Int J Clin Exp Pathol 2020;13(12):2918-2926
www.ijcep.com /ISSN:1936-2625/IJCEP0122548

Review Article

Activation of brain regions using task-state FMRI in patients with mild traumatic brain injury: a meta-analysis

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Received September 16, 2020; Accepted November 3, 2020; Epub December 1, 2020; Published December 15, 2020

Abstract: Activation likelihood estimation meta-analysis was performed to examine the activation characteristics of cognition-related brain regions in patients with mild traumatic brain injury (mTBI). The databases PubMed, Ovid, Cochrane Library, Google Scholar, CNKI, WFSD, and VIP were systematically searched. The software Ginger-ALE 3.0.2 was used for coordinate unification and meta-analysis. Seven studies with a total of 314 subjects were included. Meta-analysis results indicated that compared with healthy subjects, mTBI patients had enhanced activation in the left anterior angular gyrus, left occipital joint visual, left midbrain, right temporal angular gyrus, right cerebellar tonsil, left frontal insula, and right inferior frontal gyrus. mTBI patients had attenuated activation in the right dorsolateral prefrontal lobe, left cerebellar anterior lobe, left dorsolateral prefrontal lobe, right middle frontal gyrus, right posterior cingulate gyrus, left joint visual, left supramarginal gyrus, left middle frontal gyrus, right precuneus, left dorsolateral prefrontal cortex, right frontal eye field, right lower parietal gyrus, corpus callosum, right frontal pole region, and left prefrontal lobe. Further joint analysis revealed that the dorsolateral prefrontal lobe of the right middle frontal gyrus was a region of attenuated co-activation. The dorsolateral prefrontal lobe of the right middle frontal gyrus showing attenuated activation was the main brain region distinguishing mTBI patients from healthy subjects. Cognitive deficits could be associated with attenuated activation in the dorsolateral prefrontal lobe of the right middle frontal gyrus, which could be due to a decline in the recruitment ability of the neural network involved in controlling attention.

Keywords: Mild traumatic brain injury, task-state fMRI, activation likelihood estimation, meta-analysis

Introduction

Mild traumatic brain injury (mTBI), known as the "silent epidemic", is a global public health issue [1, 2]. Also known as a concussion, mTBI is a brain concussion, accounting for approximately 80%-90% of all TBIs [2]. As a physical brain injury, mTBI is often accompanied by a series of physical, cognitive, and psychological sequelae [3]. Task-state functional magnetic resonance imaging (fMRI) has been used for more than 20 years to study the characteristics of functional neural networks associated with post-mTBI cognition [4]. In cognitive research, task-state fMRI helps reveal the changes in the activation of brain regions. Relative to the healthy population, enhanced activation of brain regions in mTBI patients is often considered as a compensation in the cognitive domain (i.e., more neurons need to be recruited to meet the demand for cognitive tasks), whereas attenuated activation is considered a sign of cognitive decline [5]. Notably, Mcallister et al. [6], a group of scholars who studied mTBI using task-state fMRI, discovered increased activation in frontotemporal and lateral parietal brain regions during a working memory task, despite similar cognitive performance results compared with healthy controls. Many related studies have been published recently, but they were often characterized by small study samples, inconsistent activation of brain regions, and low reproducibility of results [7-13]. Therefore, we conducted this meta-analysis to investigate the distribution characteristics of brain activation in mTBI patients based on task-

state fMRI and to elucidate the neural basis of their cognitive changes.

Materials and methods

Retrieval strategy

Two meta-analytical evaluators independently searched Chinese databases (CNKI, WFSD, and VIP) and foreign databases (PubMed, Ovid, Cochrane Library, and Google Scholar) from their establishment to March 2, 2020. The keywords used were task-related (state) functional magnetic resonance imaging/fMRI/task-state fMRI/functional magnetic resonance imaging/blood oxygen level dependent/BOLD and traumatic brain injury/mild traumatic brain injury/TBI/mTBI/brain concussion/brain trauma. The specific retrieval strategy was adjusted for different databases. Any disagreement arising during the retrieval process was resolved through consultation with team members.

Literature inclusion

Inclusion criteria: 1) Experimental subjects who had a clear history of craniocerebral trauma and met the international mTBI diagnostic criteria [14, 15] (Glasgow Coma Scale, GCS 13-15), were assessed within 3 months of injury, were aged 18-70 years, and were right-handed; 2) Experimental interventions: N-back working memory or audiovisual orientation tasks; 3) Inter-group comparison: mTBI patients vs. healthy controls (baseline data such as age and literacy were not comparable between groups); 4) Outcome measures: Peak activation coordinates were reported as standard Montreal Neurological Institute (MNI) or Talairach coordinates, and statistical thresholds for differential brain regions met $P < 0.05$ with correction or $P < 0.001$ without correction; 5) Study type: Prospective or case-control study based on task-state fMRI data collection.

Exclusion criteria: 1) Data from patients with severe multisystem trauma, severe TBI, history of cerebral infarction, TBI in pregnancy, life-threatening diseases, and underlying diseases (hypertension, diabetes, and heart disease); 2) Experimental group size < 8; 3) Studies were published in the form of conference reports, abstract posters newsletters, and letters; 4) No coordinate data were reported or the report was incomplete and the author could not be contacted.

Data extraction and quality evaluation

Two reviewers independently extracted the relevant data for inclusion in the study according to a predefined form and text. Disagreements were resolved through negotiation with a third member or the whole team. The extracted data broadly included first author, publication year, study type, sample size, age, male/female ratio, inclusion criteria, MRI model, experimental intervention method, and peak activation coordinates. For studies with insufficient data, reviewers contacted the lead author when possible to obtain and verify the data. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature [16]. A star system was adopted to describe the quality of the literature, with a maximum score of 9 stars. If the score was ≥ 6 stars, the literature was considered to be of high quality.

Data analysis and results presentation

The extracted relevant data were added to the text in the format recommended by the ALE guidebook (http://www.brainmap.org/ale/). Icbm2tal software was used to uniformly convert Talairach coordinates into standard MNI coordinates (or vice versa). Specific parameters were set as follows: Gaussian filter full width at half maximum = 9 mm, P = 0.01, and voxel cluster threshold > 600 mm^3. Using the Ginger-ALE 3.0.2 software (http://www.brainmap.org/ale/), the activation likelihood estimation (ALE) method was employed to perform three-dimensional Gaussian function smoothing and permutation testing on the coordinate data and draw the ALE distribution map of brain regions (thresholding of ALE-image). When enough data were included, joint analysis was carried out for the different tasks to find co-activated brain regions. The final ALE distribution map was projected to a standard anatomical template through Mango (http://rii.uthscsa.edu/mango/mango.html) and/or Brainnet review (https://www.nitrc.org/projects/bnv/) software.

Results

Retrieval and quality evaluation results

A total of 3,368 relevant documents were identified according to the pre-established retrieval

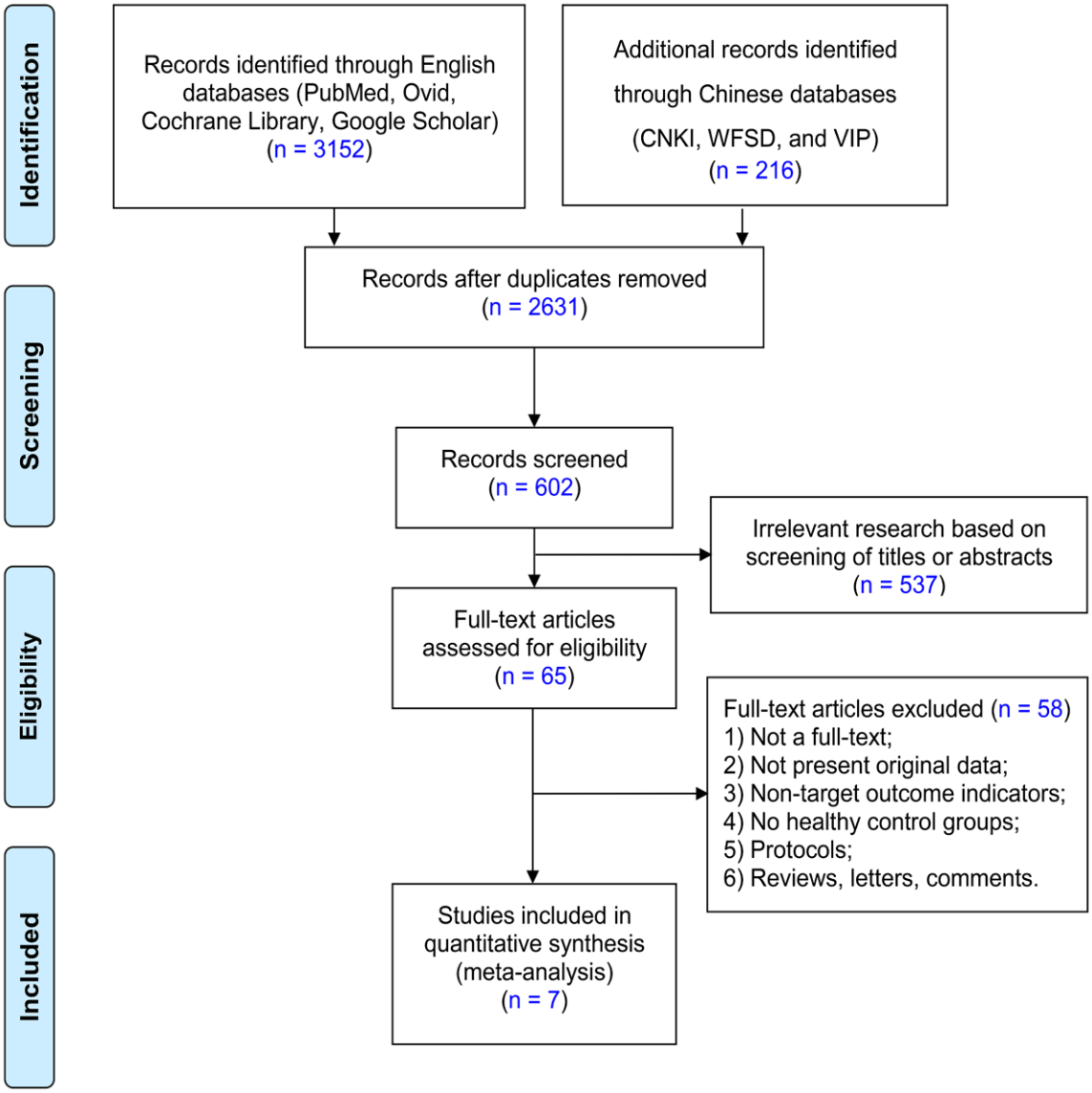

Figure 1. Literature inclusion process.

strategy. There were 2,631 articles left after eliminating 737 re-published ones. After preliminary screening of 2,631 articles, 602 articles remained. Through further reading of titles and abstracts, 537 articles that did not meet the inclusion criteria were excluded. The full-text reading of the remaining 65 articles combined with inclusion and exclusion criteria further excluded 58 articles, and eventually seven articles were included in the meta-analysis. **Figure 1** shows the literature inclusion process. The seven studies were written in English; four were prospective cohort studies and three were case-control studies. 174 mTBI patients and 140 healthy subjects were included. The patients included were aged 18-65 years. The studies were published from 2009 to 2015 and reported the authors, publication year, study type, sample size, age, male/female ratio, inclusion criteria, experimental interventions, and coordinates of brain activation peaks (**Table 1**). **Table 1** demonstrates the results of NOS quality evaluation, in which six studies were high quality (≥ 6 stars) and one study had a slightly lower quality (5 stars).

Meta-analysis of brain regions with enhanced activation in mTBI patients compared with healthy subjects

Five studies (Dettwiler et al. [8], Johnson et al. [9], Mayer et al. [10], Witt et al. [12], and Wylie

Table 1. Baseline data and quality evaluation

Authors & Publication year & Quality evaluation	Study type	Age	Number	Male/female	Inclusion criteria	Device model	Experimental method	Activation peaks
		Experimental group Control group	Experimental group Control group	Experimental group Control group	Experimental group			Experimental group > Control group Control group > Experimental group
★Wylie [13]★★★2015★★★	Prospective study	28.0±9.2	25	44%	mTBI	3.0 T	N-back working memory	1
		27.8±11.1	18	44%				0
Van der Horn [11]★★★2015★★★	Prospective study	19-64	52	67%	mTBI	3.0 T	N-back working memory	0
		18-61	20	65%				2
★Dettwiler [8]★★★2014★	Prospective study	18-21	15	80%	mTBI	3.0 T	N-back working memory	11
		18-22	15	80%				0
★Johnson [9]★★★★2014★★	Case-control study	18-21	9	67%	mTBI	3.0 T	Visual orientation task	9
		20-22	9	67%				0
★McAllister [7]★★★★★★2011★★	Prospective study	28.3±11.3	26	58%	mTBI	1.5 T	N-back working memory	0
		31.8±9.7	31	45%				7
★Witt [12]★★★★★2010★★★	Case-control study	33.6±13.9	31	67%	mTBI	3.0 T	Auditory orientation task	20
		33.2±13.8	31	67%				9
★Mayer [10]★★★★★2009★★★	Case-control study	27.2±7.62	16	50%	mTBI	3.0 T	Auditory orientation task	6
		27.3±7.43	16	50%				0

Male/female: Male to female ratio; T: Tesla.

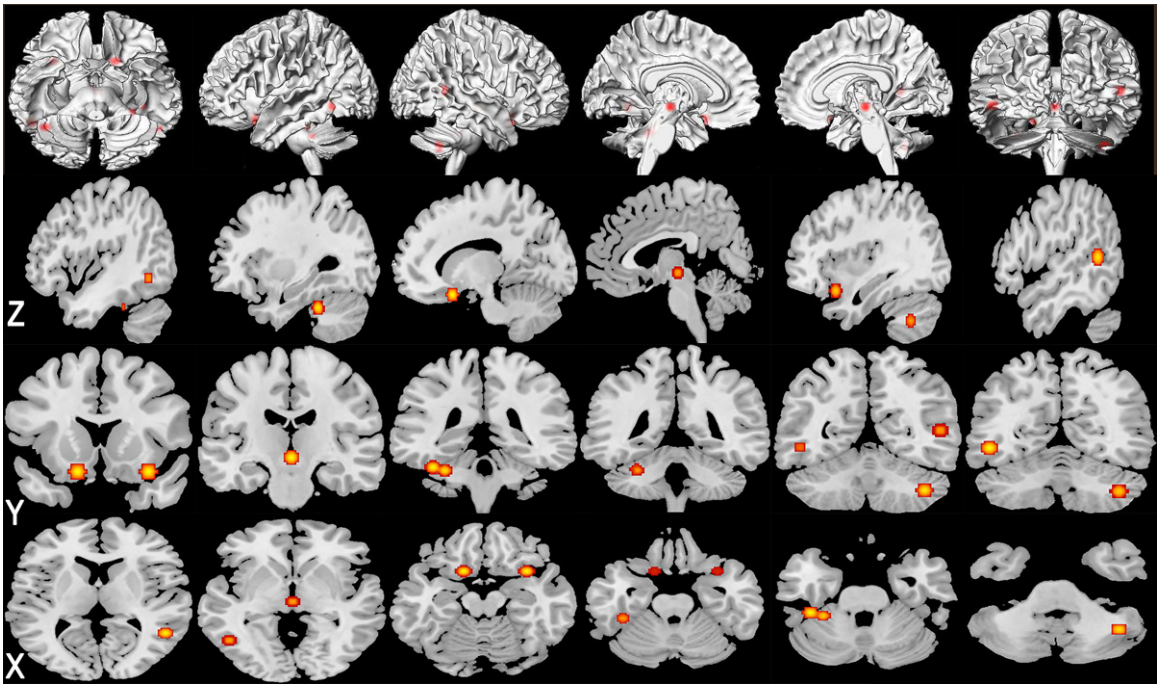

Figure 2. Brain regions with enhanced activation in mTBI patients compared to healthy subjects. (P < 0.0001, voxel > 600 mm^3).

Table 2. Brain regions with enhanced activation in mTBI patients compared to healthy subjects

Brain region	Voxel (mm^3)	MNI coordinate			ALE value (10^{-2})	*p* value (10^{-4})
		X	Y	Z		
Left anterior angular gyrus	1248	-30	-40	-30	0.90	0.64
Left occipital joint visual	648	-48	-60	-6	0.92	0.52
Left midbrain	648	0	-18	-6	0.92	0.44
Right temporal angular gyrus	648	50	-52	8	0.89	1.29
Right cerebellar tonsil	640	39	-57	-42	0.86	2.37
Left frontal insula	640	-15	15	-18	0.86	2.37
Right inferior frontal gyrus	640	33	15	-18	0.86	2.37

et al. [13]) collectively reported MNI coordinates of 41 brain regions with enhanced activation (mTBI patients vs. healthy subjects). The activation likelihood estimation (ALE) method was used to identify the activated brain regions and project the calculated 3D coordinates to a standard anatomical image template. The meta-analysis results (**Figure 2** and **Table 2**) showed that compared with healthy subjects, mTBI patients had enhanced activation in the left anterior angular gyrus (MNI (x/y/z), -30/-40/-30), left occipital joint visual (MNI (x/y/z), -48/-60/-6), left midbrain (MNI (x/y/z), 0/-18/-6), right temporal angular gyrus (MNI (x/y/z), 50/-52/8), right cerebellar tonsil (MNI (x/y/z), 39/-57/-42), left frontal insula (MNI (x/y/z), -15/15/-18), and right inferior frontal gyrus (MNI (x/y/z), 33/15/-18).

Meta-analysis of brain regions with attenuated activation in mTBI patients compared with healthy subjects

Three studies (McAllister et al. [7], Van der Horn et al. [11], and Witt et al. [12]) reported MNI coordinates of 18 brain regions with attenuated activation in the experimental group relative to the control group. The ALE method was used to identify the activated brain regions and project the calculated 3D coordinates to a standard anatomical image template. The meta-analysis results (**Figure 3** and **Table 3**) showed

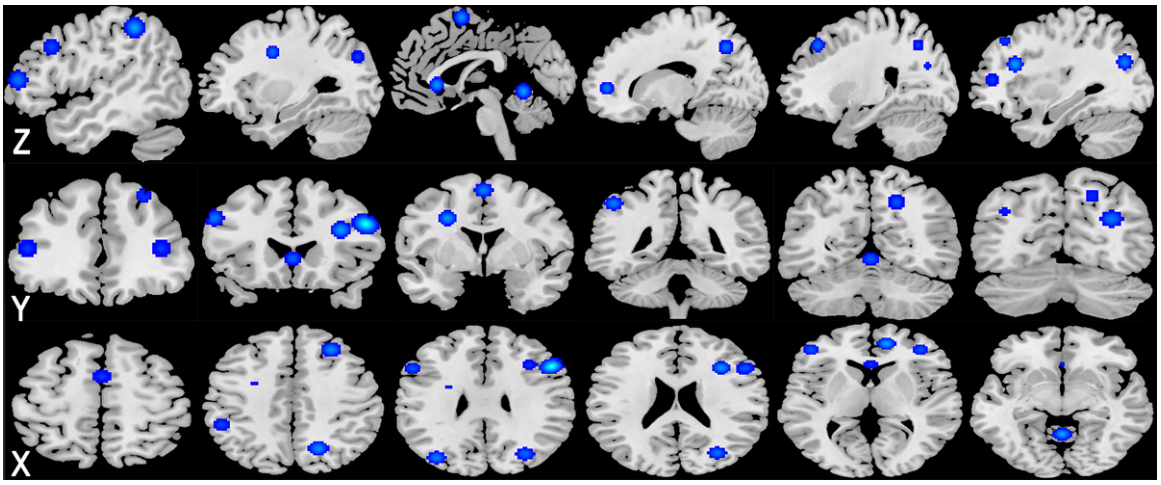

Figure 3. Brain regions with attenuated activation in mTBI patients compared to healthy subjects. ($P < 0.0001$, voxel > 600 mm^3).

Table 3. Brain regions with attenuated activation in mTBI patients compared to healthy subjects

Brain region	Voxel (mm^3)	MNI coordinate			ALE value (10^{-2})	*p* value (10^{-4})
		X	Y	Z		
Right dorsolateral prefrontal lobe	2016	50	22	30	1.37	0.0074
Left cerebellar anterior lobe	1176	0	-54	-6	0.99	0.17
Left dorsolateral prefrontal lobe	1176	-46	44	10	0.89	0.56
Right middle frontal gyrus	1176	38	44	10	0.89	0.56
Right posterior cingulate gyrus	1176	30	-72	26	0.89	0.56
Left joint visual	1176	-36	-76	32	0.89	0.56
Left supramarginal gyrus	1176	-50	-40	48	0.99	0.17
Left middle frontal gyrus	1160	0	4	62	0.89	0.56
Right precuneus	1088	18	-63	45	0.86	1.24
Left dorsolateral prefrontal cortex	1016	-54	20	34	0.89	0.56
Right frontal eye field	968	27	33	45	0.83	2.10
Right lower parietal gyrus	952	34	24	24	0.89	1.02
Corpus callosum	944	0	27	0	0.89	1.02
Right frontal pole region	944	12	51	6	0.89	1.02
Left prefrontal lobe	944	-27	0	36	0.89	1.02

that compared with healthy subjects, mTBI patients had attenuated activation in the right dorsolateral prefrontal lobe (MNI (x/y/z), 50/22/30), left cerebellar anterior lobe (MNI (x/y/z), 0/-54/-6), left dorsolateral prefrontal lobe (MNI (x/y/z), -46/44/10), right middle frontal gyrus (MNI (x/y/z), 38/44/10), right posterior cingulate gyrus (MNI (x/y/z), 30/-72/26), left joint visual (MNI (x/y/z), -36/-76/32), left supramarginal gyrus (MNI (x/y/z), -50/-40/48), left middle frontal gyrus (MNI (x/y/z), 0/4/62), right precuneus (MNI (x/y/z), 18/-63/45), left dorsolateral prefrontal cortex (MNI (x/y/z), -54/20/34), right frontal eye field (MNI (x/y/z), 27/33/45), right lower parietal gyrus (MNI (x/y/z), 34/24/24), corpus callosum (MNI (x/y/z), 0/27/0), right frontal pole region (MNI (x/y/z), 12/51/6), and left prefrontal lobe (MNI (x/y/z), -27/0/36).

Joint analysis based on different experimental paradigms

To further investigate whether different experimental paradigms showed co-activated brain regions, we used the ALE comparative analysis module for joint analysis (**Figure 4** and **Table 4**). It revealed that relative to healthy controls,

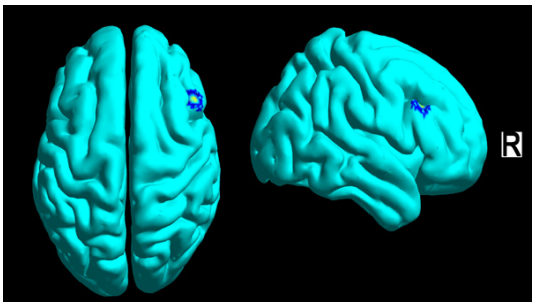

Figure 4. Brain map of N-back working memory and audiovisual task reduced activation conjunction (voxel > 300 mm^3).

mTBI patients showed attenuated co-activation in the dorsolateral prefrontal lobe of the right middle frontal gyrus (MNI (x/y/z), 50/22/28) during both N-back working memory and audiovisual orientation tasks.

Discussion

ALE meta-analysis is a voxel-based quantitative meta-analysis method that uses the coordinates reported by each study in a standard three-dimensional space to estimate the overlap between focal points by modeling the probability distribution computed at each focal point coordinate [17]. ALE meta-analysis methodology has been proposed for more than a decade. To reduce the incidence of false positives, Eickhoff et al. [17] improved the statistical method of meta-analysis and proposed an algorithm based on false discovery rates. In addition, Eickhoff et al. [17] further extended the fixed effects model to a random effects model, thus enhancing the universality of the conclusion. In short, with the continuous improvement of ALE meta-analysis methods, the objectivity, accuracy, and scientific validity of its conclusions are improving [18].

Based on the ALE meta-analysis method, the literature was screened strictly according to the inclusion and exclusion criteria, and the three-dimensional coordinate data of seven studies were finally included. The meta-analysis suggested that the dorsolateral prefrontal lobe of the right middle frontal gyrus showing attenuated activation was the main brain region distinguishing mTBI patients from healthy subjects. Enhanced or attenuated activation in relevant brain regions could be related to neural network compensation or injury.

The prefrontal lobe, which is closely involved in cognitive function, provides neural activity support for the attention and execution of working memory and related audiovisual orientation tasks [19]. This study indicated significantly attenuated activation in the dorsolateral prefrontal cortex of the right middle frontal gyrus in mTBI patients relative to the healthy population. Such a finding provides evidence in the search for a neurofunctional origin of the cognitive deficits common in mTBI patients, as this structure is considered a neural network closely related to various forms of executive power [12, 20, 21]. This constant focal deficit in mTBI patients strongly suggests that the dorsolateral prefrontal lobe of the right middle frontal gyrus may be a target for brain dysfunction in mTBI patients. However, it currently remains unclear whether this brain region detected by fMRI can effectively represent the causal mechanism of cognitive deficits or if it is the result of other forms of brain injury. In light of existing studies, we cautiously suggest that cognitive deficits could be associated with attenuated activation of the dorsolateral prefrontal lobe of the right middle frontal gyrus, which could be due to a decline in the recruitment ability of the neural network that controls attention. This could be of great significance for understanding the impact of potential brain injury in mTBI patients. The activation status of this region might be a parameter for the evaluation of cognitive deficits in mTBI patients. The low-frequency amplitude of this region can be combined with a series of commonly used neuropsychological scales to quantify the extent of cognitive deficits. Further, the region can be defined as a region of interest to explore its functional connectivity with various brain regions, thereby providing a mechanistic account of the generation of cognitive deficits in mTBI patients. The above ideas need clarification through further research.

The following brain regions tended to show enhanced activation in mTBI patients: left anterior angular gyrus, left occipital joint visual, left midbrain, right temporal angular gyrus, right cerebellar tonsil, left frontal insula, and right inferior frontal gyrus, which could be related to an underlying compensatory neural mechanism — meeting cognitive demands through activation of additional cortical brain regions. Moreover, we also found that some brain re-

Table 4. Overlapping brain regions with attenuated activation in the N-back working memory and audiovisual orientation tasks

Brain region	Voxel (mm^3)	MNI coordinate			ALE value (10^{-2})
		X	Y	Z	
Dorsolateral prefrontal lobe of the right middle frontal gyrus	1072	50	22	28	0.68

gions in mTBI patients tended to show insufficient activation. This requires further investigation on whether mTBI causes the lack of connectivity between the dorsolateral prefrontal cortex of the right middle frontal gyrus and other cognition-related brain regions, which would provide a more comprehensive neurological explanation for the formation of cognitive deficits in mTBI patients.

In summary, cognitive deficits may be associated with attenuated activation in the dorsolateral prefrontal lobe of the right middle frontal gyrus, which could be due to a decline in the recruitment ability of the neural network that controls attention.

This study has some limitations. First, the mTBI patients included not only patients with acute mTBI but also patients with subacute mTBI, and whether the wider inclusion criteria influenced the activation distribution of brain regions needs to be further studied. Second, the age of the included patients was relatively wide, between 18 and 65 years, and the effect of the age difference on the activation distribution of brain regions was unclear in this study. Third, the specific mechanisms of enhanced and attenuated activation of brain regions and their effects remained unclear, and it would be necessary to use neuropsychological scales in conjunction with related indicators of brain activation for joint analysis.

Conclusions

Despite some limitations, our meta-analysis cautiously suggests that attenuated activation in the dorsolateral prefrontal lobe of the right middle frontal gyrus is the main brain region distinguishing mTBI patients from healthy subjects. Moreover, cognitive deficits appear associated with attenuated activation in the dorsolateral prefrontal lobe of the right middle frontal gyrus, which could be due to a decline in the recruitment ability of the neural network involved in controlling attention. In future studies, it will be imperative to use neuropsychological scales in conjunction with related indicators of brain activation for joint analysis.

Acknowledgements

This study was supported by the Hospital Level Support Projects (Fcjs202050); Yangzhou City Key Research and Development Project (YZ-2019056); Jiangsu Provincial Scientific Research Project of Health Commission (H2018-064); Six-One Top Talent Research Project (LGY2017026); Jiangsu Province Key Experiments of Basic and Clinical Translation of Non-coding RNA (201902); and Jiangsu Province Natural Science Foundation (BK20190241).

Disclosure of conflict of interest

None.

Abbreviations

mTBI, mild traumatic brain injury; fMRI, functional magnetic resonance imaging; MNI, Montreal Neurological Institute; NOS, Newcastle-Ottawa Scale; ALE, activation likelihood estimation.

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