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Pain-related white matter tract abnormalities in mild traumatic brain injury patients with persistent headache

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Abstract

Background: The occurrence of debilitating chronic persistent (24/7) headache after mild traumatic brain injury represents a central neuropathic pain state. Previous studies suggest that this chronic headache state can be attributed to altered supraspinal modulatory functional connectivity in both resting and evoked pain states. Abnormalities in the myelin sheaths along the supraspinal superior longitudinal fasciculus and anterior thalamic radiation are frequently associated with alteration in pain modulation related to functional connectivity deficit with the prefrontal cortex. This study assessed the correlated axonal injury-related white matter tract abnormality underlying these previously observed prefrontal functional connectivity deficits by comparing the fractional anisotropy, axial diffusivity, and radial diffusivity of brain white matter in patients with mild traumatic brain injury-related headache to healthy controls.

Result: Diffusion tensor imaging data from patients ($N = 12$, average age $\pm$ $SD = 35.0 \pm 8.0$ years old, 10 male) with mild traumatic brain injury-headache were compared with images acquired from healthy controls. The mild traumatic brain injury cohort demonstrated two areas of significant ($P < 0.01$, F value >16, cluster size >50 voxels) white matter tract abnormalities closely related to pain affective and modulatory functions in (1) the left superior longitudinal fasciculus which connects the prefrontal cortices with the parietal cortices and (2) the right anterior thalamic radiation connecting the prefrontal cortices with the anterior cingulate cortex. In addition, a significant ($P < 0.01$) decrease in axial diffusivity and increase in radial diffusivity at the superior longitudinal fasciculus cluster were noted in the mild traumatic brain injury cohort.

Conclusion: The identified white matter tract abnormalities may represent a state of Wallerian degeneration which correlates with the functional connectivity deficit in pain modulation and can contribute to the development of the chronic persistent headache in the patients with mild traumatic brain injury.

Keywords

Mild traumatic brain injury, traumatic brain injury, diffusion tensor imaging, post-traumatic headache, pain modulation

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Introduction

Persistent head pain, which commonly perceived as headache, is one of the most prevalent debilitating conditions in patients with mild traumatic brain injury (MTBI). Recent studies found patients with MTBI-related persistent head pain have altered supraspinal connectivity between modulatory and affective functions in both resting and evoked pain states[1] with the patients demonstrating significantly less activities in the

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thalamus, pons, anterior cingulate cortex (ACC), insula (IN), and medioprefrontal cortices (MPFCs) than their healthy counterparts in the evoked pain state. In addition, the prefrontal modulatory functional connectivity to other pain processing-related regions is significantly diminished in the MTBI group in comparison with the healthy control group at both resting and evoked pain states. Previous structural imaging studies suggest MTBI can lead to axonal injury.[2–4] Similarly, pain-related studies demonstrated that deficit in white matter tracts relevant to prefrontal cortical pain modulation can lead to the development of neuropathic pain states.[5,6] Two of these tracts, most relevant to the prefrontal pain modulatory functions, are the superior longitudinal fasciculus (SLF) and anterior thalamic radiation (ATR). The SLF connects the frontal, parietal, and occipital lobes, whereas the ATR provides connection between prefrontal cortices (PFCs) and some of the key deep pain affective regions such as the cingulate gyrus. Thus, a change in the integrity of these white matter tracts can negatively impact the prefrontal pain modulatory ability and lead to the development of persistent head pain. Here, the authors hypothesized that persistent head pain after MTBI is associated with structural deficit in the white matter tracts most relevant to prefrontal cortical pain modulation. The current study compared the fractional anisotropy (FA) and axial and radial diffusivities of the MTBI patients with health controls.

Materials and methods

With institutional human subject protection committee approval, subjects (all veterans) who had participated in the functional imaging were consented, screened, and enrolled based on the following inclusion criteria: male or female with age between 18 and 60 years; history of MTBI and established diagnosis of post-traumatic headache based on the ICHD-2[7,8] diagnostic criteria including:

A. Headache, no typical characteristics known, fulfilling criteria C and D
B. Head trauma includes the following:
   1. Either no loss of consciousness or loss of consciousness of $<$30 min duration
   2. Glasgow Coma Scale $\geq$13
   3. Symptoms and/or signs diagnostic of concussion as discussed in the below diagnostic criteria of MTBI
C. Headache occurs within seven days after head trauma
D. Headache persists for $>$three months after head trauma

Additional headache inclusion criteria consisted of the following: (1) an average chronic persistent daily (24/7) headache intensity greater than 30 on the 0 to 100 mechanical visual analog scale at the screening visit (Visit 1)[9] and (2) an average intensity of this chronic persistent headache greater than 3/10 on a numerical rating scale reported in the headache diary filled out daily by the patients between Visit 1 and scanning visit (Visit 2). MTBI diagnosis was based on the published criteria from the 1993 American Congress of Rehabilitation Medicine and recent recommendation from the Department of Defense.[10] Specifically, the diagnostic criteria state that a traumatically induced physiological disruption of brain function, as manifested by at least one of the following categories: (1) any loss of consciousness $\leq$30 min, (2) post-traumatic amnesia $\leq$24 h, and (3) an initial Glasgow Coma Scale score was $\geq$13, 30 min after the injury. Exclusion criteria included history of pacemaker implant; pregnancy; ferromagnetic material such as shrapnel, bullet fragments, or implanted devices in the brain or body that would not be compatible with magnetic resonance imaging (MRI); history of life threatening diseases, dementia, or major psychiatric illnesses; documented diagnosis of post-traumatic stress disorder or Mississippi Scale for post-traumatic stress disorder score $\geq$130; documented major depression or Hamilton Rating Scale for depression score $\geq$19; presence of any other chronic neuropathic pain states or neurological diseases such as seizure; involvement of litigation; inability to understand the study instruction and to communicate in English; and history of chronic headache diagnoses such as migraine, tension, or cluster headaches prior to the incidence of MTBI. However, subjects with occasional pre-injury tension (less than once every three months and lasting no more than 24 h) or migraines (less than once every four months and lasting no more than 6 h) headaches were not excluded from the study. Patients' records were verified for the diagnoses MTBI and posttraumatic headache, the mechanisms of injury, and the duration of the headache. Although some subjects might have previous or subsequent incidences of MTBI, the MTBI mechanisms listed in Table 1 were confirmed as the direct causes leading to the onset of intractable persistent headache based on patient record review and interviews at the screening visit. Healthy controls were recruited from a healthy subject list consisting of students and health-care workers. For the current study, they were screened based on the healthy subject enrollment criteria detailed in previously published functional MRI-related studies.[11,12]

Diffusion tensor imaging (DTI) data were acquired in a GE 1.5 T EXCITE Twinspeed MRI scanner for $\sim$10 min for each scan with the following imaging parameters: repetition time = 16.1 s, TE = minimum, FOV = 25.6 cm, 60 oblique slices encompassing the whole brain, and voxel size $= 2 \times 2 \times 2$ mm^3; 54 directions were collected with a b value of 1000 s/mm^2, and

Table 1. Demographic data for the patient cohort with mild traumatic brain injury.

Subject no.	Age (year old)	Gender	Blast (B)/ non-blast (NB)	Duration of headache (months)	Intensity of headache (M-VAS score)
1	29	Female	NB	72	80
2	33	Female	NB	84	50
3	54	Male	NB	84	30
4	28	Male	B	48	60
5	39	Male	B	60	60
6	25	Male	B	84	45
7	40	Male	B	108	60
8	35	Male	B & NB	96	70
9	33	Male	B	84	100
10	40	Male	B	72	55
11	26	Male	B	156	50
12	38	Male	NB	48	50
Average±*SD*	35.0±8.0			83.0±29.2	59.1±17.9

M-VAS: mechanical visual analogue scale.

5 volumes with no-diffusion weighting. DTI data were imported into the BrainVoyager software. Standard sequence of preprocessing steps including head motion correction, drift removal, and spatial smoothing with Gaussian filter (full wide at half maximum = 5 mm) were conducted for all DTI data set. Raw diffusion data for all directions were converted to a new project type, called DMR ("diffusion MR"). The directions referenced as "x," "y," and "z" for eigenvalue computation were defined, and the information was stored in a single "DWI" (diffusion weighted images) file. The anatomical data (dicom format) of each subject was also loaded and converted into BrainVoyager's internal "VMR" data format. When the "DWR" data were aligned with the three-dimensional data set, the actual diffusion weighted image data were transformed into the new "VDW" (volumes of diffusion weighted data) format, which was further transformed into AC-PC and Talairach standard space for calculating tensors, mean diffusivity and FA and group analysis. The FA is defined as

$$\mathrm{FA} = \frac{\sqrt{3\left[(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)\right]^2}}{\sqrt{2\left(\lambda_1^2+\lambda_2^2+\lambda_3^2\right)}}$$

Fully isotropic voxels have FA = 0, whereas fully anisotropic voxels have a FA = 1.[13] In addition, axial diffusivity (AD) and radial diffusivity (RD) are calculated with the following equations[14]:

$$\mathrm{AD} = \lambda 1;$$

$$\mathrm{RD} = (\lambda + \lambda)/2$$

All individuals' FA maps were grouped and subjected to a single factor analysis of covariance to assess the statistical difference between the FA values of the two groups in the brain. The resulting significant ($P < 0.001$, and cluster size > 50 voxel) regions of difference were extracted, and their anatomical locations were identified using the FMRIB (Oxford, UK) plug-in within the BrainVoyager platform (Maastricht, Netherland).

Results

Twelve veterans (10 male) with a diagnosis of MTBI, an average age ± *SD* of 35.0 ± 8.0 years old, and daily persistent headache intensity greater than 3 on a 0 to 10 numerical rating scale, and an equal number of healthy controls (6 males) with an average age ± *SD* of 31.6 ± 7.6 completed the study. There is no statistically significant difference in age between the two groups. The average intensity of persistent headache rated by the MTBI cohort on the mechanical visual analog scale ±*SD* was 59.1 ± 17.9, and the average duration of their headache ±*SD* was 83.0 ± 29.2 months (Table 1). None of the healthy controls had any history of brain trauma, chronic pain conditions, or chronic headaches. The MTBI cohort showed a significantly lower FA in (1) the left SLF ($P < 0.01$, F value = 16.76, cluster size = 55) near the left prefrontal cortex (Figures 1 and 2) the right anterior thalamic tract ($P < 0.01$, F value = 16.57, cluster size = 139) near the right prefrontal cortex (Figure 2). Additional comparison in diffusivities indicates that the MTBI cohort has a significant decrease ($P < 0.01$)

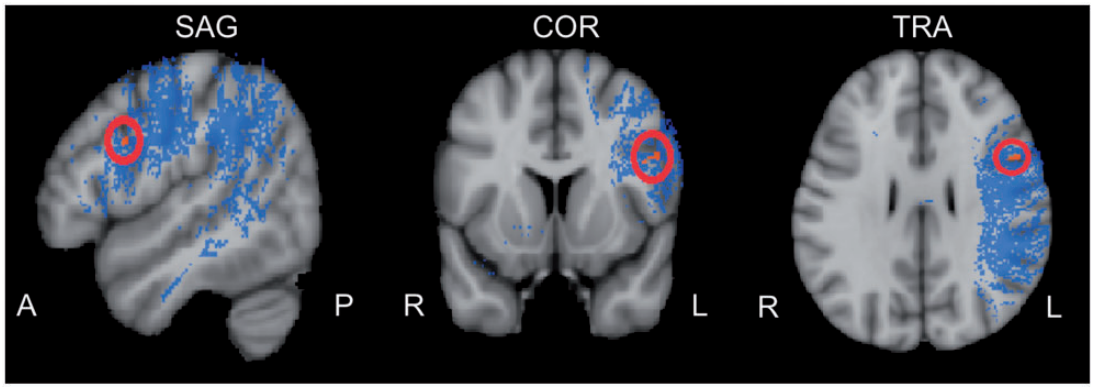

Figure 1. Area (red circle) of white matter tract fractional anisotropy deficit ($P < 0.01$, cluster threshold > 50 voxels, F value $= 16.76$, peak voxel coordinates: $x = -49$, $y = 8$, $z = 29$) found in the superior longitudinal fasciculus (blue) of patients with MTBI-related headache in comparison with healthy controls.

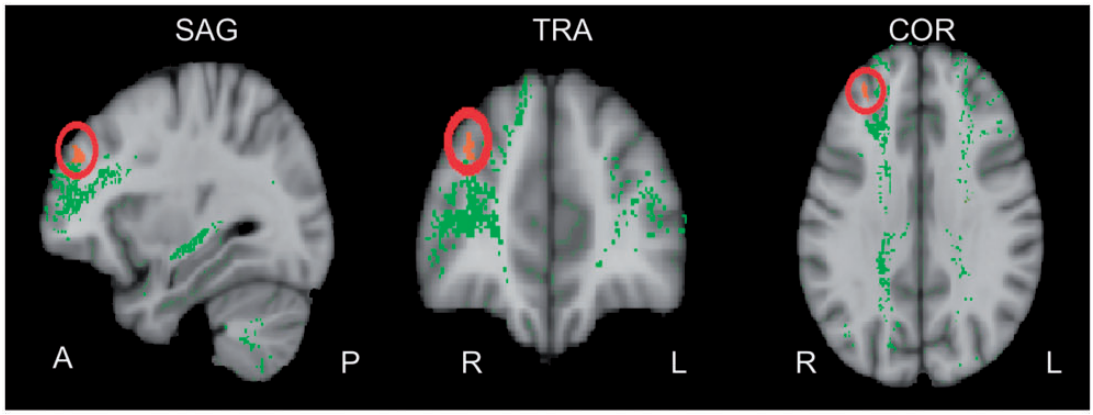

Figure 2. Area (red circle) of white matter tract fractional anisotropy deficit ($P < 0.01$, cluster threshold > 50 voxels, $F = 16.57$, peak voxel coordinates: $x = 35$, $y = 50$, $z = 33$) found in the anterior thalamic radiation (green) patients with MTBI-related headache in comparison with healthy controls.

in the mean AD in both the left SLF and right ATR in comparison to the controls. While the MTBI group also presented with a significantly higher value in the mean RD in the SLF, such an increase in the mean RD was not statistically significant in the right ATR cluster (Table 2). Gender-based comparisons were conducted within and between groups. No significant differences were observed in FA, AD, and RD comparisons.

Discussion

Although structural lesions associated with MTBI are usually not detected by conventional anatomical brain neuroimaging techniques such as MRI or computer tomography, studies with DTI suggest that MTBI patients suffer from diffuse axonal injury in white matter tracts crucial for intracortical connectivity.[15] An impairment in intracortical connectivity often leads to deficiency in cortical excitability and conductivity in brain areas associated with pain modulation/adaptation.[16] In addition, these structural and electrophysiological abnormalities found in MTBI population are also highly correlated with findings in a blood perfusion study, which demonstrated MTBI patients presented with a hypoperfusion state in the basal ganglion, a key relay center between the prefrontal cortical areas (particularly the prefrontal cortical area and parietal cortices) and the limbic system, suggesting a dissociative state between the affective (hyperactive) and modulatory (hypoactive) aspects of supraspinal pain-related activities.[3] This pattern of functional and structural abnormalities is known to be associated with a supraspinal

Table 2. Mean axial and radial diffusivity differences (MTBI minus health controls) in the left superior longitudinal fasciculus (left SLF) and right anterior thalamic radiator (right ATR).

Clusters with decreased FA	Mean axial diffusivity (AD) Difference (±*SD*)	Mean radial diffusivity (RD) Difference (±*SD*)
Left SLF	−16.86 (±4.89)*	28.96 (±3.23)*
Right ATR	−16.93 (±2.30)*	1.77 (±2.71)

FA: fractional anisotropy; SLF: superior longitudinal fasciculus; ATR: anterior thalamic radiation; SD: standard deviation.
*$P < 0.01$.

dissociation state with correlated functional or mood deficits.

In the area of chronic pain or headache development, it is well known that supraspinal pain processing network consists of (1) the thalamus and pons, which relate sensory afferent signals to other supraspinal regions; (2) the sensory discriminatory regions including the primary and secondary somatosensory cortices (SSC1 and SSC2) and the inferior parietal lobe; (3) the affective regions such as the ACC and IN; and (4) the modulatory regions involving the dorsolateral prefrontal cortex and various regions of the PFCs.[17,18] The IN is also implicated in assessing the magnitude of pain.[17,19,20] Furthermore, the inferior parietal lobe is also known to be involved in spatial discriminatory functions of pain perception.[21–23] Structural connectivity is vital to the efficiency of functional connectivity in these pain-related supraspinal regions. Central neuropathic pain conditions such as headaches occur when there is a maladaptation in neuronal modulatory functions which often are caused by abnormalities in the structural integrity of the neuronal system.[11,24,25]

Previous studies demonstrated that with MTBI, supraspinal functional connectivity is impaired in the prefrontal brain regions corresponding to mood and cognitive functions.[1,26–28] One of these studies specifically demonstrated supraspinal pain modulatory functional connectivity impairment in patients with MTBI-related headache, specifically at the MPFCs in both resting and evoked pain states.[1] However, how these functional connectivity deficits may correlate with any underlying structural axonal abnormality requires further assessments. The current study addressed this knowledge gap by providing additional structural assessments corresponding to these supraspinal functional deficits. It demonstrated that patients with MTBI presented with a diminished white matter tract FA index in two major cortical tracts highly relevant to pain perception and modulation in comparison to the healthy controls. These tracts include the left SLF and right ART.

The SLF connects the front and the back of the cerebrum including the frontal, parietal, and occipital lobes. The frontal and parietal cortical regions correspond to the modulatory and somatosensory aspects of pain processing, respectively. The integrity of the white matter tract connecting these regions can affect the effectiveness of the PFCs in modulating the sensory discriminatory aspect of pain perception. Thus, a deficit in the white matter tract connecting these supraspinal regions can lead to an interference in sensory or pain perception and modulation. This interference can inadvertently lead to the development of chronic pain or headaches. While the intrinsic functions of these tracts may have a laterality difference, assessing such a difference will be outside the scope of the current study. Nevertheless, the identified deficit in the left SLF appears to be highly correlated with the functional connectivity deficits in the MPF identified in a previous study. In addition, several previous published studies have demonstrated a similar association between the deficits in the SLF and chronic pain states.[5,29,30] Previous studies have also shown that the parallel organization of white matter fiber bundles is the basis for diffusion anisotropy, whereas myelin appears to modulate the amount of anisotropy.[31] In addition to FA, assessing the axial and radial diffusivities (or diffusion eigenvalues) provide more specific information about diffusion tensor changes or differences, and the potential mechanisms leading to the changes. While all three eigenvalues appear to decrease with aging, demyelination is associated with an increase in the radial diffusion orientations.[32] Song et al.[33] found the absence of myelin appeared to increase the RD but did not significantly affect the AD in a rat model. Subsequent studies have confirmed an increased RD in models of both dysmyelination and demyelination, and a few other studies observed decreased AD with dys/demyelination as well.[34–36] In addition, decreases in both FA and AD and an increase in RD are suggestive of Wallerian degeneration.[37,38]

In the current study, the structural deficits found in the left SLF among the MTBI patients consists of decreased FA and AD, and increased RD in comparison to controls, suggesting a state of Wallerian degeneration and demyelination. These structural deficits correspond to previous functional connectivity findings indicating a diminished level of outward (to affect) modulatory functional connectivity from the MPFCs to other pain perception regions including the secondary somatosensory cortices located in the parietal regions.[1] Such an observation argues against the assertion that the observed white matter tract FA abnormalities are primarily due to some types of cortical dysfunction unrelated to the head trauma. In addition, the ATR provides connection between the PFCs and the cingulate gyrus. Similar abnormalities in this area of white matter tract are also

known to present in patients with chronic pain conditions.[5,6,39] In the current study, the diminished FA along the thalamic radiation is accompanied by a significant decrease in AD and an insignificant increase in RD in comparison to the controls, suggesting that while there may be axonal injury, such an injury did not lead to definitive Wallerian degeneration or demyelination. These overall identified structural abnormalities provide the structural evidence underlying the previously observed pain modulatory functional deficits in this patient population with chronic persistent head pain.

Several areas of the study which can be considered for improvement are worthy of discussion. First, the current study adopted healthy subjects as controls. The authors realize that adopting MTBI subjects without headache as controls may enhance the specificity of the study. However, it is well known that MTBI subjects suffer from a colossus of cognitive and mood symptoms aside from headache. Thus, adopting this group of patients without headache but potentially with other neuropsychological dysfunctions can result in more complex confounding issues for result interpretation. Alternately, veterans without a history of traumatic brain injury can be considered as alternate group of study control. While the age difference between the two groups is insignificant, future studies may limit the age range so that specific comparisons of similar age group can be conducted. Furthermore, while the sample size of the study is relative small, it is compatible with some of the previously published articles in this field of research.[15,40–42] However, future studies with larger sample sizes should be conducted to further validate the current findings.

Conclusion

The observed white matter tract deficits in regions linking the prefrontal cortex and the sensory discriminatory regions of pain perception among patients with MTBI-HA can contribute to the development of persistent headache after MTBI.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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