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RESEARCH ARTICLE

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Mild traumatic brain injury is associated with effect of inflammation on structural changes of default mode network in those developing chronic pain

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Abstract

Background: Mild traumatic brain injury (mTBI) has a higher prevalence (more than 50%) of developing chronic posttraumatic headache (CPH) compared with moderate or severe TBI. However, the underlying neural mechanism for CPH remains unclear. This study aimed to investigate the inflammation level and cortical volume changes in patients with acute PTH (APTH) and further examine their potential in identifying patients who finally developed CPH at follow-up.

Methods: Seventy-seven mTBI patients initially underwent neuropsychological measurements, 9-plex panel of serum cytokines and MRI scans within 7 days post-injury (T-1) and 54 (70.1%) of patients completed the same protocol at a 3-month follow-up (T-2). Forty-two matched healthy controls completed the same protocol at T-1 once.

Results: At baseline, mTBI patients with APTH presented significantly increased GM volume mainly in the right dorsal anterior cingulate cortex (dACC) and dorsal posterior cingulate cortex (dPCC), of which the dPCC volume can predict much worse impact of headache on patients' lives by HIT-6 ($\beta = 0.389$, $P = 0.007$) in acute stage. Serum levels of C-C motif chemokine ligand 2 (CCL2) were also elevated in these patients, and its effect on the impact of headache on quality of life was partially mediated by the dPCC volume (mean [SE] indirect effect, 0.088 [0.0462], 95% CI, 0.01–0.164). Longitudinal analysis showed that the dACC and dPCC volumes as well as CCL2 levels had persistently increased in patients developing CPH 3 months postinjury.

Conclusion: The findings suggested that structural remodelling of DMN brain regions were involved in the progression from acute to chronic PTH following mTBI, which also mediated the effect of inflammation processes on pain modulation.

Trial registration: ClinicalTrials.gov ID: [NCT02868684](https://clinicaltrials.gov/ct2/show/study/NCT02868684); registered 16 August 2016.

Keywords: Mild traumatic brain injury, Posttraumatic headache, Voxel-based morphometry, Inflammation effect

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Introduction

Traumatic brain injury (TBI) is a major global public health problem that affects 50 million people each year, and it is estimated that about half the world's population will have one or more TBIs over their lifetime [1, 2]. The US Centers for Disease Control and Prevention reports that mild TBI is experienced in 70%–90% of TBI-related emergency department (ED) visits [3]. Post posttraumatic headache (PTH) is a high prevalence of disabling trauma- and pain-related disorder [4, 5], and may developed into the chronic pain in patients with TBI [1, 2]. Unexpectedly, mild TBI (mTBI) is identified as one of the most vulnerable risk to develop chronic PTH (CPTH) (prevalence rate: 72.7%–77.9%), compared with much sever cases (moderate or severe TBI, prevalence rate: 29.3%–34.9%) [6]. Our recent study found that acute PTH (APTH) following mTBI led to the disrupted functional connectivity between the periaqueductal grey (PAG) and default mode network (DMN). This pain-related cognitive dysregulation may partially due to the over-attention on brain injury-related symptom. However, the underlying neurobiological basis and modulatory component remained unclear.

TBI can induce a multitude of inflammatory biomarkers perpetuating the secondary injury to the brain [7, 8], which upregulates central nerve system (CNS) excitability contributing to the generation and persistent of concomitant headache [9–11]. Multiple pain disorders have altered grey matter volume (GMV) within the pain matrix [12, 13]. Notably, peripheral inflammatory cytokines/chemokines can interact with multiple central pathways as a principal channel for inflammation-brain communication in the development of pain states [14, 15]. Considering the potential effect of trauma-induced systemic inflammation on brain cell reaction [16, 17], we hypothesized that the inflammatory cytokines level might lead to changes in pain perception via inflammation-brain mechanism [18, 19], specifically by affecting cortical morphology alternations in pain-related cognitive modulation following mTBI [20].

The present study investigated modifications of GM volume to identify those brain regions related to the emergence and persistence of pain condition known as PTH following mTBI, and contrasted patients without PTH, in addition to healthy controls. This study was aimed to examine whether GMV changes mediated the relationship between inflammation and PTH in acute mTBI patients. Longitudinally, we hypothesized that both inflammatory response and brain morphological alterations contributed to those mTBI patients who finally developed into CPTH.

Material and methods

Participants

Seventy-seven patients (45 male, ages of 34.7 ± 12.2 years, education level of 8.6 ± 3.8 years) with mTBI and

forty-two matched healthy controls (HC, 21 male, ages of 35.3 ± 11.2 years, education level of 10.5 ± 5.2 years) were recruited in the study (Clinical trial: NCT02868684). All consecutive patients from the local emergency department (ED) with non-contrast head CT due to acute head trauma enrolled as the initial population. Inclusion criteria for mild TBI were based on the World Health Organization's Collaborating Centre for Neurotrauma Task Force [21]. Mild TBI patients were excluded: 1) history of a previous brain injury, preexisting headache, neurological disease, long-standing psychiatric condition, or concurrent substance or alcohol abuse, 2) structural abnormality on conventional neuroimaging (CT and MRI), 3) intubation and/or presence of a skull fracture and administration of sedatives, 4) the manifestation of mild TBI due to medications by other injuries (e.g., systemic injuries, facial injuries, or spinal cord injury), 5) other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions), 6) caused by penetrating craniocerebral injury. Patients with structural abnormality on conventional neuroimaging and a premorbid condition, such as history of a previous brain injury, preexisting headache, neurological disease, concurrent substance or alcohol abuse were excluded. MRI scanning for mTBI patients was originally evaluated within 7 days post-injury (acute phase) and follow-up at 3 month post-injury (chronic phase). Measures for patients were circulating markers of inflammation, clinical and neuropsychological assessments within 48 h of MRI scans.

MTBI patients were divided into two groups based on the presence of PTH at the acute stage (within 7 days post-injury): mTBI with and without acute posttraumatic headache (APTH) according to the Third Edition of the International Classification of Headache Disorders (ICHD-3) [22]. If the headache persists for longer than 3 months after head trauma, it is described as the chronic/persistent PTH (CPTH/PPTH).

Healthy subjects carefully screened for history of acute/chronic pain, neurological or psychiatric disorder, were also recruited. Forty-two age-, sex- and education-matched healthy volunteers completed an identical neuroimaging scan and assessments at a single time point as a control group. The study was approved by the local ethics committee in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. (see online [supplementary eMethods](#)).

Serum biomarker collection and assay

Serum samples for both patients and controls were collected in the morning around 7–8 am. Sample were aliquoted and stored at -80°C until the time of assay after collection and centrifugation. Serum cytokine levels (pg/mL) were measured using reagents on a Luminex

multiplex bead system (Luminex Austin, TX, USA). A fluorescence detection laser optic system was used to analyze binding of each individual protein on the microsphere simultaneously, which permits multiplexed analysis of several analytes in one sample. Intra- and inter-assay coefficients of variation observed for Luminex quantification were less than 20% and 25%, respectively. Samples with levels that were undetectable by the assay were set to the value of 0.01 pg/mL. The criteria for cytokines selection were mainly based on whether it's related to TBI or clinical symptoms such as PCS and pain function [23, 24]. The cytokines included (i) the archetypal pro-inflammatory cytokines: IL-1 β , IL-6 and IL-12, and the anti-inflammatory cytokines IL-4, IL-10; (ii) chemokine (C-C motif) ligand 2 or monocyte chemoattractant protein-1 (CCL2 or MCP-1) and member of the CXC chemokine family (CXCL8) IL-8; (iii) interferon- γ (IFN- γ); and (iv) tumor necrosis factor α (TNF- α).

Clinical evaluations and pain symptom measurement

Clinical evaluations included post-injury days, duration for both the posttraumatic amnesia (PTA) and loss of consciousness (LOC). Intensity of pain symptoms were assessed by the Visual Analogue Scale (VAS, range 0–10) [25]. The Pain VAS confines to patient-report (PR) measures including pain subscales for the current headache and current general pain as well as mean, best and worst levels of general pain intensity experienced in the preceding week. The VAS ranges from 0 to 10, with 0 meaning “no pain at all” and 10 “the worst possible pain” and reliably tested in previous reports [26, 27]. The impact of headache on patients' lives was also evaluated with the Short-Form Headache Impact Test (HIT-6) [28, 29].

Neuropsychological assessment

A comprehensive neuropsychological assessments included: *i*) Trail-Making Test Part A and Digit Symbol coding score from the Wechsler Adult Intelligence Scale III (WAIS-III) to examine cognitive information processing speed; *ii*) Forward Digit Span and Backward Digit Span from the WAIS-III to assess immediate auditory span, working memory, and executive function; *iii*) Verbal Fluency Test to assess verbal fluency including language ability, semantic memory and executive function; *iv*) Depression severity was assessed using the Beck Depression Inventory (BDI-II); *v*) Posttraumatic stress disorder (PTSD) Checklist - Civilian Version (PCL-C); *vi*) Fatigue Severity Scale, Insomnia Severity Index. In addition, post concussive symptoms (PCS) were measured with the Rivermead Post-Concussion Symptom Questionnaire (RPQ) [30] consisting of 16 items, which was specifically developed to assess the severity of symptoms experienced after brain injury.

Image acquisition

The protocol for scanning included a non-contrast CT scan for acute head injury. MRI scanning was conducted on 3 T MRI scanner (GE 750) and included the T1-weighted 3D BRAVO sequence, conventional T1- and T2-weighted image, and susceptibility weighted imaging (SWI) (see online [supplementary eMethods](#)).

MRI data processing

The T1-MRI images were processed using the Computational Anatomy Toolbox (CAT12) in Statistical Parametric Mapping 12 (SPM12; <https://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Anatomical images were firstly segmented into the gray matter, white matter, and cerebrospinal fluid (CSF), spatially normalized into the Montreal Neurological Institute (MNI) template space, and then smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum. Group differences on GMV using the total intracranial volume, the white matter volume, age, and sex as covariates were performed with a cluster forming (voxel-wise) threshold of uncorrected $p < 0.001$ and then corrected for multiple comparisons at the cluster level ($p < 0.05$, family-wise error (FWE) rate correction). To explore the influence of depression on GMV, we repeated the above analyses of between-group differences after adding the BDI-II score as covariate. Absolute threshold masking was set at 0.1 to avoid edge effects between gray and white matter. Based on the previous studies of pain-related diseases [31], we performed region of interest (ROI) analysis within the pain matrix including the anterior and posterior cingulate cortex, prefrontal cortex, insula, hippocampus, middle and inferior temporal gyrus, and thalamus, according to the Brodmann template using Slice Viewer in REST V1.8.

Mediation analysis

To examine whether regional GMV could mediate the effect of inflammation cytokines on pain symptom in the acute PTH, a mediation analysis was performed by using the PROCESS tool [32] as implemented in SPSS v.21. Firstly, a stepwise regression model was used to calculate the odd ratio of the serum biomarker for pain symptom measurements in mTBI patients. Secondly, based on the results of the stepwise regression analysis, resulting serum biomarker was entered as the independent variable, pain symptom measurements as the dependent variable. The mean GM volume for each region showing significant group difference was tested separately as the mediator variable in the mediation analyses, and age, sex, education and injury time as covariates of no interest.

Longitudinal analysis in CPTH

Changes of the acute serum biomarker related to the pain symptom were compared over time from acute to 3 months post-injury within each group (mTBI + CPTH and mTBI – CPTH groups), using the general linear model of repeated measure analysis of variance (RM-ANOVA) respectively.

Statistical analysis

Statistical analysis was performed using the Statistical Package SPSS version 20. The Shapiro-Wilk W test was used to test for normality distribution of all continuous variables. Logarithmic transformations were computed if those variables that were not normally distributed (ie, the inflammatory biomarkers). The independent two-sample t-test and the Mann-Whitney test were used to compare group differences based on data normality. Chi-square analyses were applied to assess categorical variables. Continuous variables were compared between three groups using one-way analysis of variance (ANOVA), Bonferroni's post hoc test and Kruskal-Wallis H Tests. $P < 0.05$ were considered to indicate a significant difference. Between-group difference in both acute and chronic post-injury GM volume abnormalities was conducted using the general linear model in the SPM12. Using a conjunction analysis [33], the different subgroups of mTBI patients (with PTH and without PTH) were compared to each other and to controls in both acute and chronic phases respectively. Additionally, the relationship between the GM volume for each identified ROI and pain measures were conducted using the multivariate linear regression analysis after adjusting for confounding covariates (age, sex, education and injury time). For each model, pain symptom measurements (P-VAS and HIT-6) were entered as dependent variables and brain regions showing significant GMV group difference were entered as independent variables. This procedure was repeated for both initial and follow-up data, and corrected for multiple comparisons using Bonferroni correction.

Results

Demographic, clinical and neuropsychological measures

Demographic, behavioral and conventional MRI characteristics of the mTBI subgroups (for both initial and follow-up stages) and HC participants were summarized in the Table 1. In the acute phase (2.39 ± 1.47 days, range: 0–6 days), a seventy-seven patients were divided into two subgroups: 1) mTBI + APTH, 60 individuals with APTH after mTBI, 2) mTBI – APTH, 17 individuals with mTBI without headache. Forty-two matched healthy controls were recruited in the study. Fifty-four patients (70.1%) from the original sample (mTBI + CPTH: 15; mTBI – CPTH: 39) returned for their follow-

up visit at 3 months post-injury (111.4 ± 22 days, range: 93–198). At follow-up, there were significant difference between groups in years of age and education. Post-hoc analysis further showed mTBI + CPTH was significantly older than that of mTBI – CPTH ($p = 0.007$) and HCs ($p = 0.046$). The years of education in the mTBI + CPTH was lower than that of HCs ($p = 0.017$). Twenty-three patients were excluded for refusing or indefinitely postponing follow-up request. 25% of mTBI + APTH patients converted to persistent PTH known as CPTH during a follow-up 3 month post-injury.

In both acute and chronic stages, there were significant differences among the three groups for pain ratings and impact of pain on patients' lives, such as 5-item subscale of P-VAS scores and HIT-6 using Kruskal-Wallis H Tests ($p < 0.0001$). Post-hoc analysis further showed mTBI + APTH presented more pain complaints and higher HIT-6 scores, compared with both mTBI – APTH and HCs. Similarly, mTBI + CPTH also experienced more pain complaints and higher HIT-6 scores than that of the mTBI – CPTH and HCs. Additionally, mTBI + APTH group reported more PCS complaints than that of the mTBI – APTH group ($p = 0.007$). Additionally, in comparison with the mTBI – CPTH group, mTBI + CPTH group developed more PCS complaints ($p = 0.003$). Other key clinical measurement of TBI severity showed no between-group differences in patients (Table 2).

Global tissue volume changes

For both initial and follow-up stages, there were no significant differences in the total intracranial volume ($p = 0.873$; $p = 0.825$), gray matter volume ($p = 0.283$; $p = 0.779$), white matter volume ($p = 0.067$; $p = 0.151$), or cerebrospinal fluid volume ($p = 0.129$; $p = 0.799$) among these three groups (Table 1).

Regional GM volume abnormalities at acute post-injury stage - effect of onset of PTH

For the ROI-based analysis, mTBI + APTH exhibited increased GM volume in the right ventrolateral prefrontal cortex/orbitofrontal cortex (VLPFC/OFC), dorsal anterior cingulate cortex (dACC), dorsal posterior cingulate cortex (dPCC), and bilateral parahippocampal gyrus compared with both mTBI – APTH and HC groups (Table 3 and Fig. 1). There was no significantly decreased GM volume of regions in the mTBI + APTH groups. No other regions that fell outside a priori regions of interest was detected.

Regional GM volume abnormalities at chronic post-injury stage - effect of PTH progression

The increased GM volumes in the dACC and dPCC were still persistent in the mTBI + CPTH, while there

Table 1 Demographic and clinical characteristic for acute/chronic mTBI subgroups and HC participants

	HCS n = 42	Acute phase		P value*	Chronic phase		P value ⁺
		mTBI + APTH n = 60	mTBI - APTH n = 17		mTBI + CPTH n = 15	mTBI - CPTH n = 39	
Demographic							
Age in years	35.3 ± 11.2	37.47 ± 12.6	30.4 ± 12.8	0.109	44.1 ± 12.8	32.8 ± 12.2	0.009 ^e
Males (%) ^c	21 (50%)	37 (61.7%)	8 (47%)	0.381	6 (40%)	24(61.6)	0.313
Years of education	10.5 ± 5.2	8.6 ± 4.0	9.0 ± 2.8	0.095	7.0 ± 4.8	9.2 ± 3.5	0.016 ^f
Pain measurement							
Present headache pain intensity ^k	0	4(1–10)	0	<i>p</i> < .0001 ^a	2(1–4)	0	<i>p</i> < .0001 ^g
HIT-6 ^k	36	48(36–68)	36	<i>p</i> < .0001 ^a	50(36–68)	36	<i>p</i> < .0001 ^g
Present general pain intensity ^k	0	1(0–6)	0(0–4)	<i>p</i> < .0001 ^a	0(0–2)	0(0–1)	<i>p</i> < .0001 ^g
Average pain intensity over the past week ^k	0	4(1–8)	0(0–4)	<i>p</i> < .0001 ^a	2(0–5)	0(0–4)	<i>p</i> < .0001 ^g
Best pain intensity ^k	0	0(0–8)	0(0–2)	<i>p</i> < .0001 ^a	0(0–2)	0	<i>p</i> < .0001 ^g
Worst pain intensity ^k	0	6(2–10)	0(0–6)	<i>p</i> < .0001 ^a	4(0–6)	0(0–6)	<i>p</i> < .0001 ^g
Neuropsychological ratings							
PCL-C ^k	28 ^A /23.5 ^B	78.0	76.3	<i>p</i> < .0001 ^b	81.7	62.6	<i>p</i> < .0001 ^h
WAIS-III Coding	36.1 ± 15.8	33.7 ± 16.0	31.3 ± 13.8	<i>p</i> < .0001 ^c	33.7	50.8	<i>p</i> = .126
Trail Making A (s)	46.7 ± 16.8	61.1 ± 49	43.4 ± 32.0	0.118	68.7 ± 59.4	38.6 ± 22.3	<i>p</i> = .021 ⁱ
Forward Digit Span	45.9 ± 33.1	10.2 ± 9.4	8.5 ± 2.8	0.358	7.7 ± 1.7	8.7 ± 1.5	<i>p</i> = .137
Backward Digit Span	8.3 ± 1.5	4.2 ± 2.1	4.2 ± 1.7	0.693	4.1 ± 1.9	4.6 ± 1.5	<i>p</i> = .623
Verbal Fluency Test	4.5 ± 2	14.8 ± 5.9	15.0 ± 4.8	0.003 ^b	17.3 ± 7.0	17.8 ± 5.4	<i>p</i> = .668
BDI-II	18.7 ± 6.4	5.2 ± 5.1	4.2 ± 4.5	<i>p</i> < .0001 ^c	5.8 ± 3.9	4.4 ± 2.5	<i>p</i> < .0005 ^j
FSS ^k	60.5 ^A /48.5 ^B	57.7	67.1	0.138	48.5	48.5	<i>p</i> = 1
ISI	1.6 ± 2.3	7.3 ± 5.8	4.3 ± 3.7	<i>p</i> < .001 ^d	4.4 ± 4.3	2.9 ± 3.3	<i>p</i> = .008 ^k
MRI characteristics							
Total intracranial volume	1467.2 ± 149.4	1462.8 ± 141.4	1446.2 ± 119.1	0.873	1454.3 ± 153.9	1448.5 ± 115.1	0.825
Gray matter volume	631.7 ± 70.5	627.0 ± 64.9	602.4 ± 48.5	0.283	617.9 ± 49.9	627.0 ± 64.0	0.779
White matter volume	519.9 ± 66.9	508.5 ± 52.1	480.4 ± 57.8	0.067	505.9 ± 59.7	493.9 ± 51.1	0.151
Cerebrospinal fluid	314.8 ± 89.7	326.4 ± 106.2	374.5 ± 119.2	0.129	329.7 ± 94.3	327.0 ± 99.1	0.799

Mean ± standard deviation are reported. Sex is reported as frequencies. ^c Chi-square; ^k Kruskal Wallis (median (range) reported for pain measurement; mean ranks reported for the other measurement); ^A Comparisons of mTBI + APTH, mTBI-APTH and HCs; ^B Comparisons of mTBI + CPTH, mTBI-CPTH and HCs

Abbreviations: HIT-6 Short Form Headache Impact Test, PCL-C PTSD Checklist – Civilian Version, WAIS Wechsler Adult Intelligence Scale – Third Edition, BDI-II the Beck Depression Inventory- Second Edition, FSS Fatigue Severity Scale, ISI Insomnia Severity Index, mTBI + APTH mild traumatic brain injury and acute post-traumatic headache, mTBI-APTH mild traumatic brain injury without acute post-traumatic headache, HCs healthy controls, mTBI + CPTH mild traumatic brain injury and chronic post-traumatic headache, mTBI-CPTH mild traumatic brain injury without chronic post-traumatic headache

* For comparisons among acute mTBI subgroups and HC participants. ⁺ For comparisons among chronic mTBI subgroups and HC participants

^amTBI + APTH > mTBI - APTH, HCs; *p* < .0001

^bmTBI + APTH, mTBI - APTH > HCs; *p* < .005

^cmTBI + APTH, mTBI - APTH < HCs; *p* < .005

^dmTBI + APTH > HCs; *p* < .001

^emTBI + CPTH > mTBI - CPTH, HCs; *p* < .05

^fmTBI + CPTH < HCs; *p* < .05

^gmTBI + CPTH > mTBI - CPTH, HCs; *p* < .0001

^hmTBI + CPTH, mTBI - CPTH > HCs; *p* < .0001

ⁱmTBI + CPTH > mTBI - CPTH; *p* < .05

^jmTBI + CPTH, mTBI - CPTH < HCs; *p* < .00005

^kmTBI + CPTH > HCs; *p* < .05

were also decreased GM volume in the right dorsolateral prefrontal cortex/orbitofrontal cortex (DLPFC/OFC), in comparison with both the mTBI - CPTH and HC groups (Table 3 and Fig. 2). In addition, mTBI + CPTH

group also showed brain volume increase in the left primary motor cortex (M1) and cerebellum by using exploratory whole-brain analysis of GMV. The repeated analyses with adding the BDI-II score as covariate at

Table 2 Patients's clinical data

Initial (acute phase)	mTBI + APTH	mTBI - APTH	P (2-tailed)
Duration after onset of mTBI, day	2.42 ± 1.45	2.29 ± 1.57	0.65
Duration of LOC (min)	9.70 ± 8.94	10.76 ± 12.96	0.78
Duration of PTA (h)	0.28 ± 1.01	0.18 ± 0.53	0.86
PCS (RPQ-6)	10.37 ± 6.95	5.59 ± 3.18	0.007
Follow-up (chronic phase)	mTBI + CPTH	mTBI - CPTH	P (2-tailed)
Duration after onset of mTBI, day	104 ± 12	114.1 ± 23.92	0.14
Duration of LOC (min)	7.9 ± 6.2	9.74 ± 10.2	0.433
Duration of PTA (h)	0.2 ± 0.56	0.15 ± 0.49	0.767
PCS (RPQ-6)	15 ± 7.09	8.13 ± 5.48	0.003

Mean ± standard deviation are reported. *mTBI + APTH* mild traumatic brain injury and acute post-traumatic headache, *mTBI - APTH* mild traumatic brain injury without acute post-traumatic headache, *mTBI + CPTH* mild traumatic brain injury and chronic post-traumatic headache, *mTBI - CPTH* mild traumatic brain injury without chronic post-traumatic headache, *PCS* Post concussive symptoms, *RPQ* Rivermead Post-Concussion Symptoms Questionnaire, *LOC* Loss of consciousness, *PTA* Posttraumatic amnesia

Table 3 Regions showing significant GM volume changes at initial and follow-up among different subgroups of mTBI patients and HCs

Comparisons	Findings	Cerebral regions	Area (Brodmann area)	Cluster size Voxels	t	Peak coordinate		
						x	y	z
Initial GM volume abnormalities (acute phase)								
mTBI + APTH vs Control groups^a	Increased GM volume	L, R Parahippocampal gyrus	Parahippocampal (BA 35)	54	4.38	20	−20	−2
		R Anterior cingulate	dACC (BA 32)	105	4.68	11	15	0
		R Posterior cingulate	dPCC (BA 31)	47	4.07	6	−24	45
		R Inferior frontal gyrus	VLPFC/OFC (BA 47, 10)	39	4.50	26	27	48
Follow-up GM volume abnormalities (chronic phase)								
mTBI + CPTH vs Control groups^b	Increased GM volume	L Anterior cingulate	dACC (BA 32)	64	4.54	−	12	41
		L Posterior cingulate	dPCC (BA 31)	78	4.47	−11	−	36
		L Precentral gyrus	M1 (BA 4)	53	4.20	−18	−32	69
		L Temporal gyrus	ITG (BA 20)	66	4.67	−59	−48	−15
		L Cerebellar declive	−	65	5.14	−45	−59	−27
mTBI + CPTH vs Control groups^c	Decreased GM volume	R Inferior frontal gyrus	DLPFC/OFC (BA9,10)	53	4.92	9	59	33

Data were thresholded of $P < 0.05$ with FWE correction at the cluster level for multiple comparison. Peak coordinates refer to the MNI atlas dACC dorsal anterior cingulate cortex, dPCC dorsal posterior cingulate cortex, VLPPC Ventrolateral prefrontal cortex, OFC Orbitofrontal cortex. M1 primary motor cortex, ITG Inferior temporal gyrus, DLPFC Dorsolateral prefrontal cortex, *mTBI + APTH* Mild traumatic brain injury and acute post-traumatic headache, *mTBI - APTH* Mild traumatic brain injury without acute post-traumatic headache, *HCS* Healthy controls. *mTBI + CPTH* mild traumatic brain injury and chronic post-traumatic headache, *mTBI - CPTH* mild traumatic brain injury without chronic post-traumatic headache, *FWE* Family-wise error

^aConjunction analysis of mTBI + APTH vs mTBI - CPTH and mTBI + APTH vs HCs corrected for age, sex, the white matter volume and total intracranial volume ($p < 0.05$, FWE corrected)

^bConjunction analysis of mTBI + CPTH vs mTBI - CPTH and mTBI + CPTH vs HCs corrected for age, sex, the white matter volume and total intracranial volume ($p < 0.05$, FWE corrected)

^cConjunction analysis of mTBI + CPTH vs mTBI - CPTH and mTBI - CPTH vs HCs corrected for age, sex, the white matter volume and total intracranial volume ($p < 0.05$, FWE corrected)

MTBI patients with APTH > MTBI patients without APTH

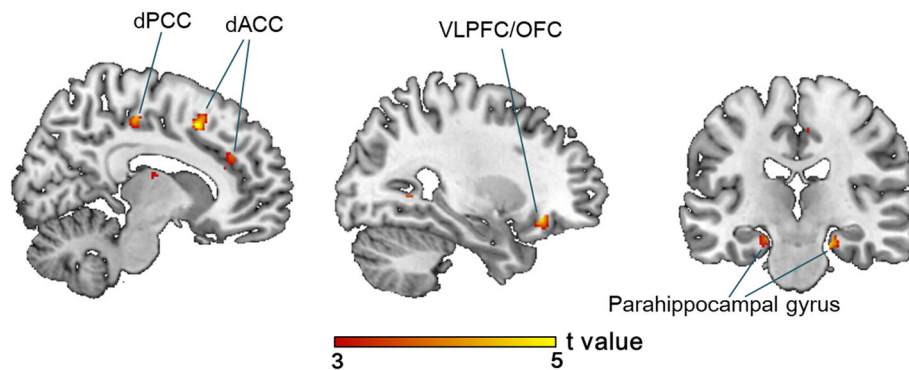
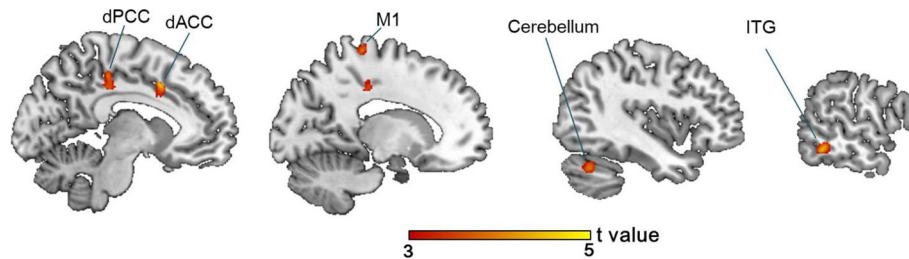


Fig. 1 GM volume changes in mTBI + APTH. Areas showing GM volume changes in patients with mTBI + APTH, compared with HC and mTBI – APTH groups (conjunction $p < 0.05$, FWE corrected), represented on a high-resolution T1-weighted template. Regions of increased GM volume are represented in red (color-coded for their t value). dACC = dorsal anterior cingulate cortex, dPCC = dorsal posterior cingulate cortex, VLPFC = ventrolateral prefrontal cortex, OFC = orbitofrontal cortex. mTBI + APTH = mild traumatic brain injury and acute post-traumatic headache, mTBI – APTH = mild traumatic brain injury without acute post-traumatic headache, HCs = healthy controls

MTBI patients with CPTH > MTBI patients without CPTH



MTBI patients with CPTH < MTBI patients without CPTH

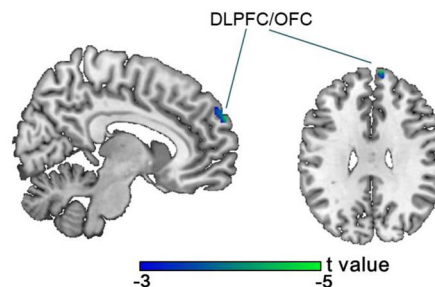


Fig. 2 GM volume changes in mTBI + CPTH. Areas showing GM volume changes in patients with mTBI + CPTH, compared with HC and mTBI – CPTH groups (conjunction $p < 0.05$, FWE corrected), represented on a high-resolution T1-weighted template. Regions of increased GM volume are represented in red (color-coded for their t value), and regions of decreased GM volume are shown in blue (color-coded for their t values). dACC = dorsal anterior cingulate cortex, dPCC = dorsal posterior cingulate cortex, M1 = primary motor cortex, ITG = inferior temporal gyrus, DLPFC = dorsolateral prefrontal cortex, OFC = orbitofrontal cortex. mTBI + CPTH = mild traumatic brain injury and chronic post-traumatic headache, mTBI – CPTH = mild traumatic brain injury without chronic post-traumatic headache, HCs = healthy controls

both acute and chronic post-injury stage yielded similar results. Thus, the possible influence of depression level on GM volume changes can be excluded.

Regression analysis

Further regression analysis was restricted within the clusters showing significant between-group differences in the GMV for both acute and 3-month follow-up (Table 3). During the acute stage, higher levels of HIT-6 were significantly correlated with increased GM volume in the right dACC ($\beta = 0.333$, $p = 0.005$) and dPCC ($\beta = 0.459$, $p = 0.001$) in the whole mTBI cohort, while still significant in the right dPCC ($\beta = 0.389$, $P = 0.007$) in mTBI + APTH group. There was no correlation between GMV and pain symptom measured by P-VAS and HIT-6 at follow-up stage. Further, Serum biomarker was used to build a stepwise regression model with pain symptom measurement. Only higher CCL2 level in the acute stage was associated with greater severity of HIT-6 scores in the whole mTBI cohort during the acute phase and selected for further mediation analysis ($p = 0.002$, effect size = 0.355) (Table 4). In addition, there were significant differences among the three groups for acute CCL2 level using one-way analysis of variance (ANOVA) ($F(2, 116) = 3.165$, $p = 0.046$). Post-hoc analysis further showed that CCL2 was significantly elevated in mTBI + APTH group, compared with mTBI-APTH group ($p = 0.039$). It indicated a nonstatistically significant trend of increased CCL2 level in mTBI + APTH group, compared with the HCs group ($p = 0.052$). There was no significant difference in CCL2 level between the mTBI-APTH and HCs group ($p = 0.534$).

Mediation analysis

We tested whether GM volume (i.e. increased GM regions) mediates the association between CCL2 levels and

HIT-6 scores. The independent factor was CCL2 levels, and dependent variable was headache impact severity indicated by the HIT-6, with identified GM volume alterations as mediators. Results indicated that increased volume in the dPCC partially mediated CCL2 level on HIT-6 scores (Fig. 3, mean [SE] indirect effect, 0.088 [0.0462], 95% CI, 0.01–0.164) in acute mTBI patients.

Longitudinal analysis of CPTH

The CCL2 level significantly increased from acute stage to 3 months post-injury only in the mTBI + CPTH group ($F(1, 14) = 6.53$, $p = 0.023$), but not in the mTBI – CPTH group ($F(1, 38) = 3.23$, $p = 0.08$) (Fig. 4). In addition, increased GMV of the dPCC and dACC in acute PTH also exhibited persistent increases in mTBI + CPTH group, compared with both mTBI – CPTH and HC groups.

Discussion

The major findings were increased inflammation levels accompanied by increased GMV of the dPCC and dACC in mTBI patients with APTH, relative to both the control groups (mTBI – APTH and HCs). The inflammation effect on the headache impact was partially mediated by the GMV of dPCC. Longitudinally, greater upregulation in the CCL2 level accompanied by consistently increased GMV in the dPCC and dACC contributed to those patients who finally developed into the CPTH.

The observed pattern of increased GMV differs from some previous studies that commonly reported decreased GMV in pain-related disorders, partly due to the fact that APTH patients experienced a traumatic exposure that can lead to both physical and psychological reactivity, and thus developed an adaptive anti-nociceptive mechanism manifesting as regional hypertrophy in pain-

Table 4 Stepwise multiple regression analysis

Inflammatory Level	Correlation coefficient	T	P	Partial correlation	Collinearity statistics	
					Tolerance	VIF
CCL2 ^a	0.355	3.283	0.002*	0.355	1.000	1.000
IL-1 β ^b	0.015	0.139	0.890	0.016	1.000	1.000
IL-4 ^b	0.010	0.093	0.927	0.011	0.999	1.001
IL-6 ^b	–0.106	–0.981	0.330	–0.113	0.994	1.006
IL-8 ^b	–0.027	–0.185	0.854	–0.022	0.542	1.843
IL-10 ^b	0.025	0.229	0.819	0.027	0.991	1.009
IL-12 ^b	0.017	0.156	0.876	0.018	1.000	1.000
IFN- γ ^b	0.038	0.347	0.730	0.040	0.999	1.001
TNF- α ^b	0.032	0.291	0.772	0.034	1.000	1.000

^aEntered variables

^bExcluded variables

* $p < .05$

Outcome: HIT-6

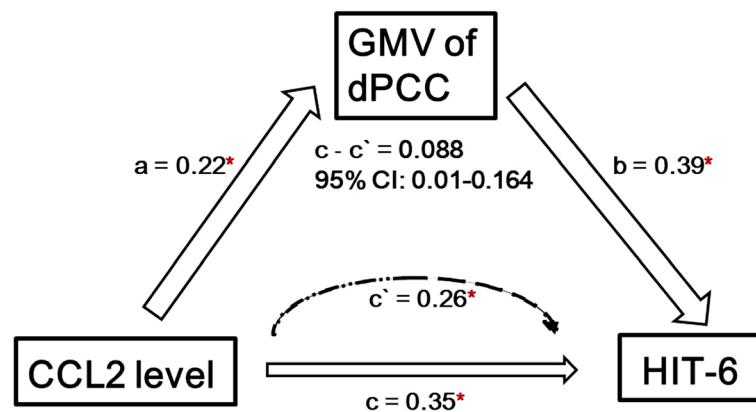


Fig. 3 Mediation model. The relationship among CCL2 level, GMV of dPCC from conjunction analysis and HIT scores. Alteration of gray matter volume in the dPCC mediates the relationship between CCL2 level and HIT scores in early mTBI patients. Covariates (age, sex, education, injury time) were included in the model. Abbreviations: dPCC = dorsal posterior cingulate cortex; CCL2 = C-C motif chemokine ligand 2; HIT = short form headache impact test

related areas [34]. Also, prior structural studies in PTH were typically conducted on patients with chronic course of headache, confirming that patients with persistent PTH had significantly reduced grey matter volume (GMV) or less cortical thickness [13, 35]. To our knowledge, it remained unknown that if brain morphologic abnormality is associated with the acute onset of PTH. Our findings indicated that acute brain trauma-related headache (within 7 days) may shift the brain into a state that fostered rapid defence mechanisms seen in increased GMV. Interestingly, the increased GMV pattern was found in regions primarily located in the default mode network (DMN), including dACC, dPCC and parahippocampal gyrus. Our previous study had found disruption of periaqueductal grey-DMN functional connectivity in APTH after mTBI. Thus, these findings

complement and extend existing literature by indicating a potential structural basis for the disrupted functional connectivity of the DMN involved in the antinociceptive descending modulation network following mTBI [36].

Neuropsychological assessment showed that both the mTBI + APTH and mTBI + CPTH groups reported higher insomnia severity index (ISI) scores than HC group, which support the notion that PTH has impacts on sleep quality and can lead to poor recovery after mTBI [37]. Correlation analysis further revealed that the higher GMV in the right dACC and dPCC contributed to the impact of PTH on the poorer quality of life. DMN dysfunction has been reported to be involved in both acute and chronic pain conditions, serving as a potential biomarker for pain-related cognitive regulation (i.e., attention impairment) [38, 39]. Importantly, our previous

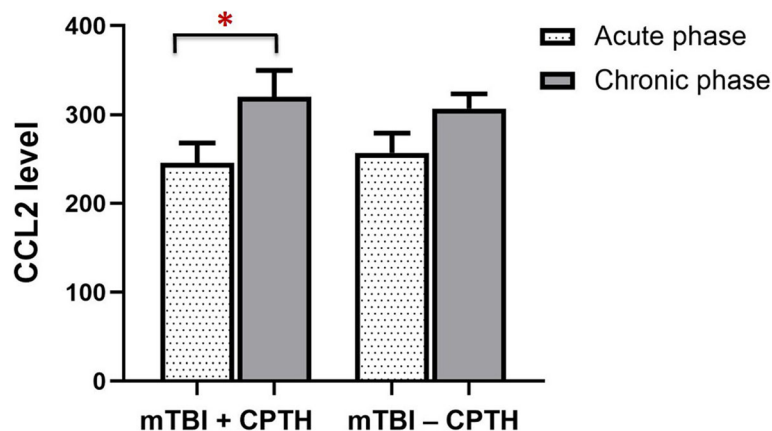


Fig. 4 CCL2 level changes at acute and chronic phase post-injury. The CCL2 level significantly increased between the acute and chronic phase post-injury in the mTBI + CPTH group ($*p < 0.05$, repeated measures analysis of covariance [RM-ANCOVA]), but not in the mTBI - CPTH group ($p = 0.08$, RM-ANCOVA). mTBI + CPTH = mild traumatic brain injury and chronic post-traumatic headache, mTBI - CPTH = mild traumatic brain injury without chronic post-traumatic headache

study have demonstrated that patients with APTH exhibit more attentions on injury-related pain symptoms [20]. In the current study, mTBI + CPTH group showed worse information processing speed (IPS) performance indicated by higher Trail Making A scores than mTBI – CPTH group, accompanying with the persistent GM increase in the dACC and dPCC, which can be engaged in cognitive regulation [40]. These structural changes may be coupled with alterations in the high-order brain areas within the DMN in mTBI + APTH group [41], reflecting the DMN dysfunction in pain cognitive modulation. It also suggested that morphometric alterations can be an appropriate parameter for monitoring PTH in the early stage following mTBI.

The current study also provided some promising to explore the cellular basis for such increased GMV. We found that increased CCL2 level is an independent risk for more headache impact on lives in patients with mTBI. CCL2 is one of chemokines that increases rapidly after various forms of experimental mTBI [42, 43], contributing to secondary brain damage through attracting monocytes to sites of injury and inflammation [44]. Moreover, mTBI-induced disruption of the blood-brain barrier (BBB) [45] allows the passage of inflammatory cells out of the injured brain, and initiates an elevated systemic immune response to the genesis of nociceptor hypersensitivity post-TBI [11]. Of particular interest is the finding of macroscopic GM hypertrophy in the dPCC (a core region in the DMN), which is related to the arousal, self-reference and breadth of attention [40], can mediate the contribution of circulating inflammatory biomarker (i.e. CCL2 level) on pain impact severity during early stage after mTBI. This inflammation-brain communication can be supported by the evidence that astrocytes, which constitute 90% cortical tissue volume, can be activated by proinflammatory cytokines released in the early stage of inflammation and exhibit morphological changes (e.g. hypertrophy) [46, 47]. Thus, we speculate that GM tissue cells can become hyper-reactive by trauma-induced neuroinflammatory effect, and then undergo plastic changes reflected by GMV increases. Unfortunately, VBM-based analysis was limited to determine the specific histopathology underlying GM macrostructural changes. Further study still need to explore the neural mechanism underpinning the bi-directional changes of GMV observed in the progression of chronic PTH. Nevertheless, significant CCL2 rise over time and GM volume increase in dPCC were found in patients developing the CPTH, suggesting that the consistently observed associations of inflammation on PTH were at least partially attributable to their effect on GMV alternations. Taken together, the current study highlighted the role of the circulating CCL2 level in the pathogenesis and progression of PTH [48–50], and

emphasized on the neuroinflammatory mechanism in morphological alternations associated with pain modulation in cognitive domain.

Conclusions

In the current study, we demonstrated that GMV alteration can mediate the relationship between the inflammation and pain dysfunction following early mTBI, and such regional change was primarily located within key DMN region (dPCC). Our finding also held the possibility that both the significant upregulation of CCL2 level and persistent GMV increase (dACC and dPCC) only in the patients with CPTH and can be served as potential predictors and targets of response for therapeutic method.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s10194-020-01201-7>.

Additional file 1.

Abbreviations

dACC: Dorsal anterior cingulate cortex; dPCC: Dorsal posterior cingulate cortex; VLPFC: Ventrolateral prefrontal cortex; OFC: Orbitofrontal cortex; mTBI + APTH: Mild traumatic brain injury and acute post-traumatic headache; CCL2: C-C motif chemokine ligand 2; HIT: Short form headache impact test; mTBI – APTH: Mild traumatic brain injury without acute post-traumatic headache; HCs: Healthy controls; mTBI + CPTH: Mild traumatic brain injury and chronic post-traumatic headache; mTBI – CPTH: Mild traumatic brain injury without chronic post-traumatic headache

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Authors' contributions

XN, HL and LB designed the study and draft of the manuscript. GB, BY performed the experiments. YS, YW, SW, SG and XJ analyzed the data. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the local ethics committee in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication

Not application.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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