Pain Medicine, 20(11), 2019, 2198–2207
doi: 10.1093/pm/pnz058
Advance Access Publication Date: 2 April 2019
Original Research Article

An Exploratory Study of Endogenous Pain Modulatory Function in Patients Following Mild Traumatic Brain Injury

Christopher Carey, MS,* Jonathan Saxe, MD,† Fletcher A. White, PhD,‡,§ and Kelly M. Naugle, PhD*

*Department of Kinesiology, School of Health and Human Sciences, Indiana University Purdue University Indianapolis, Indianapolis, Indiana; †Trauma Department, St. Vincent Indianapolis Hospital, Indianapolis, Indiana; ‡Department of Anesthesia, School of Medicine, Indiana University Indianapolis, Indianapolis, Indiana; §Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, Indiana, USA

Funding sources: This research was funded by the Indiana State Department of Health's Indiana Spinal Cord and Brain Injury Fund Research Grant Program (KMN and FAW) and the St. Vincent Foundation (FAW).

Conflicts of interest: The authors have no conflicts of interest to declare.

Correspondence to: Kelly M. Naugle, PhD, Department of Kinesiology, School of Health and Human Sciences, Indiana University Purdue University Indianapolis, 901 W New York St., Indianapolis, IN 46202, USA. Tel: 317-274-0601; Fax: 317-278-2041; E-mail: kmnaugle@iupui.edu.

Abstract

Background. Recent animal research suggests that mild traumatic brain injury (mTBI) facilitates abnormal endogenous modulation of pain, potentially underlying the increased risk for persistent headaches following injury. However, no human studies have directly assessed the functioning of endogenous facilitory and inhibitory systems in the early stages after an mTBI. **Objective.** The purpose of this exploratory study was to examine trigeminal sensitization and endogenous pain inhibitory capacity in mTBI patients in the acute stage of injury compared with matched controls. We also examined whether post-traumatic headache pain intensity within the mTBI sample was related to sensitization and pain inhibitory capacity. **Methods.** Twenty-four mTBI patients recruited from emergency departments and 21 age-, race-, and sex-matched controls completed one experimental session. During this session, participants completed quantitative sensory tests measuring trigeminal sensitization (pressure pain thresholds and temporal summation of pain in the head) and endogenous pain inhibition (conditioned pain modulation). Participants also completed validated questionnaires measuring headache pain, depression, anxiety, and pain catastrophizing. **Results.** The results revealed that the mTBI group exhibited significantly decreased pressure pain thresholds of the head and decreased pain inhibition on the conditioned pain modulation test compared with the control group. Furthermore, correlational analysis showed that the measures of trigeminal sensitization and depression were significantly associated with headache pain intensity within the mTBI group. **Conclusions.** In conclusion, mTBI patients may be at risk for maladaptive changes to the functioning of endogenous pain modulatory systems following head injury that could increase risk for post-traumatic headaches.

Key Words: Conditioned Pain Modulation; Post-traumatic Headache; Brain Injury; Temporal Summation of Pain

Introduction

Traumatic brain injury (TBI) is one of the leading causes of disability and even death in the United States [1]. More than 1 million traumatic brain injuries (TBIs) occur in adults each year in the United States, and mild TBIs (mTBI) account for at least 79% of those injuries [2]. Mild TBI is an injury to the brain usually caused by a mild blow to the head or a violent shaking of head or body. Although the immediate symptoms of mTBI (e.g., disorientation and confusion, short-term memory loss, dizziness) usually dissipate rapidly, long-term complications can develop. Post-traumatic headache (PTH) is one of the worst, most prominent, and longest-lasting complications of mild TBI, and it seriously complicates rehabilitative efforts in civilian and military populations [3]. Post-traumatic headache is defined as a secondary headache that develops within seven days after the head trauma and is considered chronic when the headache

lasts more than three months after the head injury [4]. Prevalence rates of PTH range from 47% to 95% following mTBI in adult and pediatric populations [5,6]. Furthermore, a longitudinal study revealed that the cumulative incidence of headache over one year following an mTBI was 71–91% [5]. Despite its high prevalence and disruption to recovery, the pathophysiology of PTH following mTBI is still not well understood.

Clinical pain reflects to a substantial extent the interplay of complex endogenous systems that both facilitate and inhibit pain. In many chronic pain conditions, including chronic headache conditions, the interplay of these endogenous systems becomes unbalanced, characterized by deficient descending pain inhibition and enhanced excitability of central nociceptive circuits that elicits pain hypersensitivity (i.e., central sensitization) [7–9]. Recent animal and human research suggests that mTBI may facilitate altered and unbalanced endogenous modulation of pain, perhaps underlying the increased the risk of intense and persistent headaches following injury. Indeed, Sahbaie et al. revealed increased sensitization to noxious mechanical stimuli in mice following mTBI, which lasted about two weeks [10]. Additionally, mice with the mTBI exhibited greatly diminished descending inhibition of pain, as measured by diffuse noxious inhibitory controls, compared with a sham condition. In line with this animal study, a recent cross-sectional human study found that mTBI patients with chronic PTH had diminished pain inhibitory capacity on a dynamic quantitative sensory test compared with control groups [11]. Furthermore, the magnitude of headache pain intensity correlated negatively with the magnitude of pain inhibition. Despite the potential for disrupted endogenous pain modulation following mTBI and its implications for PTHs, no human studies have directly assessed the state of these endogenous facilitory and inhibitory pain systems in the early stages following an mTBI.

The primary purpose of this cross-sectional study was to explore early pain modulatory profiles (trigeminal sensitization and endogenous pain inhibitory capacity) after mTBI that may serve as vulnerability biomarkers for PTHs. Central sensitization and descending pain inhibitory capacity were measured with established quantitative sensory tests. We hypothesized that mTBI patients, within two weeks of head injury, would exhibit greater trigeminal sensitivity and deficient pain inhibitory capacity on dynamic quantitative sensory tests compared with sex-, age-, and race-matched controls. We also hypothesized that greater sensitization and poorer pain inhibition would be associated with greater intensity of PTHs in the mTBI sample. Because clinical pain is often related to psychological variables, we also assessed several psychological outcomes (i.e., depression, anxiety, pain catastrophizing) and examined the relationship of these variables with pain modulation and headache pain intensity in mTBI patients.

Methods

Participants

Twenty-four participants with mTBI participated in this study (29.42 ± 8.4 years, 16 females). The racial composition of the sample included six African Americans, 13 Caucasians, three Hispanics, and two other. These participants had to have an mTBI diagnosis according to the criteria recommended by the World Health Organization Task Force [12]: 1) a Glasgow Coma Scale score between 13 and 15 when examined at the emergency center; 2) no abnormal findings on a computed tomography scan of the brain to exclude secondary disorders such as hematoma, cerebral vein thrombosis, cerebral hemorrhage, or epilepsy; and 3) the presence of one or more of the following: confusion or disorientation, post-traumatic amnesia for less than 24 hours, or a loss of consciousness for less than 30 minutes. The mTBI could not be due to drugs, alcohol, medications, caused by other injuries or treatments for other injuries, caused by other problems (i.e., coexisting medical conditions, psychological trauma), or a penetrating craniocerebral injury.

Twenty-one control participants also participated in this study (29.33 ± 8.4 years; 14 females). The racial composition of the sample included five African Americans, 13 Caucasians, two Hispanics, and one other. Control participants could not have experienced a previous TBI and were sex-, age-, and race-matched to mTBI patients. Exclusion criteria for all participants included chronic cardiovascular disease or uncontrolled hypertension, metabolic disease, renal disease, neurological disease, serious psychiatric conditions or hospitalization within the preceding year for psychiatric illness, chronic headaches (before the head injury for mTBI participants), current involvement in litigation, current use of narcotics, and chronic opioid use. Polytrauma was also an exclusion criterion for the mTBI group.

Recruitment

The mTBI participants were recruited from Level 1 trauma centers within hospitals located in the Indianapolis area. Potentially eligible patients had their electronic medical records screened by study recruiters to identify patients who met the inclusion/exclusion criteria. An mTBI diagnosis was also confirmed by the attending emergency department (ED) physician. Potentially eligible patients were then approached in the emergency room and handed a study information sheet describing important details of the study. If the patient expressed interest in the research, his/her identification was put into a secure database. At this point, the research staff would contact the potential participant within 48 hours by phone or e-mail to review the inclusion and exclusion criteria again and give particular details of the study to the potential participant. For those still interested, the laboratory session was scheduled within two weeks of the injury. Approximately 33% of patients who were entered

into the database by the recruitment staff were enrolled in this study.

Control participants were recruited directly by the research staff based on the mTBI participants' demographics. The researcher recruited individuals from the university's campus and local community with flyers and e-mail advertisements.

Procedures

The Indiana University and St. Vincent Indianapolis Hospital Human Subject Review Boards approved this study. During the laboratory session, participants reviewed and signed a written informed consent form approved by the institutional review board. To verify that participants met inclusion/exclusion criteria, participants completed a health history questionnaire, supplemented by interview and blood pressure measurement. Once eligibility was verified, participants completed several questionnaires and quantitative sensory tests (QSTs). These assessments are described below. All participants were asked to refrain from pain relief medication and consuming caffeine on the day of testing before their session. All assessments were conducted by one investigator.

Measures of Pain Modulatory Function

At the beginning of the QST portion of the session, subjects were made familiar with each sensory test to be performed and were taught the 0–100 pain rating system. After the familiarization portion of the session, the tests of central sensitization (pressure pain hyperalgesia, temporal summation of pain) were performed first, followed by the CPM test. A minimum of 10 minutes separated each central sensitization and CPM test.

Central Sensitization Measures. Several quantitative sensory tests in human experimental studies have been used to identify the presence of central sensitization, including temporal summation of pain and generalized pressure hyperalgesia [13].

Pressure Pain Hyperalgesia of the Head/Neck Area. Pressure pain thresholds (PPTs) were tested on the following five sites of the head and neck areas, as has been conducted in prior research [7]: 1) middle of the forehead, 2) left temple, 3) parietal area (top of the head), 4) posterior neck/C2, and 5) left trapezius. A digital, handheld, clinical grade pressure algometer (AlgoMed, Medoc Advanced Medical Systems, Durham, NC, USA) with a 1.0-cm^2 probe was used for the mechanical procedures. During the test, the device was placed against the skin of one of the five sites, and pressure was gradually increased at a slow constant rate (30 kPA/s). The participant was instructed to verbally signal when (s)he first experienced pain caused by the pressure device, at which time the algometer was removed. Two trials were performed at each site, with 20-second intervals between each trial. The PPTs at all sites were averaged for a single PPT score (PPT-Head) to be used in the data analysis [7].

Mechanical Temporal Summation. Temporal summation can be assessed by administering short-duration repeated noxious stimuli of a constant intensity and measuring the consequent increase in pain as an indirect method of evaluating hyperexcitability of the central nervous system [13]. Mechanical temporal summation was tested on the back of the hand and on the forehead using a von Frey filament of 6.65 mN (300 g). First, a single pinprick stimulus using the von Frey filament was applied to the body site. Participants rated the perceived pain intensity using a numeric rating scale (NRS) of 0 = no pain at all to 100 = worst pain imaginable. Then, a series of 10 pinprick stimuli using the same monofilament was administered at a rate of one tap per second, applied to the body site within an area of 1 cm^2. Participants were asked to immediately rate the greatest pain intensity experienced during the 10 pinprick stimuli using the 0–100 NRS. The temporal summation value was calculated as the difference between the pain rating after the 10 stimuli and the first stimulus. This procedure was repeated twice at each body site with a 60-second rest interval between trials. The two trials at each site were averaged for a single MTS-Hand and MTS-Forehead score.

Conditioned Pain Modulation. The most frequently used test of endogenous pain inhibition in humans is condition pain modulation (CPM). CPM refers to the reduction of pain produced by a test stimulus by a second noxious conditioning stimulus in a remote body site (i.e., "pain inhibition by pain") [14,15]. For the CPM test, pressure pain thresholds (test stimulus) on the left arm were measured before and immediately after the submersion of the right hand in a cold water bath (conditioning stimulus). Seven minutes separated the pre-PPT trials and the initiation of the conditioning stimulus, during which the participants sat quietly. This period of rest was included to prevent within-session adaptation, as prior work has shown complete recovery of primary afferent responsiveness after 10 minutes of no pain stimulation [16].

Test Stimulus. The test stimulus was PPTs administered on the left volar forearm. Using a digital, handheld, clinical grade pressure algometer, the experimenter applied a slow constant rate of pressure (30 kPA/s) to the left volar forearm. Participants were instructed to verbally indicate when the pressure sensation first became painful, at which the algometer was removed. Pressure pain threshold was defined as the amount of pressure in kilopascals (kPa) at which the participant first reported experiencing pain. Two trials were administered consecutively during each pre- and postconditioning test. The post-test trials were administered immediately after participants removed their hand from the cold water bath (conditioning stimulus). These trials were averaged for a single pre- and post-test PPT score.

Conditioning Stimulus. Participants immersed their right hand up to the wrist in a cold water bath (VersaCool 7, Thermo Scientific) maintained at 10°C for up to one minute or until they reported intolerable pain. Cold pain was assessed every 15 seconds using the 0–100 NRS. The pain ratings were averaged across time for a single cold water immersion pain score for each participant.

Calculation of CPM. A percent change score was calculated for the test stimulus with the following formula: [(post-PPT trial score – pre-PPT trial score)/pre-PPT trial score]*100. A positive percent change score indicated an increase in PPTs following the conditioning stimulus, and thus pain inhibition.

Clinical Pain Measures of the Headache

Headache Survey

A headache survey that has been used successfully in previous studies of post-traumatic headache was administered to all patients [5,17]. The survey included questions about ongoing headache (frequency, intensity, medication use, other treatments), history of problems with headache pre-injury, and characteristics of ongoing headache (headache symptoms). Participants rated the average pain intensity of their headaches since their injury using a 0–10 numeric rating scale (NRS), with 0 being no headaches at all and 10 being the worst pain possible. This 0–10 rating was used for data analysis (HA intensity).

McGill Pain Questionnaire

The McGill Pain Questionnaire (MPQ) provides a quantitative evaluation of a person's pain experience with separate sensory, affective, evaluative, and miscellaneous dimensions [18]. The MPQ is composed of a list of 78 words categorized into 20 groups of words representing the four dimensions. From each group of words, respondents choose the word that best describes their experience of pain. The sensory dimension represents the temporal, spatial, pressure, thermal, and other properties of pain. The affective dimension represents reactive emotions to pain such as tension, fear, punishment, and autonomic aspects of pain. The evaluative dimension represents the subjective overall intensity of the pain experience. The last dimension represents the miscellaneous qualities of pain. Multiple measures can be derived from this questionnaire. For data analysis, we calculated the pain rating index (PRI), which sums the rank values of the words chosen by the participant from the word list. The PRI was derived for all dimensions, as well as a total PRI score. The MPQ has been used extensively in clinical and research settings and has been validated within TBI populations [18,19].

Psychological Questionnaires

State Trait Anxiety Inventory–State Version

The State Trait Anxiety Inventory–State Version (STAI) has extensive normative data and is a frequently used measure of anxiety in pain studies [20]. The State subscale consists of 20 items that evaluate how respondents feel "right now" at this moment. The scores range from 20 to 80, with a higher score indicating greater anxiety. The STAI was administered before the QST.

Center for Epidemiological Studies–Depression Scale

The CES-D is a 20-item measure of symptoms of depression that has been shown to be reliable and valid in both general and clinical populations [21]. The score can range from 0 to 60, with higher scores indicating greater depression. A cutoff score of 16 or higher has been used as identifying individuals at risk for clinical depression [22].

Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS) assesses negative mental responses to anticipated or actual pain [23]. The PCS has 13 items that are scored on a Likert scale with three subcategories: rumination, magnification, and helplessness. Higher PCS scores are indicative of higher pain catastrophizing. Scores on the PCS have been associated with clinical and experimental pain measures. The highest possible score on the PCS is 52, with prior studies showing a cutoff range of more than 20–24 points to be related to clinical relevance [24,25].

Statistical Analysis

Descriptive statistics were calculated for all the outcome variables and for average days from injury to experimental session. Shapiro-Wilk's test of normality indicated that all variables were not normally distributed. Thus, to address the first hypothesis, Mann-Whitney *U* tests were conducted to determine if the primary outcomes assessing endogenous pain modulatory function differed between the mTBI and control groups (i.e., measures of central sensitization and CPM). To determine whether the pressure pain hyperalgesia was more widespread or localized to the head area, the CPM pretest PPT score (forearm) was included in the analyses as a separate outcome variable. Ninety-five percent confidence intervals and effect sizes were also calculated for the primary outcomes. Effect sizes were calculated to determine the magnitude of difference in measures of central sensitization and CPM between the control and mTBI groups. Cohen's *d* was defined as the control group mean minus the mTBI group mean, divided by the pooled within-group standard deviation ($\underline{d} = [X_{\text{control}} - X_{mTBI}]$/pooled SD). Positive effect sizes indicated a greater value for the control group compared with the mTBI group. We also conducted Wilcoxon signed rank tests to determine whether each group exhibited significant pain inhibition on the CPM test (pre-PPT vs post-PPT). The *P* value for

significance was set at $P < 0.05$. Due to the exploratory nature of the study, we did not adjust the P values for multiple comparisons [26].

We also wanted to explore whether having headaches more frequently influenced the primary outcome measures within the mTBI group. Therefore, we conducted an exploratory analysis that divided the mTBI sample into two groups based on headache frequency. Patients who reported no headaches (N = 2) or headaches one to several times per week (N = 12) formed the lower-frequency headache group, whereas mTBI patients with daily or constant headaches (N = 10) formed the high-frequency headache group. Nonparametric tests were used to determine whether the measures of pain modulatory function differed between headache frequency groups.

To address the second hypothesis, Spearman's *rho* bivariate correlation analyses were conducted to determine the associations between measures of pain modulatory function, psychological variables, and headache pain (Headache-NRS, MPQ PRI) within the mTBI sample. The P value for significance was set at $P < 0.05$.

Results

Participant Characteristics

All participants enrolled in this study completed the entire experimental session from which the data for this study were obtained. Means ± SDs and P values for participant characteristics are presented in Table 1. For the mTBI, patient-reported causes of head injury included falls, motor vehicle crashes, hit by object on the head, hit by car/truck, and bike accident. Fourteen mTBI participants reported loss of consciousness for under 30 minutes following the head injury. The average number of days between the head injury and the experimental session was 9.7 ± 4.8 days. The average reported headache pain on the 0–10 NRS was 5.9 ± 2.7 for the mTBI patients, with 22/24 mTBI participants reporting headaches. In the mTBI participants, headaches were reported to occur once a week for three participants, several times per week for nine participants, daily for nine participants, and constantly for one participant. Fifteen mTBI participants reported taking medications for their headaches including nonsteroidal anti-inflammatory drugs [6], acetaminophen [7], opiates [4], and medicine that treats muscle spasms [3]. However, these medications were not taken on the day of testing, before the session took place. As expected, the Mann-Whitney U tests showed that the mTBI group reported significantly greater headache pain on all assessments measuring headache pain (HA intensity, MPQ-PRI) compared with controls. Furthermore, mTBI patients reported significantly greater pain catastrophizing, depression, and state anxiety compared with the control group.

Group Differences in Pain Modulatory Function

See Table 2 for the means and SDs, 95% confidence intervals (CIs), and effect sizes for all the variables measuring pain modulatory function, as well as the P values from the Mann-Whitney U tests. The results revealed significant differences between the mTBI and control groups on the PPT-Head test. The mTBI group demonstrated lower PPTs of the head area (i.e., greater pressure pain sensitivity) compared with the control group. The Mann-Whitney U test also revealed a significant difference between groups on the CPM test, with the mTBI group exhibiting lower pain inhibition on the CPM test compared with the control group. The Wilcoxon signed rank test indicated that controls exhibited significant pain inhibition on the CPM test ($P = 0.005$: pre-PPT = 308.7 ± 219.1 kPA vs post-PPT = 361.3 ± 237.0 kPA), whereas mTBI patients did not exhibit significant pain inhibition ($P = 0.108$: pre-PPT = 281.0 ± 222.6 kPA vs post-PPT = 300.7 ± 257.2 kPA). No significant differences existed between groups on the cold water bath pain ratings during the CPM test ($P = 0.728$; controls = 56.8 ± 20.6 vs mTBI group = 59.4 ± 27.5). Additionally, no significant differences were found for the temporal summation tests or PPT of the forearm.

The exploratory analysis conducted to determine whether the outcome measures of pain modulatory function differed between mTBI groups of higher and lower headache frequency revealed a significant effect of group ($P = 0.033$) on PPT-Head. The high-frequency headache group exhibited greater pressure pain hyperalgesia (M = 169.2 ± 148.9 kPA) compared with the lower-frequency headache group (M = 212.6 ± 116.5 kPA). Group differences in TS-Hand ($P = 0.198$), TS-Forehead ($P = 0.722$), CPM ($P = 0.198$), and PPT-Forearm ($P = 0.169$) were not significant.

Correlations of Pain Modulatory Function Variables with Psychological and Headache Variables in the mTBI Sample

No significant relationships existed between any of the variables and the number of days from head injury to the experimental session. Additionally, no significant relationships were found between MTS-Hand and the headache pain or psychological variables ($P > 0.05$). CPM score was also not significantly related to any variables. PPT-Head was negatively related to MTS-Forehead, HA pain intensity on the NRS scale, pain catastrophizing, and state anxiety. Thus, greater pressure pain hyperalgesia on the head was associated with greater temporal summation on the forehead, greater intensity of headaches, and greater pain catastrophizing and anxiety. PPT-Forearm was positively correlated with PPT-Head and negatively correlated with headache pain intensity, pain catastrophizing, and state anxiety. Mechanical temporal summation of pain was positively related to state anxiety. See Table 3 for the Spearman's *rho* bivariate correlations between QST tests performed on the head, CPM score, headache pain variables, and psychological variables.

Table 1. Participant characteristics

	mTBI Group (N = 24)	Control Group (N = 21)	
Variable	Mean±SD	Mean±SD	*P* Values
Age, y	29.4 ± 8.4	29.3 ± 8.4	0.945
Sex, % female	66.7	66.7	
Body mass index, kg/m^2	26.0 ± 5.2	29.5 ± 8.1	0.219
Education, %			
Some HS	4.2	0	
HS degree	50	23.8	
2-y college degree	16.7	23.8	
4-y college degree	20.8	33.0	
Master's or above	4.2	19.0	
Loss of consciousness during mTBI, %	58.3	NA	
Reported headaches following mTBI, %	91.6	NA	
Taking medication for headaches, %	62.5	0	
HA intensity, 0–10 NRS	5.9 ± 2.7	1.1 ± 2.2	<0.001*
MPQ PRI	23.7 ± 13.9	4.5 ± 5.6	<0.001*
PCS	22.0 ± 11.5	7.6 ± 7.9	<0.001*
CES-D	21.4 ± 15.2	9.4 ± 8.3	0.005*
STAI State	37.3 ± 10.9	28.3 ± 9.4	0.005*

CES-D = Center for Epidemiologic Studies Depression Scale; HA = headache; HS = high school; MPQ PRI = McGill Pain Questionnaire–Pain Rating Index; NA = not applicable; PCS = Pain Catastrophizing Scale; STAI = State Trait Anxiety Inventory.

*Significant *P* values.

Table 2. Group differences in variables measuring pain modulatory function

Variable	mTBI Group, Mean±SD (95% CIs)	Control Group, Mean±SD (95% CIs)	*P* Value	Effect Size
PPT-Head, kPA	177.9 ± 103.4 (130.6 to 225.3)	251.4 ± 121.5 (201.8 to 300.8)	0.010*	0.65
PPT-Forearm, kPA	267.6 ± 217.8 (209.0 to 408.4)	308.7 ± 219.1 (175.6 to 359.6)	0.317	–0.19
MTS-Forehead	14.5 ± 16.1 (8.4 to 20.5)	12.6 ± 12.7 (6.1 to 19.0)	1.000	–0.13
MTS-Hand	13.6 ± 14.5 (8.6 to 18.5)	9.0 ± 8.1 (3.8 to 14.3)	0.451	–0.39
CPM score, % change	5.7 ± 26.2 (–4.8 to 16.2)	20.4 ± 22.5 (9.6 to 31.2)	0.046*	0.60

CI = confidence interval; CPM = conditioned pain modulation; MTS = mechanical temporal summation; PPT = pressure pain threshold.

*Significant *P* values.

Table 3. Correlations between pain modulation variables, psychological variables, and headache pain measures within the mTBI sample

	1	2	3	4	5	6	7	8	9
1. PPT-Head	1.000								
2. PPT-Forearm	0.878**	1.000							
3. MTS-Forehead	–0.435*	–0.357	1.000						
4. CPM score	–0.052	0.004	0.003	1.000					
5. HA intensity	–0.493*	–0.537**	0.321	–0.159	1.000				
6. MPQ PRI	–0.329	–0.350	0.286	–0.198	0.429*	1.000			
7. PCS	–0.415*	–0.503**	0.191	–0.315	0.192	0.297	1.000		
8. CES-D	–0.300	–0.389	0.270	–0.033	0.067	0.485*	0.491*	1.000	
9. STAI State	–0.631**	–0.703**	0.414*	0.159	0.385	0.238	0.442*	0.326	1.000

CES-D = Center for Epidemiologic Studies Depression Scale; CPM = conditioned pain modulation; HA = headache; MPQ PRI = McGill Pain Questionnaire–Pain Rating Index; MTS = mechanical temporal summation; PCS = Pain Catastrophizing Scale; PPT = pressure pain threshold; STAI = State Trait Anxiety Inventory.

*$P < 0.05$;

**$P < 0.01$.

The MPQ-PRI total score was not significantly related to any of the pain modulatory function variables. However, the evaluative dimension of the MPQ was significantly correlated with TS-Forehead ($r = 0.430$, $P = 0.036$) and PPT-Head ($r = -0.422$, $P = 0.040$), with greater MPQ evaluative scores associated with greater temporal summation of pain and greater pressure pain sensitivity on the head.

Correlations of Psychological Variables with Headache Variables in the mTBI Sample

Depression scores on the CES-D significantly and positively correlated with MPQ-PRI. Thus, greater depression was associated with greater intensity of headaches. Examination of the correlations between CES-D and the separate dimensions of the MPQ revealed significant relationships between CES-D and the affective ($r = 0.458$, $P = 0.024$) and miscellaneous ($P = 0.569$, $P = 0.004$) dimensions. Additionally, pain catastrophizing was significantly correlated with depression on the CES-D and state anxiety on the STAI, with greater pain catastrophizing associated with greater depression and anxiety.

Discussion

This study provides the first evidence in humans that pain modulatory profiles are altered in the early stages following mTBI, as evidenced by greater pressure pain hyperalgesia of the head/neck and deficient descending pain inhibition. Additionally, and as expected, mTBI patients suffered from greater headache pain than their matched controls, reaffirming that mTBI increases risk for post-traumatic headaches. Within the mTBI sample, greater sensitization was associated with more intense headache pain.

Deficient Pain Inhibitory Capacity Following mTBI

Supporting our hypothesis, we revealed that pain inhibitory capacity was diminished on the CPM test in mTBI patients compared with controls. As evidenced by the effect size, the magnitude of the group difference in CPM was moderate. This is in line with a recent animal study demonstrating profound disruption of descending noxious inhibitory controls (DNICs) in mice three weeks after an mTBI compared with a sham condition [10]. DNIC is the corresponding test in animals to CPM in humans [15]. Although the mechanism for impaired pain inhibition following mTBI is not known, it could be related to central damage to the ascending spinothalamatic/thalamocortical tracts potentially induced by TBI [27]. Additionally, the brainstem, which is integral to major descending pain inhibitory tracts, is a brain region known to be particularly vulnerable to damage following TBI [28]. Such damage may reduce the descending inhibitory control that is triggered by ascending nociceptive information, leading to increased neuronal hyperexcitability [29]. Nonetheless, future research is needed to investigate mechanisms underlying poor pain inhibitory control following mTBI.

A recent human cross-sectional study provided the first evidence that poor pain inhibitory capacity may be associated with chronic post-traumatic headaches. Specifically, Defrin et al. found that mild TBI patients (all at least one year postinjury) with chronic post-traumatic headaches had diminished pain inhibitory capacity on the CPM test compared with mTBI patients without headaches and mTBI-free individuals [11]. Furthermore, greater post-traumatic headache pain was associated with worse pain inhibition in the mTBI patients with chronic headaches. This is in contrast to the current study, in which no relationship was found between CPM and reported post-traumatic head pain. One key difference between the two studies is the focus on acute (current study) vs chronic PTHs (Defrin et al. study). Evidence suggests that deficient descending pain inhibition can predict the transition from acute to chronic pain [9,30], whereas efficient engagement of descending pain inhibitory pathways can protect against the chronification of pain [31]. Therefore, deficient CPM may be more predictive of who develops chronic vs acute PTHs; however, future longitudinal studies are needed to test the predictive utility of CPM for chronic PTHs.

Pain Sensitization Following mTBI

As hypothesized, sensitization of the head/neck area was elevated in mTBI patients compared with controls, as evidenced by lower PPTs of the head. Notably, the high-frequency headache mTBI group exhibited the greatest pressure pain hyperalgesia. No differences were observed between groups for PPTs of the forearm, suggesting that sensitization was localized to the head area. While only speculation, an elevated or prolonged neuroinflammatory response following mTBI could underlie the increased sensitization in the head area observed in mTBI patients. Following TBI, inflammation is rapidly elicited as a response to the primary injury to brain tissue. These neuroinflammatory events may become excessive or can persist beyond the beneficial effect and cause secondary injury to the central nervous system (CNS) [32,33]. Elevated pro-inflammatory cytokines in the central nervous system can induce sensitization of second-order neurons in the spinal dorsal horn/trigeminal nucleus, thereby facilitating pain hypersensitivity [34]. However, it should be noted that in the current study, temporal summation, which is considered a "hallmark" sign of dorsal horn neuron sensitization, was not elevated in mTBI patients compared with controls.

Importantly, our results also revealed that greater sensitization was associated with greater intensity of headaches. Interestingly, mTBI patients who exhibited greater pressure pain hyperalgesia of the head and forearm

reported greater pain intensity of headaches on the NRS scale. Additionally, greater pressure pain hyperalgesia and temporal summation of pain at the forehead was associated with higher scores on the evaluative dimension of the MPQ. The evaluative dimension represents the subjective overall intensity of the pain experience. In line with these results, a prior cross-sectional human study provided evidence for the presence of central sensitization in patients with chronic headaches [7], regardless of headache type. Notably, TS-Forehead and PPT-Forearm significantly correlated with headache pain intensity but were not different between groups. It is possible that enhanced sensitization before the mTBI, rather than increased sensitization caused by the mTBI, increased susceptibility for more intense headaches following injury. Unfortunately, due to the cross-sectional nature of the current and prior studies, we cannot determine the time course of the development of sensitization in relation to the injury, nor can we determine whether greater sensitization leads to more intense headaches or more intense headaches increase sensitization.

Psychological Factors Following mTBI

Although not the primary focus of the current study, we also evaluated psychological variables following injury. The psychological data demonstrated that mTBI patients exhibited significantly higher levels of depressive and anxiety symptoms and pain catastrophizing compared with controls. Furthermore, depression scores on the CES-D were positively correlated with the MPQ-PRI score, which means that mTBI participants who reported higher depressive symptoms also scored higher on the self-reporting pain index. Prior research has also shown that depression is linked with headache severity following mTBI [35]. Yilmaz et al. showed that patients with PTHs at two weeks postinjury more often reported anxiety and depression compared with those not reporting PTHs [36]. Lucas and colleagues evaluated headaches and depression in >200 mTBI patients at one week and one year postinjury [37]. Although depression and headache were not significantly related at baseline, isolated depression without headache was rare, and the co-occurrence of depression and PTHs increased over time. The depression–PTH link is in accordance with research in the general population showing a relationship between depression and headache pain severity [38–40]. As noted previously, the current study is cross-sectional, which prevents us from being able to show the direction of causality between the depression symptoms and headache pain. Without following participants over an extended period, it is not possible to conclude whether more intense headaches lead to higher depression or greater depression facilitates worse headaches. Most likely, the relationship is somewhat bidirectional. Another limitation of the current study is that the control group was not recruited from the emergency department or did not have an injury; thus, it cannot be determined if differences in the psychological variables are specific to mTBI or the traumatic experience of the injury itself.

Notably, pain catastrophizing was not associated with headache pain but was positively correlated with depression. Little research has evaluated pain catastrophizing in the early stages following mTBI. Chaput et al. investigated pain levels and pain catastrophizing in mTBI patients one month and eight weeks following injury [41]. Headache pain severity was associated with pain catastrophizing at eight weeks post-mTBI, but not at one month. Based on these results, perhaps pain catastrophizing is a more important risk factor for the development of chronic PTHs than acute headaches.

A few more limitations of this study should be noted. First, we did not have a control group with chronic headaches or a group with mTBI and no headaches, as almost all mTBI patients recruited experienced headaches in the acute stage of injury. The prevalence of headaches in the acute stage of mTBI is extremely high, and thus an mTBI group of this nature is difficult to obtain. Due to the lack of an mTBI group without headaches or a control group with headaches, we cannot not determine whether altered pain modulation is specific to mTBI, headache, or to mTBI with PTH. However, our exploratory analysis involving headache frequency suggested that pressure pain hyperalgesia was greater in mTBI patients with higher compared with lower frequency of headaches. Second, due to the exploratory nature of the current study, we did not adjust for multiple comparisons in our statistical analysis. If we would have adjusted for multiple comparisons, the group difference on CPM score would not have been significant. However, the results indicating that the control group exhibited significant inhibition on the CPM test and that the mTBI group did not exhibit significant CPM would have remained the same. In regard to the correlations, many of the significant correlations would have disappeared after adjusting for multiple comparisons. For example, even though PPT-Head was significantly correlated with headache pain intensity with an R value indicating a moderate to strong relationship, Bonferroni corrections would have rendered this result insignificant. Third, we used the same assessor for all outcome measures; therefore, the assessor was not blinded to participant group. Fourth, we asked participants to refrain from consuming caffeine before the experimental session. It is possible that some participants were regular caffeine consumers and could have experienced caffeine withdrawal headaches on the date of the experimental session; however, we did not assess for this possibility. Additional larger studies that can address these limitations are needed to confirm these results.

Conclusions

In conclusion, the current study is the first to demonstrate altered and maladaptive endogenous pain

modulation in humans in the early stages following mild TBI. Sensitization of the head/neck area was enhanced and associated with headache pain intensity in the mTBI sample. Individuals with mTBI also demonstrated less efficient descending pain inhibition compared with controls, although this variable was not associated with headache pain. These maladaptive pain modulatory processes may place mTBI patients at risk for the development of chronic pain. Future prospective studies are needed to evaluate whether pain modulatory profiles in the early stages following mTBI predict the transition from acute to chronic post-traumatic headaches. Such findings will provide important mechanistic insights and may help identify treatment targets for the prevention of chronic headaches after mild TBI.

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