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The Influence of Chronic Cigarette Smoking on Neurocognitive Recovery after Mild Traumatic Brain Injury

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Abstract

The majority of the approximately 1.7 million civilians in the United States who seek emergency care for traumatic brain injury (TBI) are classified as mild (MTBI). Premorbid and comorbid conditions that commonly accompany MTBI may influence neurocognitive and functional recovery. This study assessed the influence of chronic smoking and hazardous alcohol consumption on neurocognitive recovery after MTBI. A comprehensive neurocognitive battery was administered to 25 non-smoking MTBI participants (nsMTBI), 19 smoking MTBI (sMTBI) 38 ± 22 days (assessment point 1: AP1) and 230 ± 36 (assessment point 2: AP2) days after injury. Twenty non-smoking light drinkers served as controls (CON). At AP1, nsMTBI and sMTBI were inferior to CON on measures of auditory-verbal learning and memory; nsMTBI performed more poorly than CON on processing speed and global neurocognition, and sMTBI performed worse than CON on working memory measures; nsMTBI were inferior to sMTBI on visuospatial memory. Over the AP1-AP2 interval, nsMTBI showed significantly greater improvement than sMTBI on measures of processing speed, visuospatial learning and memory, visuospatial skills, and global neurocognition, whereas sMTBI only showed significant improvement on executive skills. At AP2, sMTBI remained inferior to CON on auditory-verbal learning and auditory-verbal memory; there were no significant differences between nsMTBI and CON or among nsMTBI and sMTBI on any domain at AP2. Hazardous alcohol consumption was not significantly associated with change in any neurocognitive domain. For sMTBI, over the AP1-AP2 interval, greater lifetime duration of smoking and pack-years were related to significantly less improvement on multiple domains. Results suggest consideration of the effects of chronic cigarette smoking is necessary to understand the potential factors influencing neurocognitive recovery after MTBI.

Key words: cigarette smoking; cognition; mild traumatic brain injury; recovery

Introduction

Annually, approximately 1.7 million civilians in the United States seek emergency care for traumatic brain injury (TBI) secondary to motor vehicle accidents, falls, assaults, sports-related events, and other mechanisms.[1] The majority (70–90%) of these TBI cases are classified as mild.[1,2] In addition, 10–25% of the 2.3 million military personnel deployed to Iraq and Afghanistan since 2001 have sustained a mild traumatic brain injury (MTBI) during their service.[3]

Within the first month after MTBI, variable levels of dysfunction on measures of attention, learning, and memory, information processing speed, and working memory are frequently observed. In the majority of cases, the neurocognitive abnormalities demonstrated following MTBI are principally resolved within approximately 3 months post-injury.[4] There is still considerable controversy, however, regarding the influence of premorbid and comorbid factors on the expected rate and extent of recovery from the acute neurocognitive sequelae associated with MTBI.[4,5] Specifically, it has long been recognized that premorbid and comorbid conditions that commonly accompany MTBI (e.g., previous MTBI, alcohol/substance abuse, post-traumatic stress disorder [PTSD], litigation) may influence neurocognitive and functional outcome.[6–9] Many previous studies, however, either excluded such premorbid/comorbid conditions to study the ''pure'' or ''uncomplicated'' consequences of MTBI, or did not consider the potential effects of these co-occurring conditions.

Excluding patients with premorbid and comorbid conditions that commonly accompany MTBI, such as alcohol and substance use disorders, may result in a selection bias that creates study cohorts that are not representative of the majority seeking medical treatment/neuropsychological assessment for MTBI. Such selection bias may

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significantly limit the clinical relevance and generalizability of the reported findings. Alternately, failure to specifically evaluate for, or consider the influence of, prevalent comorbid conditions may lead to spurious conclusions about the mechanisms promoting neurobiological and neurocognitive dysfunction secondary to MTBI.

Alcohol and substance use disorders are the most prevalent comorbid conditions across the TBI severity spectrum.[10–12] Independent of TBI, chronic hazardous alcohol consumption (i.e., ≥5 drink equivalents/day for males, ≥4 females[13,14]) and alcohol use disorders are associated with multiple neurobiological and neurocognitive abnormalities.[15,16] Nevertheless, few studies have specifically evaluated the influence of pre-injury hazardous alcohol consumption or alcohol abuse/dependence on post-TBI neurocognition or neurocognitive recovery.

In a study of TBI severity ranging from mild to severe, higher scores on the Short Michigan Alcohol Screening Test were associated with lower verbal intelligence and performance on a measure of set-shifting and visuomotor scanning 1 month post-injury and with lower verbal intelligence at 1 year post-injury.[17] In another study of mild-to-severe TBI, no significant differences in neurocognition were observed 1 month post-injury between those who demonstrated hazardous pre-injury alcohol consumption or alcohol abuse/dependence and those without an alcohol use disorder.[10] Given the mixed severities of patients with TBI of these studies, the effects of hazardous alcohol consumption on neurocognitive recovery following MTBI is essentially unknown.

Chronic cigarette smoking is also robustly associated with significant neurobiological and neurocognitive abnormalities in non-clinical cohorts and those with various neuropsychiatric conditions.[16,18–20] In contrast to hazardous alcohol consumption, the prevalence of cigarette smoking in MTBI is unclear, and there are no published studies that have specifically assessed the potential effects of chronic smoking on neurocognitive recovery in MTBI.

The primary goal of this study was, therefore, to assess the influence of chronic smoking and hazardous alcohol consumption on changes of neurocognitive function over approximately 7 months after MTBI. We predicted that:

1. At baseline (approximately 5 weeks post-injury) and follow-up assessments (approximately 7 months post-injury), smoking persons with MTBI (sMTBI) perform worse than non-smoking persons with MTBI (nsMTBI) and non-smoking controls (CON) on the domains of executive skills, learning, and memory, processing speed, and working memory.
2. Between baseline and 7-month follow-up assessments, sMTBI show significantly lower rates of improvement on the above neurocognitive domains than nsMTBI.
3. In MTBI, greater smoking severity (i.e., pack-years and lifetime years of smoking) and greater drinking severity are related to poorer performance on the above neurocognitive domains at baseline and follow-up assessment, and to diminished recovery on these domains.

Methods

Participants

MTBI was defined as closed-head trauma with witnessed loss of consciousness (LOC) of less than 30 min, an initial Glasgow Coma Scale (GCS) score of 13–15 in the Emergency Department (ED), post-traumatic amnesia of less than 24 h, and no radiologic evidence of depressed skull fracture. Forty-four persons with MTBI (35 ± 12 years of age) were enrolled prospectively (Table 1) from the ED at San Francisco General Hospital. Injury mechanisms involved bicycle/skateboard accidents ($n = 22$, 50%), motor-vehicle-related accidents ($n = 6$, 13.6%), falls ($n = 6$, 13.6%), assaults ($n = 6$, 13.6%), and pedestrian versus motor vehicle ($n = 4$, 9%). Baseline assessment point (AP1) for MTBI participants (25 nsMTBI; 19 sMTBI) was 38 ± 22 days after injury, and follow-up assessment point (AP2) was 230 ± 36 days post-injury (22 nsMTBI, 17 sMTBI).

Twenty never-smoking CON (40 ± 9 years of age) were recruited from the community. All CON were free of any biomedical or psychiatric conditions known to influence our dependent measures and were compared with nsMTBI and sMTBI on neurocognitive and clinical variables. Ten CON were reassessed on neurocognitive measures 255 ± 55 days after their baseline assessment.

Two nsMTBI reported a single previous TBI with LOC (less than 5 min) that occurred approximately 20 years before the study. One nsMTBI reported daily marijuana use for approximately 10 consecutive years, but no marijuana or other substance use in the year before the study. One sMTBI reported almost daily methamphetamine use for approximately 3 consecutive years, which ended 5 years before the study, and no other substance use. All nsMTBI reported they never smoked cigarettes or did not smoke consistently during their lifetime (i.e., <50 cigarettes over lifetime and no tobacco use within 10 years of study); all sMTBI were actively smoking at AP1 and AP2, and their cigarette consumption was unchanged between assessment points. The MTBI participants reported no other biomedical or psychiatric conditions and no participant was involved in litigation, or had litigation pending, at any assessment point.

Medical, psychiatric, alcohol and substance use history

AP1. MTBI medical history was obtained from self-report and confirmed via available medical records. All participants were screened for mood, anxiety, and psychotic disorders via an adapted version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV Axis I disorders, Patient Edition, Version 2.0 [SCID-I/P; [21]]. All participants completed the Alcohol Use Disorder Identification Test (AUDIT),[22] a version of the AUDIT modified to assess the past 30 days of alcohol consumption (AUDIT-past-30-days), and an in-house questionnaire assessing type, quantity, and frequency of substance use.[23] The AUDIT is a widely used, cross-national, clinical and research measure used to identify hazardous/harmful alcohol use. AUDIT scores ≥8 are indicative of hazardous and harmful levels of alcohol consumption.[22]

All participants completed self-report measures of depressive (Beck Depression Inventory, BDI[24]) and anxiety symptomatology (State-Trait Anxiety Inventory, form Y-2, STAI [25]) as well as nicotine dependence (Fagerstrom Tolerance Test for Nicotine Dependency [FTND]).[26] The total number of cigarettes currently smoked per day and the number of years of smoking at the current level were also recorded, and pack years (i.e., number of cigarettes per day/20 × number of years of smoking) were calculated for sMTBI (Table 1). All participants were reassessed with the AUDIT, AUDIT-past-30-days, BDI, STAI, and FTND again at AP2.

Neurocognitive assessment

At both assessment points, participants completed a comprehensive neurocognitive battery (approximately 2 h), which evaluated neurocognitive functions known to be adversely affected by MTBI,[27] alcohol use disorders,[28] and chronic cigarette smoking.[29] sMTBI were allowed to smoke *ad libitum* before assessment and to take smoke breaks during assessments, if requested. At AP1 and AP2, the domains evaluated and the constituent measures were as follows: Executive skills: Short Categories Test,[30] Stroop Test: Color-Word,[31] Trail Making Test part B,[32] Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) Similarities,[33] Wisconsin Card Sorting

Table 1. Group Demographic and Clinical Variables

Variable	*Controls (n = 20)*	*Non-smoking MTBI (n = 25)*	*Smoking MTBI (n = 19)*
Age (years)	40.2 (9.4)	34.6 (12.1)	35.7 (10.9)
Education (years)	16.0 (2.0)	15.8 (2.4)	15.2 (2.2)
Caucasian (%)	70%	72%	74%
Male (%)	74	76	72
GCS 13/14/15 (%)	NA	4/28/68	6/26/68
Interval from injury to AP1 (days)	NA	40 (22)	36 (22)
Interval from injury to AP2 (days)	NA	230 (37)	231 (35)
Positive AP1 radiological findings (%)	NA	52	63
AMNART	119 (8)	119 (10)	119 (7)
Beck Depression Inventory	3.5 (3.4)	7.0 (7.9)	9.6 (6.7)
AUDIT-past-30-days	NA	4.7 (4.7)	8.7 (6.2)
AUDIT	2.2 (1.0)	8.0 (6.5)	13.4 (7.2)
STAI-State	30.0 (8.0)	33.5 (9.7)	35.2 (7.9)
STAI-Trait	35.1 (8.2)	36.4 (11.3)	38.6 (8.5)
FTND	NA	NA	3.5 (1.4)
Cigarettes/day	NA	NA	11 (6)
Total lifetime years of smoking	NA	NA	11.4 (7.5)
Pack years	NA	NA	7.0 (7.4)

MTBI, mild traumatic brain injury; GCS, Glasgow Coma Scale; AP1, assessment point 1; AP2, assessment point 2; AMNART, American National Adult Reading Test; AUDIT, Alcohol Use Disorders Identification Test; STAI, State-Trait Anxiety Inventory; FTND, Fagerstrom Test for Nicotine Dependence; Mean (standard deviation).

Test-64: Computer Version 2-Research Edition (non-perseverative errors, perseverative errors, and perseverative responses). Learning and memory: Auditory-verbal: California Verbal Learning Test-II (CVLT-II),[34] Immediate Recall trials 1–5 (learning), Short and Long Delay Free Recall (memory). Visuospatial: Brief Visuospatial Memory Test-Revised (BVMT-R),[35] Total recall (learning) and delayed Recall (memory). Processing speed: WAIS-III Digit Symbol, Stroop Test-Color & Word,[31] WAIS-III Symbol Search,[33] Trail Making Test-A.[32] Visuospatial skills: WAIS-III Block Design, Luria-Nebraska Item 99.[36] Estimated premorbid verbal intelligence: American National Adult Reading Test (AMNART).[37] Visuospatial skills: WAIS-III Block Design; Luria-Nebraska Item 99.[36] Working memory: WAIS-III Arithmetic, WAIS-III Digit Span. Premorbid verbal intelligence was estimated with the AMNART.[37]

Raw scores for the BVMT-R, CVLT-II, Short Categories Test, Stroop Color–Word Test, and WAIS-III subtests were converted to age-adjusted standardized scores via the normative data accompanying each test. WCST-64 variables and Trails A and B were converted to age-and-education adjusted standardized scores via Heaton Compendium Norms.[38] Standardized scores were then converted to z-scores for all measures. The score of domains with multiple measures represents the arithmetic mean of the individual z-scores of the constituent measures. A global neurocognitive score was calculated from the arithmetic mean of z-scores for all of the individual domains.

Magnetic resonance imaging

As part of this longitudinal study, all MTBI participants completed structural magnetic resonance imaging involving three-dimensional T1- and T2-weighted imaging and fluid attenuated inversion recovery (FLAIR) sequences. For this report, any MTBI participant, who demonstrated evidence of contusion or diffuse axonal injury on FLAIR at AP1 (defined as focal signal abnormalities in the cortex, white matter or gray/white matter boundary), was considered to have a positive radiological finding. FLAIR images were independently evaluated by two of the authors (GEG and TCD) with formal training and extensive experience in reading clinical and research MRIs of MTBI; there was 100% agreement between raters on the presence or absence of focal signal hyperintensities. The purpose of indentifying those with positive radiological findings was to determine if nsMTBI and sMTBI differed on the frequency of macroscopic structural indicators of brain trauma (e.g., contusion). Previous studies reported that those with positive neuroradiological findings in the acute/sub-acute stage (i.e., ''complicated'' MTBI) may have an increased risk for delayed or incomplete recovery after MTBI.[9] Results from morphological comparisons of these groups will be detailed elsewhere.

Data analyses

Cross-sectional. The Fisher exact test or pairwise *t* tests, where appropriate, assessed for group differences on demographic and clinical variables. Multivariate analyses of covariance (MANCOVA) examined effects of group (CON, non-smoking MTBI, and smoking MTBI) at AP1 and AP2 on the nine domains of neurocognition (Table 2); education, AMNART, and AUDIT scores served as primary covariates in cross-sectional analyses at AP1 and AP2. BDI, STAI were entered as covariates in secondary analyses. AP1 domain scores for CON were used in group comparisons at AP2, because only 10 CON were reassessed AP2, and CON showed no significant changes in any domain between AP1 and AP2. There were no significant differences among nsMTBI, sMTBI, and CON on education or AMNART. Nevertheless, because AMNART was a significant predictor of several neurocognitive domains in our previous work examining the influence of chronic smoking on neurocognition in alcohol use disorders,[39,40] we specifically examined if years of education and estimated premorbid verbal intellectual ability were significant predictors of performance in all group comparisons.

Significant MANCOVA omnibus effects ($p < 0.05$) for group were followed up with pairwise *t* tests among nsMTBI, sMTBI, and CON. Although we had specific *a priori* predictions, all group pairwise comparisons at AP1 and AP2 were corrected for multiplicity of tests. Significance levels ($p = 0.05$) for pairwise comparisons for each neurocognitive domain were adjusted according to the number of neurocognitive domains (i.e., nine) and the average intercorrelation among the domains for all groups (i.e., $r = 0.54$), resulting in a corrected p value $= 0.019$.[41] Effect sizes (ES) for pairwise comparisons at each AP were calculated via Cohen's *d*.[42] Associations between AUDIT and AUDIT-past-30-days were evaluated with bivariate correlations (Spearman Rho).

Table 2. Group Performance on Neurocognitive Domains

Domain	*Group*	*AP1 mean (SD)*	*AP2 mean (SD)*	*AP1-AP2 % change*	p *value AP1-AP2 change*	*AP1 effect size (Cohen's* d*)*	*AP2 effect size (Cohen's* d*)*
Auditory-verbal learning	CON	0.98 (0.96)	1.02 (1.02)	3.6	NS	CON vs. nsMTBI: 0.80	CON vs. nsMTBI: 0.34
	nsMTBI	0.23 (0.92)	0.64 (0.96)	7.8	0.04	CON vs. sMTBI: 0.69	CON vs. sMTBI: 0.74
	sMTBI	0.32 (0.96)	0.28 (0.93)	−0.8	NS	nsMTBI vs. sMTBI: 0.10	nsMTBI vs. sMTBI: 0.39
Auditory-verbal memory	CON	0.60 (0.89)	0.63 (0.95)	4.9	NS	CON vs. nsMTBI: 0.89	CON vs. nsMTBI: 0.36
	nsMTBI	−0.20 (0.92)	0.27 (0.97)	9.8	0.03	CON vs. sMTBI: 0.82	CON vs. sMTBI: 0.70
	sMTBI	−0.15 (0.92)	−0.08 (0.97)	1.5	NS	nsMTBI vs. sMTBI: 0.10	nsMTBI vs. sMTBI: 0.36
Executive skills	CON	0.07 (0.67)	0.07 (0.72)	3.3	NS	CON vs. nsMTBI: 0.15	CON vs. nsMTBI: 0.12
	nsMTBI	−0.03 (0.68)	0.15 (0.63)	3.6	0.08	CON vs. sMTBI: 0.53	CON vs. sMTBI: 0.02
	sMTBI	−0.28 (0.67)	0.08 (0.62)	7.8	0.01	nsMTBI vs. sMTBI: 0.38	nsMTBI vs. sMTBI: 0.11
Processing speed	CON	0.17 (0.63)	0.17 (0.69)	0.3	NS	CON vs. nsMTBI: 0.66	CON vs. nsMTBI: 0.05
	nsMTBI	−0.25 (0.65)	0.14 (0.67)	8.2	<0.01	CON vs. sMTBI: 0.47	CON vs. sMTBI: 0.33
	sMTBI	−0.13 (0.63)	−0.05 (0.67)	1.6	NS	nsMTBI vs. sMTBI: 0.19	nsMTBI vs. sMTBI: 0.28
Visuospatial learning	CON	0.04 (0.94)	0.04 (0.99)	1.3	NS	CON vs. nsMTBI: 0.44	CON vs. nsMTBI: 0.36
	nsMTBI	−0.40 (1.01)	0.48 (0.74)	19.2	<0.01	CON vs. sMTBI: 0.02	CON vs. sMTBI: 0.01
	sMTBI	0.06 (1.01)	0.05 (0.74)	−0.3	NS	nsMTBI vs. sMTBI: 0.46	nsMTBI vs. sMTBI: 0.59
Visuospatial memory	CON	0.15 (1.07)	0.15 (1.12)	1.9	NS	CON vs. nsMTBI: 0.49	CON vs. nsMTBI: 0.32
	nsMTBI	−0.39 (1.08)	0.43 (0.72)	18.0	0.01	CON vs. sMTBI: 0.23	CON vs. sMTBI: 0.31
	sMTBI	0.40 (1.09)	0.38 (0.72)	−0.4	NS	nsMTBI vs. sMTBI: 0.72	nsMTBI vs. sMTBI: 0.08
Visuospatial skills	CON	0.28 (0.94)	0.29 (1.00)	4.5	NS	CON vs. nsMTBI: 0.23	CON vs. nsMTBI: 0.05
	nsMTBI	0.06 (0.94)	0.44 (0.94)	7.4	0.05	CON vs. sMTBI: 0.21	CON vs. sMTBI: 0.33
	sMTBI	0.47 (0.95)	0.44 (0.95)	−0.6	NS	nsMTBI vs. sMTBI: 0.44	nsMTBI vs. sMTBI: 0.28
Working memory	CON	0.53 (0.74)	0.53 (0.79)	2.0	NS	CON vs. nsMTBI: 0.37	CON vs. nsMTBI: 0.05
	nsMTBI	0.25 (0.73)	0.49 (0.75)	4.6	NS	CON vs. sMTBI: 0.71	CON vs. sMTBI: 0.33
	sMTBI	0.00 (0.74)	0.15 (0.75)	2.9	NS	nsMTBI vs. sMTBI: 0.34	nsMTBI vs. sMTBI: 0.28
Global Neuro-cognition	CON	0.35 (0.56)	0.36 (0.59)	1.9	NS	CON vs. nsMTBI: 0.85	CON vs. nsMTBI: 0.12
	nsMTBI	−0.12 (0.55)	0.39 (0.46)	11.0	<0.01	CON vs. sMTBI: 0.47	CON vs. sMTBI: 0.42
	sMTBI	0.09 (0.54)	0.16 (0.46)	1.3	NS	nsMTBI vs. sMTBI: 0.37	nsMTBI vs. sMTBI: 0.55

AP1, assessment point 1; AP2, assessment point 2; CON, non-smoking controls; nsMTBI, non-smoking mild traumatic brain-injured participants; sMTBI, non-smoking mild traumatic brain-injured participants; p values > 0.10 listed as not significant (NS).

For sMTBI, associations between the nine neurocognitive domains, FTND score, cigarettes smoked per day, pack-years, and lifetime years of smoking were examined with multiple linear regression (semi-partial coefficients are reported), controlling for AUDIT or AUDIT-past-30-days.

Longitudinal. Comparisons of longitudinal change between nsMTBI and sMTBI on neurocognitive domains across the AP1-AP2 interval were conducted with linear mixed modeling. Education, AMNART, and AUDIT scores served as primary covariates. BDI and STAI scores were entered as covariates in secondary analyses. Main effects and interactions were considered to be statistically significant at $p < 0.05$. Paired t tests for nsMTBI and sMTBI were corrected for multiple comparisons as described in the Cross-Sectional section. Changes between AP1 and AP2 in AUDIT, AUDIT-past-30-days, BDI, and STAI for nsMTBI and sMTBI were also evaluated with linear mixed models. Ten CON were reassessed on neurocognitive measures 255 ± 55 days after their baseline assessment. Paired t tests for CON were corrected for multiple comparisons as described in the above Cross-Sectional section. Statistical analyses were completed with SPSS v 19.0.

Results

Participant demographic and clinical variables

Forty-three percent of MTBI participants were chronic smokers. sMTBI and nsMTBI participants were younger than CON (both $p < 0.05$). At AP1, sMTBI had higher BDI than CON. sMTBI and nsMTBI showed higher AUDIT than CON; sMTBI had a higher AUDIT-past-30-days than nsMTBI. Groups were equivalent on education, AMNART score, ethnic frequency, and STAI-state-and-trait scores. The foregoing findings were identical at AP2. nsMTBI and sMTBI were not significantly different on the interval from injury to AP1 or AP2, on the frequency of GCS scores (13/14/15), or on the proportion of positive radiological findings at AP1 (Table 1).

AP1 Cross-sectional comparisons

MANCOVA yielded a significant effect for group on the following measures: visuospatial memory ($F[2, 60] = 3.20$, $p = 0.049$), auditory-verbal learning ($F[2, 60] = 3.63$, $p = 0.033$), auditory-verbal memory ($F[2, 60] = 5.00$, $p = 0.010$), and global neurocognition ($F[2, 60] = 3.99$, $p = 0.024$), with trends for processing speed ($p = 0.081$), and working memory ($p = 0.096$). Planned pairwise comparisons indicated that nsMTBI and sMTBI were inferior to CON on auditory-verbal learning and auditory-verbal memory (both $p < 0.019$). nsMTBI performed more poorly than CON on processing speed and global neurocognition (both $p \leq .0019$), and worse than sMTBI on visuospatial memory ($p = 0.019$). sMTBI performed worse than CON on working memory ($p < 0.019$). AMNART was a significant predictor of all domains (all $p < 0.024$), where higher AMNART scores were associated with better performance. Education, AUDIT, AUDIT-past-30-days, and measures of depressive (i.e., BDI) and anxiety (i.e., STAI State and Trait) symptomatology were not significant predictors of any domain at AP1, and did not alter the differences among CON, nsMTBI, and sMTBI reported above. The performance of persons with previous MTBI and premorbid heavy substance use were within ± 0.5 standard deviation of the MTBI group mean on all domains.

Longitudinal comparison

nsMTBI vs. sMTBI. Significant group (nsMTBI, sMTBI) × AP (AP1, AP2) interactions were observed for the following domains: processing speed ($F[1, 34] = 5.66$, $p = 0.023$), visuospatial learning ($F[1, 37] = 6.55$, $p = 0.015$), visuospatial memory ($F[1, 34] = 4.23$, $p = 0.048$), visuospatial skills ($F[1, 48] = 4.81$, $p = 0.033$), and global neurocognition ($F[1, 32] = 5.47$, $p = 0.026$). nsMTBI showed significant improvement on processing speed, visuospatial learning, visuospatial memory, and global neurocognition over the AP1-AP2 interval (all $p < 0.019$), with trends for improved visuospatial skills ($p = 0.044$). sMTBI showed no significant improvement on any of the above domains (all $p > 0.10$). These findings indicate the group × AP interactions were driven by significant improvements in nsMTBI. See Figure 1 for the general pattern of change demonstrated by groups.

Main effects for AP were seen for executive skills ($p < 0.019$), where sMTBI showed significant improvement ($p < 0.019$) and nsMTBI demonstrated a trend for improvement ($p = 0.05$). No main effects for AP were apparent for auditory-verbal learning, auditory-verbal memory, or working memory, indicating the MTBI group, as a whole, did not show statistically significant recovery on these domains over the AP1-AP2 interval. nsMTBI, however, showed trends for improvement on auditory-verbal learning ($p = 0.04$) and auditory-verbal memory ($p = 0.03$). AMNART was a significant predictor of all domains (all $p < 0.019$), where higher AMNART scores were associated with greater improvement in performance. AUDIT-past-30-days showed trends for associations with executive skills ($p = 0.056$) and auditory-verbal learning (both $p = 0.071$), where higher scores were related to less improvement on these domains. AUDIT and measures of depressive and anxiety symptomatology were not significant predictors of change for any neurocognitive domain over the AP1-AP2 interval.

There were no significant changes observed in the MTBI groups for AUDIT, AUDIT-past-30-days, BDI, and STAI (State and Trait). The FTND and cigarettes smoked per day in sMTBI did not change significantly from AP1 to AP2.

CON. No significant changes were observed for CON ($n = 10$) on any domain (all $p > 0.20$), reflecting generally stable neurocognitive performance in this small subsample across the AP1-AP2 interval (see Table 2).

AP2 Cross-sectional comparisons

MANCOVA yielded trends for group main effect for auditory-verbal learning ($F[1, 50] = 2.44$, $p = 0.097$] and auditory-verbal

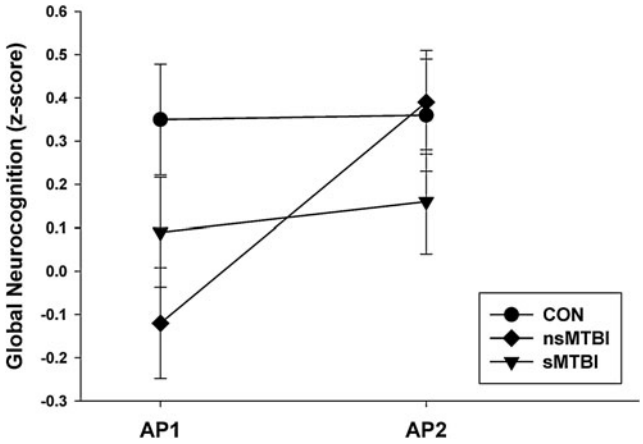

FIG. 1. Longitudinal change in global neurocognition. AP1, assessment point 1; AP2, assessment point 2; CON, controls; nsMTBI, non-smoking mild traumatic brain-injured participants; sMTBI, smoking mild traumatic brain-injured participants.

memory (F[1, 50] = 2.43, $p = 0.097$]. Planned pairwise comparisons showed sMTBI were inferior to CON on auditory-verbal learning and auditory-verbal memory (both $p < 0.019$). There were no significant differences between nsMTBI and CON or among nsMTBI and sMTBI on any domain at AP2. AMNART was a significant predictor of all domains (all $p < 0.036$), where higher AMNART scores were related to better performance. AUDIT and AUDIT-past-30-days depressive (i.e., BDI) and anxiety symptomatology (i.e., STAI State and Trait) were not significant predictors of any domain at AP2.

Associations of hazardous/harmful alcohol consumption, and smoking severity with cross-sectional and longitudinal neurocognitive measures

Cross-sectional. At AP1, higher AUDIT-past-30-days score was related to poorer executive skills (Rho = −0.39; $p = 0.009$) in the whole MTBI cohort (i.e., nsMTBI and sMTBI combined); nsMTBI and sMTBI individually showed a similar magnitude of correlation. At AP2, AUDIT scores did not correlate significantly with neurocognition. For sMTBI, at AP1 and AP2, greater lifetime duration of smoking and pack-years (controlled for AUDIT or AUDIT-past-30-days score) were associated with poorer performance on visuospatial learning, visuospatial memory, visuospatial skills, working memory, and global neurocognition; these relationships were moderate to strong in magnitude (Table 3). Level of nicotine dependence (i.e., FTND score) at AP1 or AP2 was not significantly related to neurocognition.

Longitudinal. In sMTBI, over the 7-month interval, greater lifetime duration of smoking (controlled for AUDIT scores) was related to significantly less improvement on visuospatial learning ($\beta = -0.10$, standard error (SE) = 0.02, $p < 0.001$), visuospatial memory ($\beta = -0.07$, SE = 0.02, $p < 0.001$), working memory ($\beta = -0.08$, SE = 0.03, $p < 0.01$), visuospatial skills ($\beta = -0.08$, SE = 0.03, $p < 0.001$), and global cognition ($\beta = -0.05$, SE = 0.02, $p < 0.016$). Higher pack years (controlled for AUDIT score) was related to less improvement on visuospatial learning ($\beta = -0.09$, SE = 0.03, $p < 0.004$), and visuospatial memory ($\beta = -0.05$, SE = 0.03, $p < 0.033$). Virtually identical results were observed when these associations were controlled for AUDIT-past-30-days. Again, level of nicotine dependence was not related to change on any neurocognitive domain.

Table 3. Relationships Between Measures of Smoking Severity and Performance on Neurocognitive Domains for sMTBI at Assessment Point 1 and Assessment Point 2

Smoking severity measure	*Domain*	*AP*	*r**	p *value*
Lifetime duration of smoking (years)	Visuospatial learning	1	−0.71	< 0.01
		2	−0.50	0.02
	Visuospatial memory	1	−0.52	0.01
		2	−0.44	0.04
	Visuospatial skills	1	−0.55	0.01
		2	−0.53	0.02
	Working memory	1	−0.48	0.02
		2	−0.34	0.10
	Global neurocognition	1	−0.51	0.02
		2	−0.59	< 0.01
Pack-years	Visuospatial learning	1	−0.55	< 0.01
		2	−0.55	0.01
	Visuospatial Memory	1	−0.37	0.06
		2	−0.46	0.04
	Visuospatial skills	1	−0.44	0.03
		2	−0.43	0.04
	Working memory	1	−0.51	0.02
		2	−0.43	0.04
	Global neurocognition	1	−0.37	0.06
		2	−0.56	0.01
Cigarettes smoked/day	Working memory	1	−0.48	0.02
		2	−0.47	0.03

*Semi-partial correlation coefficients controlling for AUDIT; AP: assessment point; p < .05 is considered statistically significant.

Discussion

The primary findings in this longitudinal study of neurocognitive changes over approximately 7 months in MTBI persons were as follows: (1) At AP1 (approximately 38 days post-injury), nsMTBI and sMTBI were inferior to CON on measures of auditory-verbal learning and auditory-verbal memory; nsMTBI performed more poorly than CON on processing speed and global neurocognition and sMTBI performed poorer than CON on working memory; nsMTBI were inferior to sMTBI on visuospatial memory. Moderate to strong effect sizes were apparent for the above group differences. (2) Over the AP1-AP2 interval, nsMTBI showed significantly greater improvement than sMTBI on measures of processing speed, visuospatial learning and memory, visuospatial skills, and global neurocognition, whereas CON ($n = 10$) showed no significant changes on any neurocognitive domain over the AP1-AP2 interval. (3) At AP2 (approximately 7 months post-injury), sMTBI remained inferior to CON on auditory-verbal learning and auditory-verbal memory, and these group differences showed moderate effect sizes; there were no significant differences between nsMTBI and CON or among nsMTBI or sMTBI on any domain at AP2. (4) For sMTBI, greater lifetime duration of smoking and pack-years were related to significantly less improvement on multiple domains over the AP1-AP2 interval; similarly, at AP1 and AP2, greater lifetime duration of smoking and pack-years were associated with poorer performance on multiple neurocognitive domains. (5) Forty-three percent of the MTBI sample were chronic smokers; 59% of MTBI participants demonstrated hazardous/harmful levels of alcohol consumption at AP1, and 62% at AP2.

The most clinically relevant findings were the significantly greater recovery shown by nsMTBI compared with sMTBI on measures of processing speed, visuospatial learning and memory, visuospatial skills, and global neurocognition. The differential recovery demonstrated by these groups was not mediated by education, estimated premorbid verbal intelligence (i.e., AMNART), hazardous alcohol consumption (i.e., AUDIT scores), or depressive (i.e., BDI) and anxiety (i.e., STAI) symptomatology. Further, nsMTBI and sMTBI did not differ on the frequency of positive radiological findings or GCS scores at AP1, indicating the greater improvements shown by nsMTBI across the AP1-AP2 interval were not attributable to baseline group differences in macrostructural indicators of injury severity. nsMTBI showed steep improvement on processing speed, visuospatial learning and memory, visuospatial skills, and global neurocognition, with trends for improvement on auditory-verbal learning and memory. The percent change on these domains demonstrated by nsMTBI were substantially larger than CON, suggesting the increases exhibited by nsMTBI were beyond measurement error and/or practice effects. The modest-sized group of CON with follow-up assessment

evidenced no significant changes in any domain over the AP1-AP2 interval. sMTBI, essentially showed a flat trajectory over the 7-month interval for all domains, except for improved executive skills. The overall pattern exhibited by nsMTBI and sMTBI over the AP1-AP2 interval indicates that chronic smoking in this cohort of MTBI was associated with significantly diminished recovery in multiple neurocognitive domains over approximately 7 months post-injury.

The group differences observed at AP1 and AP2 were not influenced by education, estimated premorbid intelligence, hazardous alcohol consumption, or depressive and anxiety symptomatology. Although, nsMTBI and sMTBI performed worse than CON on the auditory-verbal learning and auditory-verbal memory domains at AP1, the performance of the MTBI groups was in the average range of function (42nd–58th percentile). Similarly, the performance of nsMTBI and sMTBI on executive skills, processing speed, visuospatial learning and memory, working memory, and global neurocognition at AP1 were in the average range (34th–66th percentile). CON performed in the average range on all domains (50th–73rd percentile), except auditory-verbal learning, which was in the high average (84th percentile) range of function. At AP2, sMTBI continued to perform significantly worse than CON on auditory-verbal learning and memory. Alternately, auditory-verbal learning and memory in nsMTBI improved over the AP1-AP2 interval, and nsMTBI showed no significant differences from CON on any domain at AP2. There were no significant differences between nsMTBI and sMTBI on any domain at AP2, and, similar to AP1, the performance of both these groups was in the average range of functioning (46th–74th percentile) on all domains at AP2. The overall results for MTBI at AP2 are consistent with previous research indicating that the acute/sub-acute neurocognitive sequelae of MTBI are largely resolved after approximately 3 months post-injury.[4]

For sMTBI, greater lifetime duration of smoking was related to less improvement on the domains of visuospatial learning and visuospatial memory, visuospatial skills, working memory, and global neurocognition, and greater pack-years was inversely associated with improvement on visuospatial learning and memory and visuospatial skills. At AP1 and AP2, greater lifetime duration of smoking and pack-years were moderately-to-strongly related to poorer performance on the domains of visuospatial learning and visuospatial memory, visuospatial skills, working memory, and global neurocognition. These findings suggest that greater smoking chronicity over lifetime in sMTBI, but not level of nicotine dependence (as measured with the FTND), was robustly associated with poorer neurocognitive recovery and lower performance on multiple measures at AP1 and AP2.

Previous research with normal controls showed greater duration of smoking over lifetime and/or dose-duration (i.e., pack-years) were inversely related to multiple domains of neurocognition in adults across a wide age range.[29] The current findings also show remarkable similarity to our studies with smoking alcohol dependent persons, where longer duration of smoking over lifetime was associated with poorer performance on measures of processing speed, visuospatial skills, and visuospatial learning and memory,[39] as well as with decreased neurocognitive recovery over approximately 8 months of abstinence from alcohol.[43]

The elevated AUDIT scores in the MTBI cohorts underscore the importance of assessing for pre-injury hazardous/harmful alcohol consumption given that across the spectrum of TBI severity, 50–70% of cases have a history of heavy alcohol use or abuse/dependence.[12] Pre-injury alcohol consumption and related problems are strongly associated with post-injury use and problems,[44] and persons with lower severity TBI tend to show similar levels of alcohol consumption over 1 year post-injury,[6] which is consistent with the findings from this report. In addition, chronic cigarette smoking is associated with significantly higher quantity and frequency of alcohol consumption.[45] It is important to note that, despite mean AUDIT scores for both nsMTBI and sMTBI that were indicative of a hazardous level of alcohol consumption, none of the participants in the current study reported pre- or-post-injury treatment for an alcohol use disorder.

There are several potential mechanisms that may operate independently or concurrently to promote the diminished neurocognitive improvement and the associations of smoking severity measures and neurocognition in sMTBI. Nicotine is only one of more than 4000 compounds composing the particulate and gas phases of cigarette smoke.[46–48] While nicotine underlies the addictive properties of tobacco,[49–53] the adverse effects of chronic smoking appear to be related to the persistent exposure of multiple peripheral organ systems and the brain to the toxic combustion products in cigarette smoke.[16, 54–57] The multitude of potentially cytotoxic compounds in cigarette smoke (e.g., carbon monoxide, aldehydes, ketones, nitrosamines, dihydroxybenzenes)[56] may directly compromise neuronal and cellular membrane function of cerebral tissue. The gas and particulate phases of cigarette smoke contain high levels of reactive oxygen species (ROS), reactive nitrogen species (RNS) and oxidizing agents (e.g., hydrogen peroxide), and these compounds in the particulate phase are long-lived (hours to weeks).[48,58]

Smoking increases plasma carbon monoxide levels[59] and alters mitochondrial respiratory chain function,[60] both of which increase oxidative stress. Chronic smoking induces nuclear factor-κB (NF-κB), resulting in amplified cerebral proinflammatory cytokine levels and radical generation by peripheral and central nervous system glial cells.[61] *In vivo* chronic cigarette smoke exposure is also associated with decreased concentrations of enzyme-based free radical scavengers (e.g., superoxide dismutase, catalase, glutathione reductase) and non-enzyme–based radical scavengers (e.g., glutathione and vitamins A, C, and E) concentrations in animal models [62,63] and humans.[64–69] This may render brain tissue more vulnerable to oxidative damage by radical species generated by normal cellular metabolism or other exogenous sources (e.g., increased oxidative stress secondary to TBI). The brain, in general, is highly susceptible to oxidative damage because of high levels of unsaturated fatty acids in the composition of cell membranes and myelin. Thus, chronic smoking may promote neuronal/glial injury and neurodegeneration in the human brain via increased oxidative stress. The entire range of TBI severity is associated with increased oxidative stress during the acute and sub-acute post-injury phases.[3,70,71]

We postulate that smoking in MTBI provides a significant and sustained direct source of exogenous free radical species and other oxidizing agents. Therefore, continued smoking after injury will increase cerebral oxidative stress, which may hinder neurobiological recovery, and, by extension, adversely affect neurocognitive recovery in sMTBI. For further discussion of potential biological mechanisms contributing to smoking-related neurocognitive dysfunction, see articles by Durazzo and colleagues.[16,29]

This study has limitations that may affect the generalizability of the findings. The sample size for this report was modest and did not provide sufficient numbers of participants to evaluate for sex differences. TBI participants were assessed 38 ± 22 after injury at AP1. Given that the greatest neurocognitive dysfunction is typically apparent during the initial 14 days after injury in MTBI,[9] a significant amount of recovery across domains may have occurred by AP1. Consequently, the actual magnitudes of change since the

time of injury observed at AP2 may be underestimated for both TBI groups. A smoking control group was not included; therefore, it is not known if chronic smoking was independently associated with neurocognition in cross-sectional analyses and longitudinal analyses. Although all MTBI participants were screened for major psychiatric syndromes, and measures of mood and anxiety symptomatology were not significantly different between nsMTBI and sMTBI, participants did not complete a full standardized structured diagnostic interview for DSM-IV Axis I disorders. In addition, we did not assess for potential group differences in nutrition, exercise, and genetic predispositions, which may have influenced performance on the neurocognitive domains evaluated in this study.

Conclusions

Chronic cigarette smoking in this cohort of MTBI participants, but not hazardous/harmful alcohol consumption, was associated with diminished recovery on multiple neurocognitive domains, and persistently poorer performance on measures of auditory-verbal leaning and auditory-verbal memory at 7 months post-injury. In addition, greater smoking severity in sMTBI was related to both poorer recovery and performance at baseline and follow-up on multiple domains. It is recommended that future studies include a group of smoking CON to specifically assess for the additive and/or synergistic effects of smoking status on longitudinal recovery in MTBI. In addition, inclusion of alcohol quantity and frequency measures (e.g., Lifetime Drinking History[72]) is necessary to better understand the influence of hazardous/harmful alcohol consumption on neurocognitive recovery in MTBI.

Comparisons of nsMTBI and sMTBI (with the appropriate nonsmoking and smoking CON) on diffusion tensor imaging measures, susceptibility-weighted imaging, regional brain metabolite makers of oxidative stress and neuronal integrity, and cerebral perfusion can assist with identification of the neurobiological correlates of the smoking-related neurocognitive findings observed in this study.

Chronic smoking and hazardous alcohol consumption are modifiable health risks, representing the first and third leading causes, respectively, of preventable mortality in the United States.[73,74] A better understanding of their potential influence on neurocognitive and neurobiological recovery from MTBI may inform the design of targeted pharmacological (prophylaxis and/or acute treatment with antioxidants and anti-inflammatory agents) and behavioral (i.e., smoking cessation programs, treatment of hazardous drinking levels) interventions to facilitate maximum rate and magnitude of recovery after MTBI.

Future research to assess the effects of smoking cessation on neurocognitive recovery after MTBI is clearly warranted. A greater understanding of the factors that influence the neurobiological and neurocognitive recovery after MTBI is also of critical importance to the U.S. Armed Services to support informed decisions in theater regarding the optimal timing for return to duty after MTBI, particularly for persons involved in combat operations.

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