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Journal

Translational Psychiatry, 4(1)

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Publication Date

2014-01-07

DOI

10.1038/tp.2013.116

Peer reviewed

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Citation: Transl Psychiatry (2014) 4, e340; doi:10.1038/tp.2013.116
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ORIGINAL ARTICLE

Too hard to control: compromised pain anticipation and modulation in mild traumatic brain injury

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Mild traumatic brain injury (MTBI) is a vulnerability factor for the development of pain-related conditions above and beyond those related to comorbid traumatic and emotional symptoms. We acquired functional magnetic resonance imaging (fMRI) on a validated pain anticipation task and tested the hypotheses that individuals with a reported history of MTBI, compared with healthy comparison subjects, would show increased brain response to pain anticipation and ineffective pain modulation after controlling for psychiatric symptoms. Eighteen male subjects with a reported history of blast-related MTBI related to combat, and eighteen healthy male subjects with no reported history of MTBI (healthy controls) underwent fMRI during an event-related experimental pain paradigm with cued high or low intensity painful heat stimuli. No subjects in either group met diagnostic criteria for current mood or anxiety disorder. We found that relative to healthy comparison subjects, after controlling for traumatic and depressive symptoms, participants with a reported history of MTBI showed significantly stronger activations within midbrain periaqueductual grey (PAG), right dorsolateral prefrontal cortex and cuneus during pain anticipation. Furthermore, we found that brain injury was a significant moderator of the relationship between anticipatory PAG activation and reported subjective pain. Our results suggest that a potentially disrupted neurocognitive anticipatory network may result from damage to the endogenous pain modulatory system and underlie difficulties with regulatory pain processing following MTBI. In other words, our findings are consistent with a notion that brain injury makes it more difficult to control acute pain. Understanding these mechanisms of dysfunctional acute pain processing following MTBI may help shed light on the underlying causes of increased vulnerability for the development of pain-related conditions in this population.

Translational Psychiatry (2014) **4,** e340; doi:10.1038/tp.2013.116; published online 7 January 2014

Keywords: concussion; dorsolateral prefrontal; emotion; imaging; PAG; post-traumatic stress

INTRODUCTION

The annual prevalence rate of mild traumatic brain injury (MTBI) in the civilian population in the United States is estimated at 1.3 million (www.cdc.gov/Traumaticbraininjury/statistics.html), and MTBI is considered as a 'signature injury' of those involved in Iraq and Afghanistan conflicts.[1–4]

MTBI is a known as vulnerability factor for developing chronic pain in both civilian[5,6] and military[1,7,8] populations. Over half of individuals with a history of TBI reported pain-related problems and complaints.[9–12] Seemingly paradoxically, some—but not all—research suggests this rate to be higher following mild compared with moderate and severe head injury.[5] The most common pain reported is headache and back pain.[12–14] Pain symptoms in individuals with a history of MTBI worsen clinical course, interfere with rehabilitative care and markedly increase treatment costs.[15–18]

Psychiatric conditions such as post-traumatic stress disorder (PTSD) and depression, which commonly co-occur with brain injury,[1,14,19,20] can contribute to the increased susceptibility to pain.[21–23] However, evidence from several recent studies has suggested that pain is physiologically linked to brain injury and these effects extend beyond that associated with comorbid psychological symptoms.[1,5–7,16] One possible mechanism is through damage to the brainstem,[24] including the periaqueductual grey (PAG), thus compromising the integrity of the endogenous pain modulatory systems.[25]

The aim of the current study was to provide the first examination of the neural correlates of pain following blast-related MTBI using functional magnetic resonance imaging (fMRI) and a validated pain anticipation paradigm.[26,27] We hypothesized that individuals with blast-related MTBI would show abnormal brain response to pain anticipation and pain processing when compared with individuals without MTBI. Furthermore, considering the physical impact of MTBI on the brainstem,[28–30] our secondary hypothesis was to test whether MTBI interferes with the endogenous pain modulation. As comorbid emotional symptoms significantly contribute to the neurocircuitry of pain processing and modulation,[31–35] we recruited individuals who did not meet criteria for comorbid psychopathology and also controlled for residual emotional symptoms in our analyses.

MATERIALS AND METHODS

Subjects

Eighteen male subjects with a reported history of blast-related MTBI during Operation Enduring/Iraqi Freedom combat, and eighteen male subjects

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Received 25 September 2013; revised 28 October 2013; accepted 29 October 2013

Table 1. Demographics, clinical and psychological variables

	18 HC (M)		*18 MTBI (M)*		*Statistics*	
	Mean	*s.d.*	*Mean*	*s.d.*	*t/ χ^2*	P
Demographic variables						
Age (years)	28.6	8.7	28.7	7.1	0.02	0.98
Education (years)	14.6	1.1	14.1	1.1	1.5	0.14
Marital status, *N*						
Married/living w/partner	6		2		8.18	< 0.05
Single	12		10			
Separated/divorced	0		6			
Race, *N*						
African-American	1		3		2.91	0.40
Asian	1		0			
Caucasian	8		10			
Other	8		5			
Clinical variables						
Time since most severe MTBI (year)	NA		4	2		
Number of MTBIs	NA		4	4		
Loss of consciousness ($<$ 1min)	NA		$N = 3$			
Psychological variables						
Clinician-administered PTSD scale	0.2	0.9	36.4	12.8	12.2	< 0.01
Beck Depression Inventory-2	1.0	2.0	3.9	4.0	2.8	< 0.01
STAI-Y						
STAI-Y state[a]	26.0	6.5	37.8	12.4	3.6	< 0.01
STAI-Y trait[b]	28.2	5.7	35.9	11.8	2.4	< 0.05
Post-scanner ratings[c]						
Low-pain intensity	1.5	1.6	1.9	1.9	0.6	0.55
High-pain intensity	3.8	2.6	3.9	2.6	0.3	0.80

Abbreviations: HC, healthy controls; MTBI, mild traumatic brain injury; NA, not applicable; PTSD, post-traumatic stress disorder; STAI, Spielberger State-Trait Anxiety Inventory. [a]Missing data in one MTBI subject. [b]Missing data in one MTBI and one HC subject. [c]Scale range from 0 to 10 (see text for details).

with no reported history of MTBI gave written informed consent to participate in this study, which was approved by the University of California San Diego Human Research Protection Program and Veterans Affairs San Diego Healthcare System Research and Development Committee. The groups did not differ significantly on age (t (34) = 0.02; $P = 0.98$), race ($\chi^2 = 2.91$; $P = 0.40$) or education (t (34) = 1.5; $P = 0.14$) (see Table 1 for details). All but four MTBI subjects were unmedicated at the time of the experiment; two were receiving bupropion, one fluoxetine and one was receiving a combination of citalopram and trazadone. *Post hoc* analysis removing these medicated subjects did not change the observed results.

All subjects completed a semi-structured clinical interview for DSM-IV (SCID),[36] Beck Depression Inventory-2 (BDI-2)[37] and Spielberger State-Trait Anxiety Inventory.[38] All MTBI subjects completed the Defense and Veterans Brain Injury Center TBI Screening Tool, that is, the Brief Traumatic Brain Injury Screen,[39] a detailed TBI questionnaire regarding concussion history, and the Clinician Administered PTSD Scale (CAPS).[40]

Subjects were excluded from the study if they (1) fulfilled DSM-IV criteria for current, or history before combat of, mood or anxiety disorder; (2) fulfilled DSM-IV criteria for alcohol/substance abuse or dependence within 30 days of study participation; (3) fulfilled DSM-IV criteria for lifetime bipolar or psychotic disorder; (4) had ever experienced a moderate or severe TBI (www.cdc.gov/Traumaticbraininjury); (5) had experienced any TBI before deployment; (6) had clinically significant comorbid medical conditions such as cardiovascular and/or neurological abnormality or any active serious medical problems requiring interventions or treatment; (7) had a history or current chronic pain disorder; (8) had irremovable ferromagnetic material; (9) were claustrophobic; and (10) were left-handed.

Experimental pain paradigm

A validated pain anticipation paradigm was used[26,27] (Supplementary Figure 1S). Briefly, the paradigm had two temporal conditions (anticipation and stimulus) with the former having three stimulus conditions (anticipation of either high pain, low pain or uninformed pain) and the latter having two stimulus conditions (high-pain stimulation or low-pain stimulation). Thermal stimuli, experienced as moderately (6 s; 47.5 °C) and mildly (6 s; 45.5 °C) painful to the subject, were delivered in a pseudo-random and counterbalanced order through a 9-cm^2 thermode (Medoc TSA-II, Ramat-Yishai, Israel) securely fastened to the subject's left volar forearm. Before scanning, subjects were pretested with several non-painful and painful temperature stimuli to ensure that temperatures were well tolerated (see Supplementary Information for further details).

Post-scanner pain ratings

To measure the subjective experience of the task, subjects rated the intensity of perceived pain (0 (no pain sensation) to 10 (extreme pain sensation) after the scan. Subjects were instructed to provide separate ratings for the low and high-pain stimuli.

fMRI protocol

Two fMRI runs (412 brain volumes per run) sensitive to blood oxygenation level-dependent contrast were collected for each subject using 3.0 Tesla GE Signa EXCITE scanner (GE Healthcare, Milwaukee, WI, USA) (T2*-weighted echo planar imaging, TR = 1500 ms, TE = 30 ms, flip angle = 90, FOV = 23 cm, 64 × 64 matrix, thirty 2.6 mm 1.4-mm-gap axial slices) while they performed the paradigm described above (Supplementary Figure 1S). FMRI acquisitions were time locked to the onset of the task. During the same experimental session, a high-resolution T1-weighted image (FSPGR, TR = 8 ms, TE = 3 ms, TI = 450 ms, flip angle = 12, FOV = 25 cm, 172 sagittal slices, 256 × 256 matrix, 1 × 0.97 × 0.97 mm^3 voxels) was obtained for anatomical reference.

fMRI statistical analysis

All imaging data were analyzed with the analysis of functional neuroimages (AFNI) software package[41] as in prior studies.[26] Briefly, preprocessed time series data for each individual were analyzed using a multiple regression model corrected for autocorrelation consisting of three anticipation-related and two stimulus-related regressors.

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Table 2. Whole brain activation during pain anticipation and experience

Brain region	*Vol*	x	y	z	*F-statistics*
Anticipation					
Task effects					
Ring anterior insula	4352	38	23	8	7.1
Left anterior insula	2688	−32	24	10	6.3
Left dorsolateral PFC	960	−21	17	53	5.9
Left precentral gyrus (BA 6)	1536	−43	−10	29	5.8
Right ventromedial PFC (BA 10)	1088	1	55	15	6
Right posterior parietal (BA 40)	2560	53	−48	31	7.4
Right middle temporal gyrus	1856	41	−67	20	5.7
Left middle temporal gyrus	832	−42	−70	13	4.7
Right inferior occipital gyrus	1472	38	−69	−3	5.1
Right parahippocampal gyrus	1088	17	−14	−24	6.8
Right midbrain	832	11	−21	−11	8.1
Left midbrain (PAG)[a]	1280	−2	−30	−16	7
Group effects (MTBI > HC)					
Right dlPFC	768	31	22	27	5.4[b]
Left cuneus	1856	−8	−75	29	5.9[b]
Left midbrain (PAG)[a]	960	−1	−35	−6	5.8[b]
Pain experience					
Task effects					
Right insula	12160	38	6	10	12.2
Left insula	4608	−41	4	7	12.3
Right dpINS	1024	35	−18	16	10.6
Right rostral ACC	2624	4	35	20	11.6
Right dorsal ACC	1152	5	9	43	9.7
Right postcentral gyrus	960	44	−27	51	10.1
Left lentiform nucleus	896	−16	10	4	11
Left cerebellum	5824	−26	−53	−31	11.2
Group effects (MTBI > HC)					
Right dlPFC	1152	30	10	39	6.8
Left middle temporal gyrus	1088	−27	−60	23	6.3
Left precuneus	960	−7	−74	36	5.1

Abbreviations: ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; dpINS, dorsoposterior insula; HC, healthy controls; MTBI, mild traumatic brain injury; PAG, periaqueductal grey; PFC, prefrontal cortex. [a]0.9 Probability www.neurosynth.org. [b]Remained significant after covarying out traumatic and depressive symptoms.

Anticipation-related regressors consisted of: (1) anticipation of moderately painful heat stimulation, that is, high-pain anticipation and (2) anticipation of mildly painful heat stimulation, that is, low-pain anticipation. As the uninformed cue did not contribute to our understanding of the specific mechanism of interest, this condition was modeled as regressor of no interest. Stimulus-related regressors consisted of: (1) application of moderately painful heat, that is, high-pain stimulation and (2) application of mildly painful heat, that is, low-pain stimulation. Six additional regressors were included in the model as nuisance regressors: one outlier regressor to account for physiological and scanner noise (that is, the ratio of brain voxels outside of 2 s.d. of the mean at each acquisition), three movement regressors to account for residual motion (in the roll, pitch and yaw directions), and regressors for baseline and linear trends to account for signal drifts. To reduce the false positives induced by cross correlations of the time series, data were fit using the AFNI program *3dREMLfit*. A Gaussian filter with a full width-half maximum of 4 mm was applied to the voxel-wise percent signal change data to account for individual variation in the anatomical landmarks. Data from each subject were normalized to Talairach coordinates.[42]

Voxel-wise percent signal change for high and low-pain anticipation and high and low pain were entered into a linear mixed effects model with Group (MTBI/healthy controls (HC)) and Task (low/high) entered as fixed factors, and subjects entered as a random factor. Analysis was done with the AFNI function *3dLME.R*, which uses statistical program R (www.cran.org) and the nlme library. Results are displayed that showed significant Task and Group effects for pain anticipation and pain experience. A Monte Carlo simulation (iterations = 10 000) using *AlphaSim* was used to determine that for a search volume within task-related areas a cluster size of 768 mm^3 was required to control for multiple comparisons maintaining an alpha of 0.05. The cluster F-values were calculated by averaging the voxel based F-values in each cluster. Finally, the average percent signal change was extracted from regions of activation for *post hoc* correlational analysis. All analyses for the behavioral data were carried out with PASWStatistics18.0 (IBM, Chicago, IL, USA).

Analysis of covariance

One of our goals was to examine relative contribution of the emotional factors to the observed between-group brain differences in pain anticipation and experience. Therefore, as a final step to all of the above analyses, we re-ran all group comparisons on the extracted clusters that survived whole brain thresholding (see above) with and without the inclusion of CAPS and BDI-2 scores as covariates. All *post hoc* analyses were corrected for multiple comparisons using the Bonferroni correction. The resultant F-values were not used to indicate the strength of groups differences, but rather to describe the influence of covariates on the observed brain effects.[43] Note that the values reported in the tables represent the mean F-values of the voxels within the significant brain clusters.

Moderation analyses

Moderation effects[44] were evaluated with the hierarchical multiple regressions after removing multivariate outliers (one MTBI and one HC). Multivariate outliers were detected by calculating and examining the Cook's Distance.[45] The moderation analysis tested whether group (MTBI and HC) x anticipatory PAG activation interaction term accounted for significant variance in subjective pain perception after group and

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anticipatory PAG activation terms had been entered in the model. This analysis was motivated by the following: (1) PAG is one of the main centers involved in endogenous pain modulation;[46] (2) the brainstem (including the PAG) is thought to be most vulnerable to blast exposure;[28–30] and (3) PAG was one of the main sites that showed significant between-group differences during anticipation of pain after controlling for anxiety and deprssion in our study (see Results below). To establish the nature of the interaction effect, correlations between anticipatory PAG and subjective pain ratings were performed for each MTBI and HC group.

RESULTS

Clinical and behavioral measures

All subjects in the MTBI group reported a history of blast-related concussion (mean ± s.d.: 4 ± 4 concussions; Table 1). The average time since most severe blast-related concussion was 4 ± 2 years, and only 3/18 MTBI individuals reported loss of consciousness (< 1 min). As can be seen in Table 1, MTBI subjects reported clinically minimal but statistically significant increases in BDI-2 and CAPS scores in contrast to controls.

Subjective pain intensity ratings

Subjects' ratings of their experience during the task are shown in Table 1. Repeated measures analysis of variance with temperature (low and high), as a within-subject factor, and group (HC and MTBI), as a between-subject factor, showed no significant effect of group on pain intensity rating ($F(1,34) = 0.189$; $P = 0.666$). This effect remained significant after covarying out traumatic and depressive symptoms severity in these subjects.

fMRI results

Pain anticipation

Task effects. Table 2 (top) shows clusters of significant activation in the whole brain analysis during pain anticipation in both groups (Figure 1a). As can be seen in Figure 1a, significant task effects were observed within bilateral anterior insulas, several regions within the prefrontal cortex, bilateral middle temporal gyri, posterior parietal lobule, right inferior occipital gyrus, right parahippocampal gyrus and the midbrain.

Group effects. Table 2 (top) shows significant whole brain activation clusters of the between-group differences during pain anticipation (Figure 1b). MTBI relative to HC subjects showed increased activation within midbrain consistent with the PAG ($P = 0.9$; www.neurosynth.org), the right dorsolateral prefrontal cortex (dlPFC) and left cuneus. No decreased activation in MTBI relative to HC was observed. As traumatic and depressive symptoms could have contributed to the observed group differences, we examined this possibility with the analysis of covariance. We found that all anticipatory group differences remained highly significant even after covarying out traumatic (CAPS) and depressive (BDI-2) symptoms severity.

Pain experience

Task effects. Table 2 (bottom) show significant clusters of activation in whole brain analysis during pain experience in both groups (Figure 2a). As can be seen in Figure 2a both groups showed significant effects within bilateral insulas, rostral and dorsal anterior cingulate, right postcentral gyrus, basal ganglia and the cerebellum.

Group effects. Table 2 (bottom) shows the significant clusters of activation in the between-group contrasts in the whole brain analysis during pain experience (Figure 2b). MTBI relative to HC subjects showed increased activation within right dlPFC, left middle temporal gyrus and left precuneus. No decreased activation clusters in MTBI relative to HC subjects was observed. Interestingly, none of the observed group differences in brain activation during pain experience survived significance after covarying out trauma and depressive symptoms severity.

Moderation analysis. In order to examine the proposed model that physical injury to the brainstem during blast exposure may damage pain modulatory pathways, we examined whether MTBI moderated the relationship between anticipatory PAG activation and subjective pain experience in our subjects (see Materials and methods section above; Figure 3). The results of the second step of the regression analysis showed that the interaction term between group (MTBI and HC) and anticipatory PAG activation explained a significant increase in variance in subjective pain intensity rating, $\Delta R^2 = 0.21$, $F(1, 30) = 8.75$; $P < 0.01$. Thus, the brain injury was a significant moderator of the relationship between anticipatory PAG activation and the reported subjective pain intensity in our study. The HC group demonstrated significant negative relationship between anticipatory PAG activation and the reported pain intensity rating ($\rho = -0.747$; $P < 0.01$). This was not observed in the MTBI group ($\rho = 0.218$; $P = 0.4$). Scatter plots of the relationship between anticipatory PAG activation and subjective pain intensity demonstrate this effect (Figure 3).

DISCUSSION

The current study provides evidence for the hypothesis that a history of blast-related MTBI specifically affects brain networks during acute pain anticipation and modulation. First, when compared with a set of healthy male subjects, individuals with a history of blast-related concussion showed increased activation within PAG, right dlPFC and cuneus during pain anticipation that remained highly significant after controlling for traumatic and depressive symptoms severity. Conversely, group findings during pain experience did not survive after controlling for anxiety and depression. Second, consistent with our hypothesis, we found that brain injury was a significant moderator in the relationship between anticipatory PAG activation and the degree of the perceived subjective pain intensity. Taken together, our results suggest that MTBI has significant effects on anticipatory pain processing and interferes with effective pain modulation. These findings were fully backed up by the results of functional connectivity analyses (please see Supplementary Information), which suggested greater utilization of modulatory resources. Specifically, we found that only increased connectivity between right anterior insula and right orbitofrontal cortex remained significantly higher in MTBI compared with HC after controlling for anxiety and depression. Our findings are thus in line with the literature, showing that concussion has independent effects on pain,[5–7,16] and extend this work through a phasic delineation of acute pain processing. The current work also substantiates a potentially disrupted neurocognitive anticipatory network that may result from damage to endogenous pain modulatory system, and in turn underlie difficulties with regulatory pain processing in MTBI.

The observed between-group differences in functional activation and connectivity pattern (please see Supplementary Information) during anticipation of pain that were more related to MTBI than to the residual emotional symptoms in our study are strikingly similar to the brain regions that are thought to be most affected by blast exposure. Computational modeling of blast showed that brainstem, orbitofrontal cortex and cerebellum, in comparison with other brain regions, were predicted to have the highest shear stresses,[47] consistent with previous studies and case reports describing neuronal and metabolic changes in similar regions.[48–51] This is consistent with findings from the experimental animal models of blast,[24] suggesting that brainstem is one of the structures that can be particularly vulnerable to blast exposure.[28–30]

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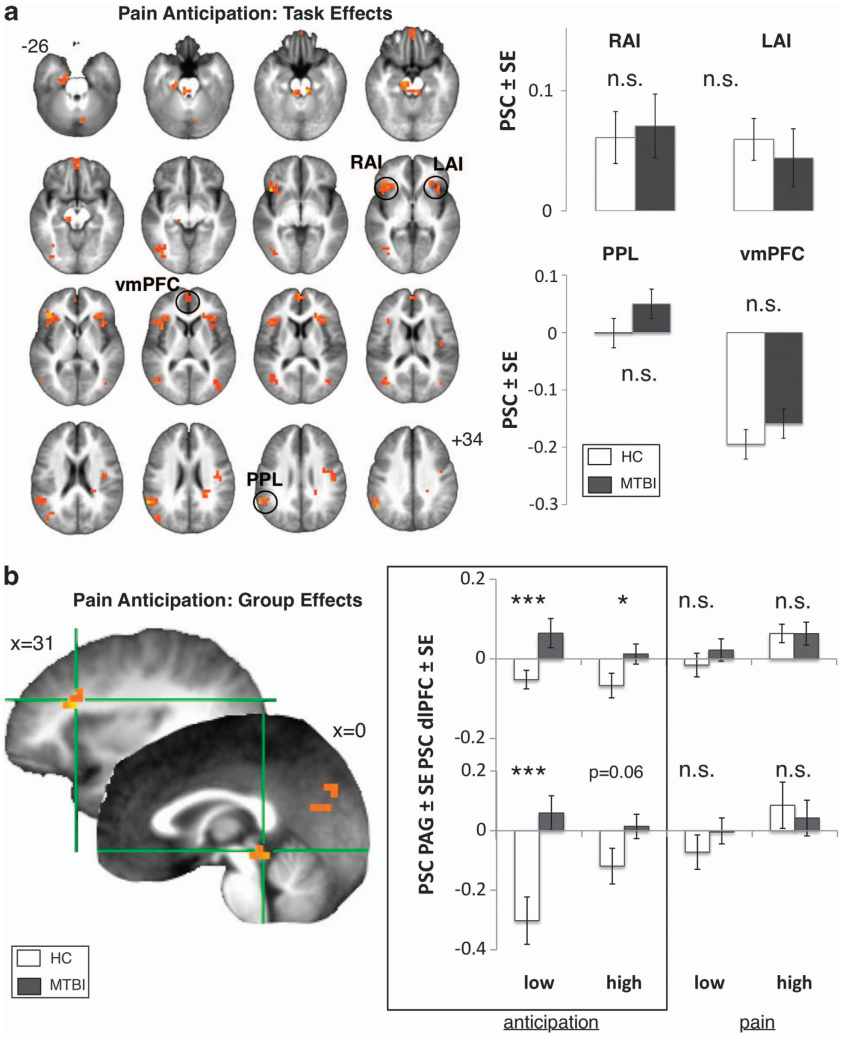

Figure 1. Whole brain activation during pain anticipation. (**a**) Significant whole brain activation during high versus low-pain anticipation in both groups (see Table 2 top for details). Both groups show significantly increased activation within bilateral anterior insulas, several regions within the prefrontal cortex, bilateral middle temporal gyri, posterior parietal lobule, right inferior occipital gyrus, right parahippocampal gyrus and the midbrain. Bar graphs indicate percent signal changes (PSC) and show that activation within these regions was comparable between the two groups. Right = left. (**b**) Significant between-group differences in whole brain activation during pain anticipation (see Table 2 top for details). Mild traumatic brain injury (MTBI) relative to healthy control (HC) subjects show increased activation within midbrain periaqueductal grey (PAG), the right dorsolateral prefrontal cortex (dlPFC), left cuneus. No decreased activation in MTBI relative to HC was observed. Bar graphs indicate PSC in right dlPFC (top) and PAG (bottom) during anticipation period (indicated by the boarder) and during pain period for comparison. Right = left. *P<0.05; ***P<0.001. LAI, left anterior insula; PPL, posterior parietal lobule; RAI, right anterior insula; vmPFC, ventromedial prefrontal cortex.

The brainstem PAG is instrumental for both facilitation and inhibition of ascending nociceptive input.[52,53] In previous studies of acute pain stimulations, the anticipatory PAG activation was positively related to the degree of experienced pain in healthy subjects.[54,55] Conversely, anticipatory PAG connectivity with the insula was negatively related to the experienced subjective pain.[56] In line with this, anticipatory PAG and dlPFC activation predicted placebo analgesia[57] and pain relief.[58] Therefore, our findings of increased PAG and dlPFC response in MTBI and increased connectivity between the insula and orbitofrontal cortex during anticipation (please see Supplementary Information) all point to increased attempt to inhibit the upcoming painful experience in MTBI.[59–64] Such pattern of anticipatory response and connectivity in non-injured brain would be associated with the decreased subjective pain response,[26,27] which was not observed as subjectively, the pain experienced by MTBI and control subjects was comparable in our study. These results are thus consistent with ineffective pain modulation in MTBI, as individuals with MTBI showed increased utilization of anticipatory subcortical and cortical modulatory resources in order to achieve similar level of subjective experience. Importantly, these results appear consistent with the premise, that in part, the dysfunction concerning effective modulation of the upcoming threat in subjects following MTBI may be more attributable to the head injury rather than being better explained by psychiatric comorbidities.[26,31,33–35] Our moderation analyses further confirmed this notion whereby only in the absence of brain injury anticipatory PAG activation explained subjective pain in our study.

Intriguingly, our results demonstrate greater influence of brain injury on pain regulatory processes, that is, anticipation and modulation, rather than on actual pain perception. Specifically, we found that increased anticipatory response to pain was more explained by the brain injury than the residual anxiety and depressive symptoms in our subjects, whereas increased response to pain stimulation was more explained by psychopathology. We

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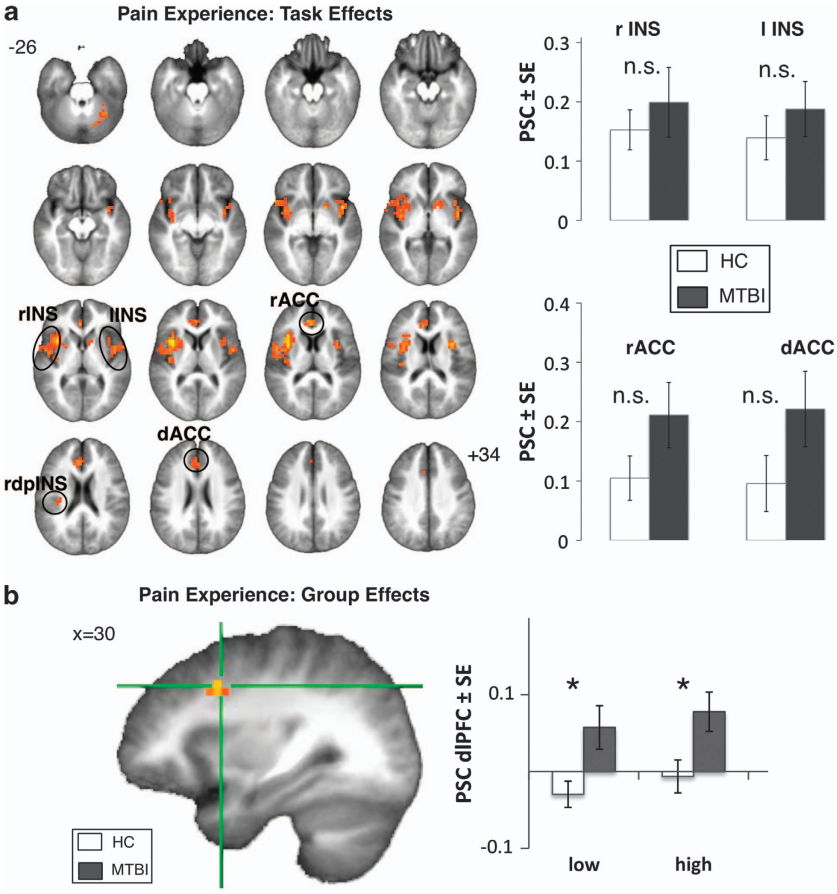

Figure 2. Whole brain activation during pain experience. (**a**) Significant whole brain activation during high versus low-pain stimulation in both groups (see Table 2 bottom for details). Both groups show significantly increased activation within bilateral insulas, rostral and dorsal anterior cingulate, right postcentral gyrus, basal ganglia and the cerebellum. Bar graphs indicate percent signal changes (PSC) and show that activation within these regions was comparable between the two groups. Right = left. (**b**) Significant between-group differences in the whole brain activation during pain experience (see Table 2 bottom for details). Mild traumatic brain injury (MTBI) relative to healthy control (HC) subjects show increased activation within right dorsolateral prefrontal (dlPFC), left middle temporal gyrus and left precuneus. No decreased activation in MTBI relative to HC was observed. Bar graphs indicate PSC in right dlPFC. Right = left. *P<0.05. rdpINS, right dorso-posterior insula; lINS, left insula; rACC, right anterior cingulate; rINS, right insula.

believe that these findings are in line and reinforce the results of our moderation analyses and the proposed model of direct and disruptive effects of brain injury on pain regulatory processes. Pain anticipation shapes pain experience (for example, Ploner *et al.*[56]), thus such regulatory processes begin to take place before actual stimulation. This model explains clinical observations whereby pain symptoms following brain injury are not fully explained by comorbid psychopathology.[1,5,6] Although multiple labs, including our own, have previously found that psychopathology has an effect on both anticipation and stimulation phases of acute pain processes,[26,33,34,65] we believe that in those with psychopathology, pain regulation is maladaptive,[26,34,66] whereas in those with brain injury it may be severed as a result of a physical damage. Tractography studies as well as paradigms that directly assess endogenous pain modulation in this population (for example, temporal summation and conditioned pain modulation) will be able to answer these questions.

In a related prior study, quantitative sensory testing was conducted in moderate to severe TBI and found significant loss of thermal and touch sensibility compared with healthy controls.[67] Although detailed quantitative sensory testing was not conducted in the current study, we found no apparent sensory loss in the MTBI group. It may be that increased neurotrama in a subset of patients following moderate and severe TBI creates a reduced pain sensitivity that explains prior findings of reduced prevalence of pain conditions in contrast to mild brain trauma or MTBI.[12–14]

One important limitation of the current study was the degree of combat exposure in our MTBI group. Although all MTBI subjects were deployed, it was the case for ~50% of the control individuals. Although we controlled for the degree of trauma and depressive symptoms in our analyses, their contribution cannot be completely ruled out, and future studies should examine the effects of deployment on pain sensitivity in more detail, as well as the effects of gender. Nevertheless, we have learned a great deal about neural signature of PTSD by using both trauma-exposed[68] and trauma-free[33] control groups. Only through these studies, we have learned that some brain differences are specific to trauma, whereas other are specific to PTSD.[69] Likewise in our study, by carefully controlling for trauma and depressive symptoms, we found which brain differences were more related to the associated emotional symptoms in our sample. Therefore this study provides an important initial step into possible brain differences in response to acute pain that remain above and beyond possible emotional disturbances in MTBI, which are in line with emerging neuropsychological[70] and imaging[71] findings in MTBI and with a cohort of literature, suggesting that concussion and pain share unique physiology.[5–7,16]

In summary, this is the first report investigating the effects of MTBI on the neural correlates of pain anticipation and perception.

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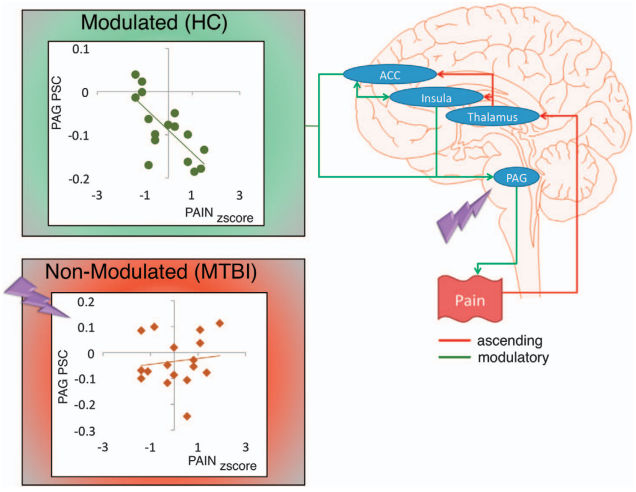

Figure 3. Schematic of the effects of brain injury on pain modulatory system based on the observed moderation functional magnetic resonance imaging (fMRI) results. Scatter plots representing significant moderation effects of brain injury on the relationship between anticipatory PAG activation and subjective pain. The healthy control (HC) group demonstrated significant negative relationship between anticipatory periaqueductal grey (PAG) activation and the reported pain intensity rating ($\rho = -0.747$; $P < 0.01$) (green). This was not observed in the mild traumatic brain injury (MTBI) group ($\rho = 0.218$; $P = 0.4$) (orange). PSC, percent signal change.

Although, the neurobiological basis of increased susceptibility to pain following MTBI still remains unknown, current findings shed light on potential mechanisms. Specifically, our results suggest that during the anticipation of pain, MTBI individuals require greater prefrontal and subcortical engagement and increased use of modulatory resources compared with control subjects to achieve comparable control over aversive experiences. This pattern of anticipatory brain response and connectivity did not seem to be related to the degree of residual emotional trauma and depressive symptoms. This may suggest a speculative model (Figure 3) in which blast exposure compromises subcortical and cortical emotion regulation centers, leading to the increased load on neural resources and creating a susceptibility to develop pain-related conditions in these individuals. This model is in line with our moderation analyses that showed that brain injury significantly moderated the relationship between anticipatory brainstem response and subjective pain in our subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We are grateful to the National Institute of Mental Health (MH080003 to IAS), to the Veterans Administration via Center of Excellence in Stress and Mental Health to ANS and IAS, and Merit Grant to ANS for supporting this work and to Elena Kosheleva and Lindsay E Reinhardt for assisting with data collection.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)

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