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Functional connectivity disruption of the substantia nigra associated with cognitive impairment in acute mild traumatic brain injury

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ABSTRACT

Purpose: Mild traumatic brain injury is known to have frequent cognitive impairment. Accumulating evidence is pointing to the malfunctioning of the substantia nigra (SN) as an important factor for head trauma. However, it remains unknown whether changes in the SN-based resting state functional connectivity following mTBI at acute stage and its relationship with cognitive function.

Materials and methods: 58 patients with mTBI and 30 age-, gender-, and years of education-matched healthy controls were enrolled in the current study. All of participants received resting state functional magnetic resonance imaging as well as neuropsychological assessment. The resting state functional MR imaging data were analyzed by using a standard seed-based whole-brain correlation method to characterize SN resting state networks. Student *t* tests were used to perform comparisons. The association between SN resting state networks and performance on neuropsychological measures was also investigated in patients with mTBI by using Pearson rank correlation.

Results: Patients with mTBI at acute stage exhibited reduced left SN-based functional connectivity with right insula and caudate and increased left SN-based functional connectivity with left precuneus and left middle occipital gyrus, and reduced right SN-based functional connectivity with left insula. Increased functional connectivity of left precuneus was negatively associated with neurocognitive functions as well ($r = -0.266$; $P = 0.049$).

Conclusion: The present study indicated that patients with acute mTBI suffer from disruption in their SN resting state networks. Moreover, abnormal functional connectivity significantly correlated with cognitive function. Taking together, these results may better improve our understanding of the neuropathological mechanism underlying the neurocognitive symptoms associated with acute mTBI.

1. Introduction

Traumatic brain injury (TBI) is a worldwide public health problem, which can be caused in various ways, including motor vehicle, sports, and blasting accidents [1]. About 85% of TBI cases are mild TBI (mTBI), which is more commonly known as concussions, which defined by the Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation [2]. Even though the acute symptoms of mTBI may be mild and transient, approximately 20%–30% of patients still complain of an array of cognitive symptoms following mTBI, including attention, memory, executive function and language deficits [3,4]. It is often assumed that the cognitive deficits will totally recover within the first 3 months after an episode of mTBI, if not,the cognitive decline may persist throughout life, leading to long-term disabilities in their work and social interactions. Therefore, early medical and rehabilitative intervention may reduce chronic cognitive sequelae. However, in most mTBI cases, it is difficult to identify high-risk patients since the cognitive impairment is nonspecific and conventional neuroimaging findings (Computed tomography (CT) and Magnetic Resonance Imaging (MRI)) are frequently normal at acute stage. Therefore, to date, the early diagnosis of mTBI patients with cognitive problems still continue to be a challenge. Moreover, one of the most significant challenges is to understand the underlying pathophysiology in cognitive impairments.

Traditionally, the cognitive impairments have been assumed to be caused by diffuse axonal injury, changes in cerebral blood flow (CBF)

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and cortical gray matter abnormalities, particularly in moderate and severe pathologic models of TBI or recurrent mTBI [5–11]. However, accumulating evidence is pointing toward malfunctioning of the substantia nigra (SN) as an important factor for head trauma [12]. It has been suggested that the SN a plays a crucial role in functions such as action selection, response inhibition and cognitive control. It is also known that several key cognitive functions are controlled by SN such as executive function deficits, memory deficits and, visuospatial deficits, these cognitive functions are often disrupted in patients with mTBI. To our knowledge, the SN is a complex deep gray matter mass which consists of many groups of nuclei and white matter bundles. Hence, the SN is an important node in the extraparimidal system and exhibit complicated afferent and efferent anatomical fiber tracts connected to other regions [13]. It is susceptible to injury during sudden acceleration or deceleration movements during midbrain and brain stem injuries that are common after trauma, particularly in those patients with poor outcome [10]. Previous animal and human studies on TBI showed that TBI can damage the dopaminergic system and cause gross and microscopic changes to the SN [14,15]. Animal models of mTBI showed volume increases in the SN in blast-exposed animals 7 days post-injury, however, Peter O Jenkins et al found reduced SN volume [10]. They yield inconsistent findings. Despite the evidence that the structure of SN changed during trauma, and the structural alterations of the SN has been associated with the presence of cognitive impairment. The functional imaging marker is still missing, and little is known about the underlying structural origin of cognitive impairments.

Resting-state functional MRI (rs-fMRI) based on spontaneous blood oxygenation level-dependent (BOLD) responses has proved to be useful noninvasive neuroimaging to reveal the disease induced neural dysfunction associated with neuropathology, including alterations after mTBI [16,17]. Although functional connectivity such as interrupted default mode networks (DMN) in patients with mTBI has been previously described [18], no studies have focused on the SN networks. The analysis of intrinsic functional architectural changes of the SN with resting-state functional MR imaging with mTBI may have more potential to improve the understanding of disease pathophysiology, aid acute diagnosis.

The aim of this study was to investigate whether SN resting-state networks are disrupted in patients with mTBI compared with healthy controls at acute stage and to explore the association between SN connectivity changes and the cognitive test in these patients. We hypothesized that there is subtle injury involving the SN neurons in patients with mTBI at acute stage as indicated at rs-fMRI and these changes are related with the cognitive performance.

2. Materials and methods

2.1. Participants

This study was approved by the Institutional Review Board of our university. All participants provided written informed consent before undergoing MR imaging. Between December 2017 and September 2018, patients with a diagnosis of mTBI were prospectively enrolled in this study. MTBI was defined based on the American Congress of Rehabitation Medicine. Inclusion criteria were as follows: (a) patients aged 18 or older; (b) loss of consciousness < 30 min, Glasgow Coma Score [GCS] of 13–15 and post-traumatic amnesia < 24 h. Exclusion criteria were: (a) previous head injury; (b)history of pre-existing neurological or psychiatric disease; (c)history of illicit drug use or substance abuse; (d) dental appliances that might distort the functional MR images; (e) left handed. The healthy control participants were recruited through local advertisements who met the same exclusion criteria applied to the patient group.

2.2. Cognitive assessment

Given the emergency care setting, it was not feasible to perform a full battery of neuropsychological assessment. Therefore, a short instrument called the Montreal Cognitive Assessment (MoCA) was used to assess the patients' neurocognitive status [19]. The MoCA is a sensitive cognitive screening test following mTBI and it only requires limited training to administer. The MoCA assesses eight cognitive domains including visuospatial/executive, naming, attention, language, abstraction, memory, and orientation. This test is administered in about 10 min and is scored on a maximum of 30 points. More than 26 was regarded as normal value with a lower score indicating greater cognitive deficit. All participants completed the MoCA test within 12 h of MRI examination.

2.3. Imaging methods

A 3.0 T magnetic resonance imaging scanner (Ingenia, Philips Medical Systems, Netherlands) with an 8-channel head coil was used for this study. Functional images were obtained axially using a gradient echo-planar imaging sequence as follows: repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; slices = 36; thickness = 4 mm; gap = 0 mm; field of view (FOV) = 240 mm × 240 mm; acquisition matrix = 64 × 64; and flip angle (FA) = 90°. The fMRI sequence took 8 min and 8 s. Three-dimensional turbo fast-echo (3D-TFE) T1WI sequence with high resolution: TR = 8.1 mm; TE = 3.7 ms; slices = 170; thickness = 1 mm; gap = 0 mm; FA = 8°; acquisition matrix = 256 × 256; FOV = 256 mm × 256 mm; Fluid-attenuated inversion recovery (FLAIR): TR =7000 ms; TE = 120 ms; slices = 18; slice thickness = 6 mm; gap = 1.3 mm; FA = 110°; Voxel size = 0.65 × 0.95 × 6 mm^3. Susceptibility weighted imaging (SWI): TR = 22 mm; TE = 34 ms; FA = 20; matrix = 276 × 319; slice thickness = 1 mm; FOV = 220 mm × 220 mm. SWI used 3D gradient echo (GRE) sequence. Diffusion tensor imaging (DTI): TR = 3000 mm; TE = 100; slices = 55; slice thickness = 2.5 mm; gap = 0; FA = 90°; b-values = 0 and 1000s/mm^2; diffusion gradient directions = 32; matrix = 128 × 128; FOV = 256 mm × 256 mm.

2.4. Image processing

Functional image analyses were preprocessed with the toolbox Data Processing Assistant for Resting-State fMRI programs based on Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and resting-state fMRI data analysis toolkit (REST, http://www.restfmri.net). The first 10 volumes were discarded and the remaining 230 consecutive volumes were used for data analysis. Afterwards, slice-timing adjustment and realignment for head motion correction were performed. Any participant who had a head motion greater than 3.0 mm or a rotation in the x, y, or z directions higher than 3.0∘ were excluded. Data were spatial normalized to the Montreal Neurological Institute (MNI) template (resampling voxel size = 3 × 3 × 3 mm^3) and smoothed with a Gaussian kernel of 6 mm full width at half maximum (FWHM) to increase signal-to-noise ratio, detrended, and filtered (0.01–0.08 Hz).

Functional connectivity was analyzed using the REST software. The seed ROIs of the left and right SN were generated using the WFU PickAtlas software. The mean time series of each ROI was acquired for reference time course. Then, Pearson's correlation coefficients were computed between the mean signal change of each ROI and the time series of each voxel. Finally, a Fisher's z-transform was applied to improve the normality of the correlation coefficients. For within-group analysis, the individual z values were entered into the SPM8 software for a random effect one-sample t-tests to determine the brain regions showing significant connectivity to bilateral SN at a threshold of $p < 0.01$ with multiple comparisons correction using the AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf) determined by Monte Carlo simulation (single voxel p value = 0.01, a minimum

cluster size of 40, within a GM mask corresponding to the AAL atlas). Two-sample t-tests were performed to investigate differences in functional connectivity of bilateral SN between mTBI patients and healthy controls with a default whole-brain mask. Thresholds were also set at a corrected $p < 0.01$, with multiple comparison correction using the AlphaSim program determined by Monte Carlo simulation.

2.5. Statistical analysis

Differences in demographic data between mTBI patients and healthy controls were analyzed using between-group *t*-test for means and 2-test for proportions ($p < 0.05$ was considered to be significant). To investigate the relationship between fMRI data and clinical cognitive characteristic of mTBI patients, regions showing significant differences between groups were extracted. Then the mean z-values of aberrant functional connectivity region mask were calculated within every subject. Pearson's correlation analysis between the mean z-values and each clinical cognitive characteristic were performed using SPSS 17.0 (version 17.0; SPSS, Chicago, IL, USA). $P < 0.05$ was considered statistically significant, corrected for age, sex and years of education. Bonferroni correction was used for multiple comparisons in the correlation analyses.

3. Results

During the study period, 247 patients with the diagnosis of mTBI presented to our emergency department. Of these, 132 (53.4%) mTBI patients could be contacted and 80 (60.6%) of 132 were willing to participate in the study. Among the 80 mTBI patients, 22 (27.5%) patients were excluded because of pre-existing neurological or psychiatric disease (n = 4), previous head injury (n = 3), dental appliance (n = 3), image distortion (n = 4), or head motion (n = 8). The remaining 58 patients obtained the MR scan at an average of 3.21 days (range, 0–10 days) after head injury. 30 age-, gender- and years of education-matched healthy control participants were finally analyzed.

Table 1 listed the basic demographic characteristics of mTBI group and healthy control group. Both groups did not show any significant difference for age ($P = 0.111$), gender ($P = 0.133$), GCS score, and years of education ($P = 0.068$). All structural MR images including T1W and SWI were normal. Table 2 showed no significant difference between bilateral SN in terms of fractional anisotropy (FA) in mTBI patients ($P = 0.958$), and no difference was found when analyzing FA in healthy controls ($P = 0.812$). FA values were not significantly different between the bilateral SN in the mTBI patients and those in healthy controls (left SN: 0.496; right SN: 0.692).

Table 1
Demographic characteristics and cognitive performance in patients with mTBI and healthy control subjects.

Characteristics	mTBI(n = 58)	Control(n = 30)	*P* Value
Age (y)	38.81 ± 10.671	42.5 ± 9.206	0.111
Gender(male/female)	33/25	12/18	0.133
Education (y)	12.40 ± 2.849	13.65 ± 3.11	0.068
GCS Score	15	15	–
Time since injury(d)	3.21 ± 1.96	–	–
Injury location			
Left	12	–	–
Right	16	–	–
Undefined	30	–	–
MoCA Score	24.78 ± 2.399	26.17 ± 2.465	0.012*
Visuospatial/executive	3.64 ± 1.003	4.20 ± 1.031	0.004*
Naming	2.91 ± 0.283	2.83 ± 0.379	0.262
Attention	5.53 ± 0.732	5.77 ± 0.568	0.093
Language	2.40 ± 0.647	2.50 ± 0.572	0.527
Abstraction	1.81 ± 0.476	1.93 ± 0.254	0.162
Memory	2.60 ± 1.31	2.73 ± 1.701	0.716
Orientation	5.76 ± 0.471	5.90 ± 0.305	0.150

Data are the mean ± standard deviation; $^{*}p < 0.05$. mTBI, mild traumatic brain injury; GCS, Glasgow Coma Scale; MoCA, Montreal Cognitive Assessment.

Table 2
Fractional anisotropy for the substantia nigra between the mTBI and control subjects.

Fractional anisotropy value	mTBI	Control	*P* Values
Left substantia nigra	0.474 ± 0.065	0.455 ± 0.082	0.496
Right substantia nigra	0.476 ± 0.078	0.463 ± 0.091	0.692
P Values	0.958	0.812	

Data are the mean ± standard deviation.

Compared with healthy controls, patients with mTBI demonstrated more widely distributed functional connectivity between the left SN and the bilateral frontal gyrus, temporal gyrus, occipital gyrus, basal ganglia and parietal gyrus during the resting state (Fig. 1). And the right SN resting state networks in patients with mTBI extended more to the frontal gyrus, temporal gyrus, compared with healthy controls (Fig. 1). The significantly decreased functional connectivity in the patient group or the difference between the two groups were found between the left SN and the right insula and caudate, while significantly increased functional connectivity were observed between the left SN and left middle occipital gyrus and left precuneus (Fig. 2A and Table 3). Additionally, patients with mTBI demonstrated significantly decreased function connectivity between the right SN and the left insula, while no significantly increased functional connectivity were observed between the right SN and other brain regions (Fig. 2B and Table 3).

Compared with healthy controls, patients with mTBI showed significantly worse performance on scale of MoCA ($P = 0.012$), there was also significant difference in performance on visuospatial/executive function ($P = 0.004$). No other significant differences in performance on naming, attention, language, abstraction, memory and orientation were revealed in this study. Our study also found that hyper-connectivity in the left precuneus was significantly negatively correlated with MoCA score in patients with mTBI ($r = -0.266$, $P = 0.049$) (Fig. 3). No other significant linear correlations were observed between the functional connectivity of the right caudate, left middle occipital gyrus and left insula and neuropsychological test in patients with mTBI.

4. Discussion

To the best of our knowledge, there is growing interest in examining patients with mTBI to elucidate the pathophysiologic mechanism underlying a variety of cognitive decline. It has been suggested that rs-fMRI is a more sensitive technique for neuropsychological assessment. More evidence is pointing to malfunctioning of the SN as an important factor for head trauma [12], Additionally, the SN plays a crucial role in cognitive control. Nonetheless, previous investigators have only explored the default mode network (DMN) [18], thalamocortical connections [20] and changes of caudate-based resting state functional connectivity [21]. In addition, the previous studies revealed variable rs-fMRI patterns in the acute phase following mTBI [22,23]. This variability is understandable because head trauma consists of both the primary injury and secondary injury during the acute period. The primary injury is a direct result of impact exposure including primarily axonal injury. The secondary injury may include brain edema, neurotransmitter release, and vascular dysfunction. To date, involvement of the SN in the cognitive deficits following mTBI has been not investigated.

Our study indicates that there is decreased functional connectivity between the left SN and the right insula which was in line with previous studies. One previous study with healthy subjects revealed that the anatomical resting-state functional connectivity maps of the SN incorporate insular cortex [13]. In fact, the insula cortex as a brain structure has many diverse functions. Emerging evidence indicates that

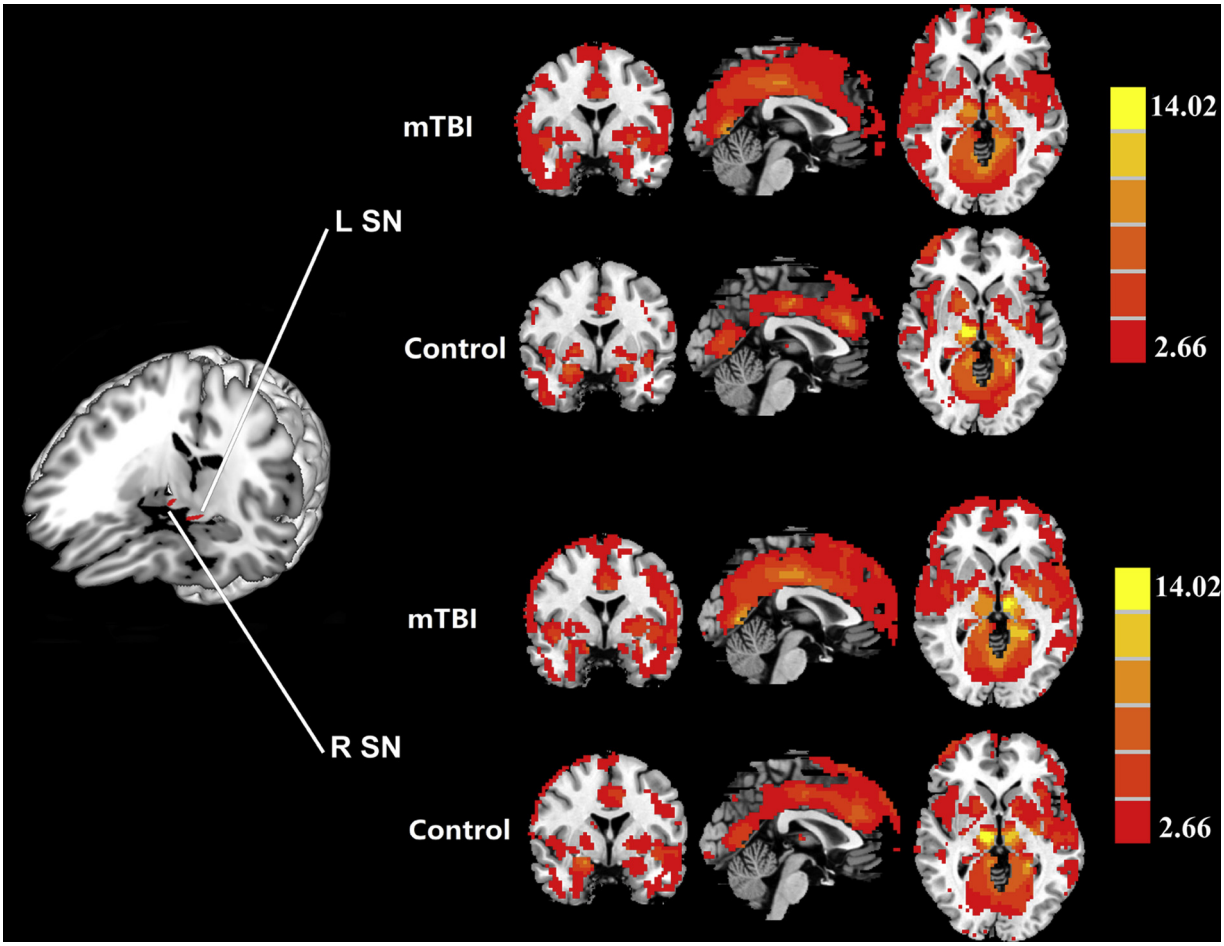

Fig. 1. Images show group substantia nigra resting-state networks obtained by using the one-sample t test in patients with mTBI and healthy controls. The patterns of the left substantia nigra (L-SN) and right substantia nigra (R-SN) functional networks were shown, respectively.

the insula cortex is a centre of salience processing across multiple sensory and cognitive domains [24]. One co-activation meta-analysis reported that the insula can be subdivided into three parts, such that the dorsal anterior portion is more involved in high level cognitive processes (such as task switching, inhibition or error processing) [25]. Furthermore, the anterior insular cortex (AIC) was thought to be a more important component which mediates the control of cognition. Actually, the real position of the insular cortex was the AIC in the current study. Several researchers have demonstrated an association between smaller insular volume and reduction in the cognitive function. Some studies revealed significantly reduced regional homogeneity (ReHo) in the left insula, additionally, this pattern of connectivity correlated with the Mini-Mental State Examination (MMSE) scores [26]. This study also demonstrated that the strength of functional connectivity in the right insula was negatively correlated with orientation score. These functional brain studies, along with the present findings were associated with cognitive sequelae, suggesting a theoretical model in which the insula is an essential integrating node in brain networks needed to control high order cognitive function. It is an important relay for cognitive switching from resting state to task-positive networks (TPNs).

In our data, the SN was found to be connected with the striatal cortex, which is consistent with the SN's neuroanatomical projections and with the role of dopamine in the modulation of brain functional connectivity. One third of patients with moderate-severe TBI had abnormal striatal dopamine transporter (DaT) on clinical reporting[10]. Furthermore, previous studies suggested that the dopaminergic system is commonly affected by TBI [10]. The striatum is subdivided into the caudate, putamen and nucleus accumbens. DaT abnormalities in the caudate were associated with reduced SN volume, and there was evidence of nigrostriatal tract damage particularly affecting projections to the caudate [10]. Consistent with previous findings, significantly decreased functional connectivity between the left SN and the right caudate was also found. The caudate is most commonly affected although all areas of the striatum can be disrupted and it was affected to a great extent than other striatal regions following TBI. Moreover, the caudate has its distinct function which is viewed as critical for cognitive processing [27], although our results showed no such correlation between functional connectivity of the caudate and the neurophycological test in mTBI population. Many neuroimaging studies have identified local changes to caudate structure and function that are associated with cognitive impairment [27].

Most literature explored the default mode network (DMN) and TPNs. The DMN is a well-established network, which typically comprises the posterior cingulated cortex (PCC), precuneus, inferior parietal, and medial prefrontal cortex (MPFC) nodes [18]. In the first 3–5 days after an mTBI, fMRI imaging studies have shown increased functional connectivity and CBF of key DMN regions [23,28]. The precuneus which is a key node within the DMN showed specially increased connectivity in the analysis. Even in the subacute stage of mTBI, the precuneus showed increased connectivity despite the diminished DMN connectivity [22]. Our results supported by other previous studies demonstrated significantly increased effective functional connectivity between the left SN and the left precuneus. Anatomically, the precuneal region has a large number of reciprocal connections with frontal systems and the SN exhibited significant connectivity with the precuneus [13]. The DMN has been described to be involved in coordinated

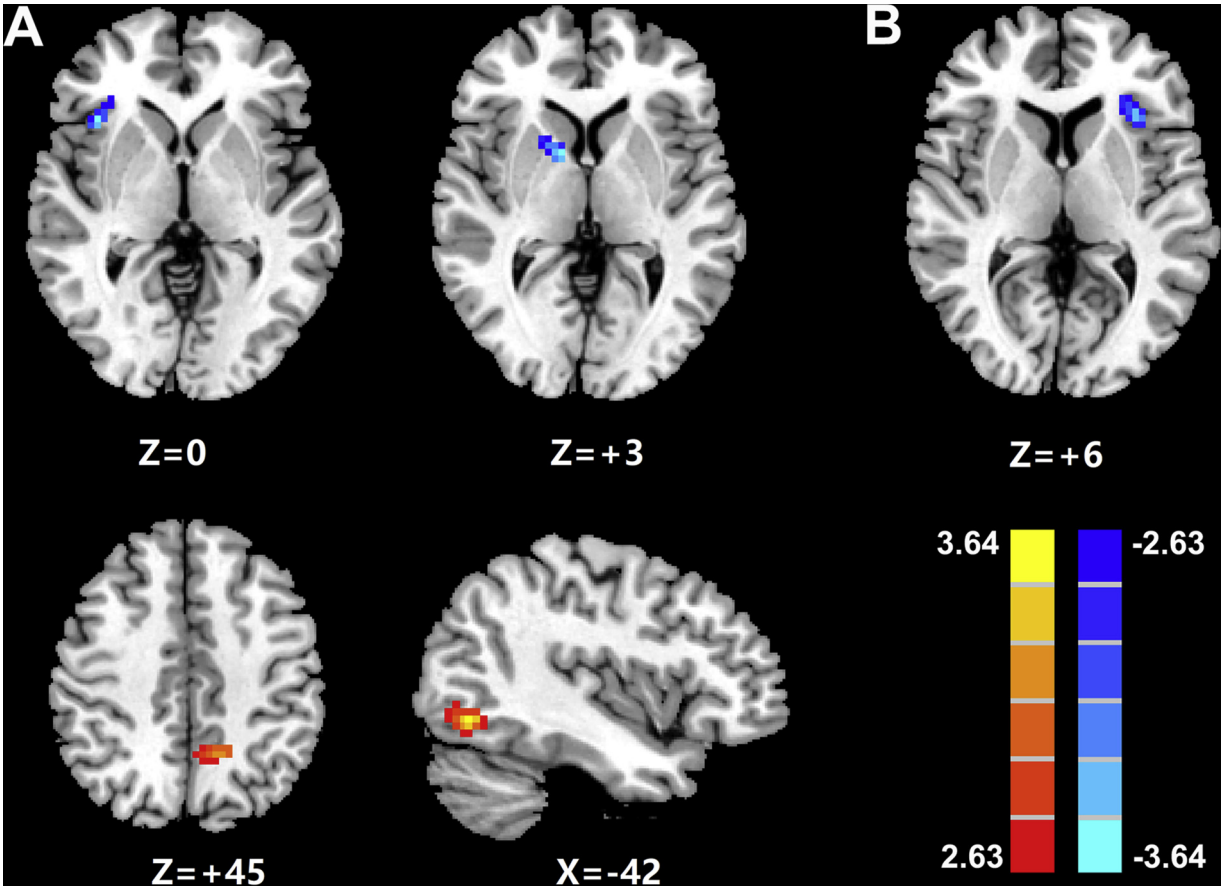

Fig. 2. Significant differences in the substantia nigra functional connectivity between patients with mTBI and healthy controls. (A) From the left substantia nigra to the whole brain regions, (B) From the right substantia nigra to the whole brain regions. Thresholds were set at a corrected $p < 0.01$, determined by Monte Carlo simulation.

Table 3
Abnormal functional connectivity of bilateral substantia nigra in patients with mTBI at acute stage.

Brain region	BA	Peak MNI coordinates x,y,z(mm)	t value	Voxels
Left substantia nigra				
Right insula	47	39,21,0	−3.442	39
Right caudate	–	12,6,3	−3.5923	43
Left middle occipital gyrus	19	−42,-69,-9	3.7417	55
Left precuneus	7	−15,-54,45	3.4145	59
Right substantia nigra				
Left insula	13	−33,21,6	−2.9476	179

A corrected threshold of $P < 0.01$ determined by Monte Carlo simulation was taken as measuring that there was significant difference between groups. BA, Brodmann area; MNI, Montreal Neurological Institute.

activities and memory, furthermore, the precuneal region is involved in cognitive function such as executive function, working memory and conscious information processing. Our study also revealed that the increased effective connectivity from the SN to the precuneus were negatively correlated with MoCA score which is in line with one previous study which showed that the increased connectivity of the precuneus was inversely related to the extent of post-concussion complaints. Increased connectivity also correlated with poorer neurocognitive functioning, suggesting that higher connectivity is associated with greater symptom burden.

In this study, the patients with mTBI presented increased functional connectivity of the left middle occipital gyrus. The rs-fMRI results in another study also showed that mTBI patients exhibit increased amplitude of low-frequency fluctuations (ALFFs) in the left middle occipital gyrus [29]. This increased connectivity may reflect short-time compensatory mechanism and during the first few days following mTBI [28]. Alternatively, impaired neurons need heightened connectivity to create the same signal.

Previously volume loss in mTBI patients has not been found bilaterally but unilaterally such as the left caudal anterior cingulum, the left cingulated gyrus isthmus, and the right precuneal gray matter [10]. In our study, this phenomenon also existed, the right SN-based resting state functional connectivity was different from the left side. Another research which studied caudate-based resting state functional connectivity in mTBI showed unilateral functional connectivity [21]. It is unclear why these findings lateralized. In the current study, the patients had variable laterality in terms of the site of their initial external injuries, with 12 patients having left-sided injuries, 16 patients having right-side injuries, and 30 patients having non-defined injuries (injuries to the front, back, or crown), therefore, it is not believed to relate to side of injury. Hemispheric dominance may potentially play a role in defining the areas injured [10].

Several potential limitations can be found with this study. First, this study included only patients with documented injury from the emergency department based on American Congress of Rehabilitation Medicine criteria. Our results are limited to a heterogeneous population of patients with mTBI, which exhibits the different injury mechanisms and various brain injury sites. Second, the severity of head injury was classified only by GCS. Duration of loss of consciousness is not available for most patients, the relationship between mTBI and this injury index is not as clear. Third, the seed used in this study covered the whole SN,

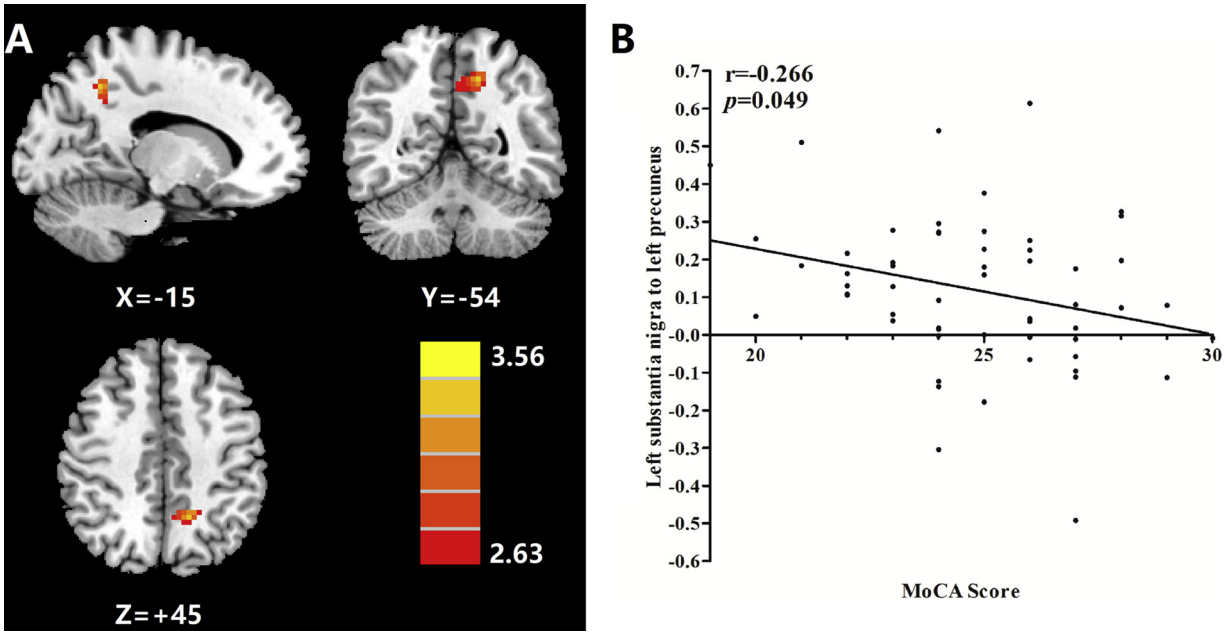

Fig. 3. The patients with mTBI had enhanced functional connectivity of the left precuneus (A). Specifically, negative correlation between the functional connectivity of the left substantia nigra-left precuneus and the MoCA score were shown in mTBI group (B).

however, the SN is subdivided into the dorsal pars compact and ventral reticulate. Different parts may have their own distinct impact, therefore more defined anatomical parcellation of the SN may exert an influence on the final seed-based functional connectivity maps which may improve the specificity of the analysis. This warrants further investigation. Finally, this study lacks sub-acute and chronic data, follow-up visits are necessary to better track the development of damage and recovery. This issue will be addressed in subsequent studies.

In conclusion, the present study indicated that patients with acute mTBI suffer from disruption in their SN resting-state networks. Our results showed that patients with acute mTBI exhibit decreased functional connectivity in the insula and caudate and increases functional connectivity in the precuneus and middle occipital gyrus in comparison with healthy control subjects. Additionally, these patients showed significantly negative correlations between function connectivity in the precuneus and cognitive score. Taking into all evidence in this study, it could be suggested that the longitudinal changes of SN-based dysfunction connectivity could serve as a neuroimaging biomarker following patients with acute mTB and help enhance our understanding of the neuropathological mechanism underlying the neurocognitive symptoms associated with acute mTBI.

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