,284 for TMTB; and n = 13,168 for GDS-15.

variables used in the propensity score (i.e., age, sex, racial/ethnicity identity, education level) and RHI, TBI, or RHI × TBI (data not shown).

Discussion

We examined the contributions of RHI and TBI to symptoms of depression and cognitive function in 13,323 middle age and older adult participants from the BHR. The results support the view that RHI and TBI contribute to mid- to later-life neuropsychiatric and cognitive functioning independent of age, sex, racial identity, and education level.

Depression has been shown to persist after TBI[36–38] due to complex reasons, including (but not limited to) post-TBI severity of disability,[39] preinjury psychiatric and psychosocial factors,[40] and pathophysiologic changes (e.g., neuroinflammation).[41] Cognitive difficulties can also persist after a TBI,[3,38,42] particularly moderate to severe TBIs.[37,42] Cognitive difficulties are often short-lived following a single mild TBI, although they can persist among a subset of individuals,[43] and mild TBI has been linked with a twofold increased risk for dementia among a large clinical cohort of veterans.[14] The executive and attention/processing speed profile of deficits associated with TBI in this sample is consistent with previous reports on the neuropsychological profile of lifetime TBI in older veterans.[44] Although a majority of the TBIs with LOC were of mild severity (i.e., LOC <30 minutes), the larger effects observed for TBI with LOC (compared to TBI without LOC) might be driven by the subset who had more severe TBIs. Overall, the literature on TBI and long-term neurologic disorders (e.g., dementia) has been inconsistent, and our findings and others[14,17] support this relationship to be a function of TBI severity. The number[15,17] and the age and timing[15] of TBIs are also key modifiers, particularly of the strength of association, that were not examined in this study.

An existing literature links RHI with worse later-life cognitive, behavioral, and mood functioning,[1,2,4,7] including for domains in which we observed effects (e.g., depression and working memory).[1,2,4] The present study extends this literature by addressing several methodologic shortcomings that have limited our understanding on the late neurobehavioral effects of RHI, including small samples, lack of unexposed control groups, reliance on retrospective reports of symptoms by family members of deceased brain donors, or focus on male former American football players. The association of RHI with depression and cognitive symptoms in this study and others may in part be related to various underlying brain alterations that have been reported to occur following RHI,[6–8,45] with subconcussions being the prominent contributor.[11,12] Because most participants who reported RHI had a TBI history, it limited the ability to causally differentiate the independent effects of RHI and TBI and draw inferences on the exact role of repetitive subconcussions. It is important to note that the effects for RHI on cognitive function were relatively small (as is true for TBI) and circumscribed. Not all individuals exposed to RHI will develop later-life neurobehavioral disorders and the presence and strength of this relationship are dependent on the duration of exposure[4,45] and other RHI exposure-related variables (e.g., intensity, frequency), as well as non–head trauma risk factors (e.g., age, genetics, medical comorbidities). Detailed information on RHI exposure characteristics (e.g., type of contact sport played, level played) was not available given the BHR was not developed to study RHI or TBI. For this reason, we also did not directly test how the effects of RHI differ by cause as it would magnify limitations related to assumptions that the nature of exposure to RHI is equal across contact sports, types of abuse histories, or military duties. There is also uncertainty whether the groups are mutually exclusive. Focusing on absence/presence of exposure to RHI minimizes the above limitations.

Exposure to RHI and TBI, especially TBI with LOC, interacted to have synergistic effects on neuropsychological test performance. In addition to worse cognitive function, those who reported a history of both RHI and TBI with LOC consistently had the greatest symptoms of depression. Our statistical models assume no association between RHI and TBI. This assumption is accurate if the TBI with LOC occurred from sources that did not involve exposure to RHI (e.g., motor vehicle accidents). In contrast, this assumption is incorrect if RHI led to the TBI with LOC (e.g., head impact that led to a mild TBI with LOC). Nevertheless, our findings on the interplay between RHI and TBI have important implications for future research. For studies investigating TBI (especially mild TBI) and neurobehavioral outcomes, a proportion of the participants likely have been exposed to RHI given sports-related concussion is the most common type of TBI.[46] The documented association between mild TBI and dementia in the epidemiologic and large clinic databases[14–17] could partially be related to RHI. Biomarker and neuropathologic studies on TBI and neurodegenerative outcomes[19,20] could also be confounded by an unknown (or unassessed) history of RHI.[9] Consideration of RHI from contact sports and other sources when investigating the relationship between TBI and mid- to later-life cognitive disorders is warranted. The emerging field on the late effects of RHI is encouraged to consider and account for the contributions from TBI across the spectrum of severity.

We did not observe interactions between RHI or TBI and demographic variables. This is partially due to the sample being demographically homogenous (discussed below). The lack of granular data on exposure characteristics also makes interpretation of these results challenging. This is particularly true for RHI by sex interactions given those who reported a history of contact sport play and physical abuse were predominantly male and female, respectively. Little is known about the late neuropsychiatric and cognitive effects due to RHI from physical abuse (e.g., intimate partner violence) among females, especially compared to male contact sport athletes. Characterization of risk for later-life neurologic disorders associated with RHI is

of high research priority, specifically in terms of the modifying roles of demographic, psychosocial (e.g., socioeconomic status), psychiatric (e.g., posttraumatic stress disorder), health (e.g., cardiovascular disease), and genetic variables.

There are additional limitations to the current findings. As alluded to above, BHR participants are mostly female, Caucasian, and have advanced education. Participants who enroll into BHR also include those who are more likely to be concerned about their cognition, have Internet access, and have the cognitive capacities to operate and navigate the Internet. Although there is validation support for the online and unsupervised administration of the CBB[25] and NCPT,[31] there is no confirmation whether the assessments were completed as intended and not all participants complete all measures. The clinical meaningfulness of the observed effects is also uncertain due to the small effect sizes and additional large sample studies are needed to examine the association between RHI/TBI and daily functioning. Exposure to RHI and TBI were self-reported through the OSU-TBI-ID and this could have resulted in RHI or TBI exposure misclassification due to recall biases. There are also repeat administrations of the OSU-TBI-ID and no assessment of interim head trauma exposure; for these reasons, we examined cross-sectional associations from the time point at which there were available neuropsychological data and nonmissing TBI and RHI data to minimize erroneous assumptions. Selection based on nonmissing TBI and RHI data could explain the higher rates of self-reported lifetime history of TBI in this sample (~55%) compared to population-based estimates of self-reported lifetime TBI (~42% mild to severe).[47] Lack of examination of the timing and number of injury events combined with the cross-sectional design limit causal inferences and the ability to differentiate acute, intermediate, and long-term effects. Longitudinal studies in this setting are also needed to disentangle the relationship between cognition and depression. The self-report measures of depression include items that assess cognitive symptoms (e.g., concentration) and the effects for RHI and TBI on the depression measures may have been driven by these items. Alternatively, depressive symptoms may have influenced the associations between RHI and TBI with the cognitive tests.

In this sample of middle-age and older adults from the online BHR, exposure to RHI and TBI were independently associated with worse depression symptom severity and cognitive functioning. Moving forward, it is critical that the different types of head impact exposures and TBIs are accounted for and examined together given their potentially unique effects on long-term neuropsychiatric and cognitive functioning.

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Zachary Baucom, BA	Boston University School of Public Health, MA	Assisted with the statistical analyses, study design and conceptualization, analysis and interpretation of data, and drafting/revising the manuscript
Jesse Mez, MS, MD	Boston University School of Medicine, MA	Data interpretation, draft and revising the manuscript
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Shannon Conneely, BA	Boston University School of Medicine, MA	Data interpretation, draft and revising the manuscript
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Rachel Nosheny, PhD	University of California, San Francisco; Department of Veterans Affairs Medical Center, San Francisco	Data interpretation, draft and revising the manuscript
Scott Mackin, PhD	University of California, San Francisco; Department of Veterans Affairs Medical Center, San Francisco	Data interpretation, draft and revising the manuscript

Continued

Appendix *(continued)*

Name	Location	Contribution
Ann C. McKee, MD	Boston University School of Medicine, MA	Data interpretation, draft and revising the manuscript
Michael W. Weiner, MD	University of California, San Francisco; Department of Veterans Affairs Medical Center, San Francisco	Study concept and design, revising the manuscript, and analysis and interpretation of data
Robert A. Stern, PhD	Boston University School of Medicine, MA	Study concept and design, revising the manuscript, and analysis and interpretation of data

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