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Research article

The possible neural mechanism of neuropathic pain evoked by motor imagery in pediatric patients with complete spinal cord injury: A preliminary brain structure study based on VBM

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ABSTRACT

In this study, we observed pediatric complete spinal cord injury (CSCI) patients receiving MI training and divided them into different groups according to the effect of motor imagery (MI) training on neuropathic pain (NP). Then, we retrospectively analysed the differences in brain structure of these groups before the MI training, identifying brain regions that may predict the effect of MI on NP. Thirty pediatric CSCI patients were included, including 12 patients who experienced NP during MI and 18 patients who did not experience NP during MI according to the MI training follow-up. The 3D high-resolution T1-weighted images of all subjects were obtained using a 3.0 T MRI system before MI training. A two-sample *t*-test was performed to evaluate the differences in gray matter volume (GMV) between patients who experienced NP and those who did not experience NP during MI. Receiver operating characteristic (ROC) analysis was performed to compute the sensitivity and specificity of the imaging biomarkers for the effect of MI on NP in pediatric CSCI patients. MI evoked NP in some of the pediatric CSCI patients. Compared with patients who did not experience NP, patients who experienced NP during MI showed larger GMV in the right primary sensorimotor cortex (PSMC) and insula. When using the GMV of the right PSMC and insula in combination as a predictor, the area under the curve (AUC) reached 0.824. Our study demonstrated that MI could evoke NP in some pediatric CSCI patients, but not in others. The individual differences in brain reorganization of the right PSMC and insula may contribute to the different effects of MI on NP. Moreover, the GMV of the right PSMC and insula in

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combination may be an effective indicator for screening pediatric CSCI patients before MI training therapy.

Abbreviations

AUC	Area under the curve
CSCI	Complete spinal cord injury
CSCI-NP	Complete spinal cord injury patients who experienced NP during MI
CSCI-NNP	Complete spinal cord injury patients who did not experience NP during MI
CSF	Cerebrospinal fluid
FWE	Family-wise error
GM	Gray matter
GMV	Gray matter volume
KVIQ	Kinesthetic and Visual Imagery Questionnaire
M1	Primary motor cortex
MI	Motor imagery
MRI	Magnetic resonance imaging
NIfTI	Neuroimaging Informatics Technology Initiative
NP	Neuropathic pain
PSMC	Primary sensorimotor cortex
ROC	Receiver operating characteristic
S1	Primary sensory cortex
VAS	Visual analog scale
VBM	Voxel based morphometry
WM	White matter

1. Introduction

Pediatric complete spinal cord injury (CSCI) is a rare but devastating condition that can cause lifelong neurological sequelae and serious emotional-cognitive harm, adversely affecting individuals and their families [1,2]. Due to the complete disruption of the ascending and descending conduction pathways, CSCI patients are unable to perform rehabilitation training that requires active limb movement assistance [3]. The treatment of pediatric CSCI is still very challenging [4]. Motor imagery (MI) is defined as a mental representation of an action without actually performing it [5]. It has the advantages of simplicity, convenience and ease of implementation. Engagement of the motor system makes MI training an emerging strategy to improve the performance of healthy athletes [6] and the rehabilitation of patients who suffer from nervous system disorders, including stroke, multiple sclerosis, and Parkinson's syndrome [7]. Recently, numerous studies have demonstrated that MI is an effective treatment not only for motor rehabilitation but also for the improvement of cognition after spinal cord injury [8,9], since it can strengthen motor and cognitive programs by repeated activation of the related brain regions and can be carried out easily by injured patients who cannot move voluntarily [10–12].

However, in addition to the rehabilitation of motor and cognitive function, MI can also modulate neuropathic pain (NP) in spinal cord injury patients [13–16]. The possible neural mechanism by which MI regulates NP has been reported in a few previous studies, but all of them focused on adult spinal cord injury patients [13,14,16]. Actually, several studies have shown a significant relationship between the motor system and pain control [15,17,18]. The motor neural network is extensively connected to pain-related neural circuits, and MI may modulate NP by altering the activity of motor-related brain regions that are involved in pain regulation [18]. However, the effect of MI on modulating NP remains unclear [19]. Some studies showed no effect [15], some showed a reduction [16], and others showed an increase [13,14]. Moreover, it has even been reported that MI may evoke NP in spinal cord injury patients without NP [13]. These inconsistent results may hinder the clinical application of MI training. Additionally, previous studies have focused on adults with spinal cord injury, rather than the pediatric population. Children are experiencing rapid growth and development [20], and MI has the potential to become an effective rehabilitation therapy after spinal cord injury in the pediatric population, particularly for those with complete injuries [3]. One previous study has demonstrated that MI may improve the sensory and motor functions of pediatric CSCI patients by activating sensory motor and cognitive-related brain regions [3]. However, whether MI training influences NP in pediatric patients after CSCI and its possible neural mechanism are still unclear.

Therefore, we explored the effect of MI training on NP in pediatric CSCI patients in this study. Additionally, we investigated brain structural alterations using voxel-based morphometry (VBM) analysis and studied the relationship between the brain gray matter volume (GMV) reorganization and the effect of MI on NP. According to the effect of MI training on NP, pediatric CSCI patients with different effects were divided into different groups. Then, the alterations in brain structure in each group before MI training were analysed to further investigate the possible neural mechanism of MI on the NP of pediatric CSCI patients, and explore the possible

predictive indicators for the application of MI in children after CSCI.

2. Materials and methods

2.1. Participants

In this study, we recruited pediatric CSCI patients who were admitted to Xuanwu Hospital. To be included in this study, all pediatric CSCI patients were required to: have a history of CSCI, be aged between 6 and 12 years old, have an injury duration of time more than 2 months, be willing to complete the MI training treatment for one week, have a Kinesthetic and Visual Imagery Questionnaire (KVIQ)-10 score of more than 25 [3,21], have no brain disorders confirmed by conventional imaging, have no history of mental illness, epilepsy or cognitive impairment, and have no contraindication to magnetic resonance imaging (MRI) scanning. Thus, 33 pediatric CSCI patients who met the inclusion criteria were enrolled in our study. Each participant underwent a complete examination, including the American Spinal Injury Association Impairment scale (*https://www.physio-pedia.com/American_Spinal_Cord_Injury _Association_(ASIA) _Impairment_Scale*) and visual analogue scale (VAS), conducted a MRI scanning, and performed one week of MI training treatment.

The research protocol for this study was approved by the Ethics Committee of Xuanwu Hospital. Pediatric CSCI patients and their guardians were informed about the research purposes, potential effects, and rehabilitation procedures, and informed consent was obtained from the parents/guardians of all pediatric participants according to the Declaration of Helsinki.

2.2. MRI

Before the MI training, MRI data were acquired using a Siemens Trio Tim 3.0 T MRI system (Erlangen, Germany) equipped with a twelve-channel phase array head coil. Before the actual MRI examination, a mock MRI suite was used to ease children's concerns. Then, participants were instructed to lie down on their backs while closing their eyes and relaxing. Noise reduction earplugs were used to reduce the children's agitation and protect their fragile auditory hair cells. MRI-compatible goggles were used to minimize their anxiety and claustrophobia during the scan. Conventional fluid-attenuated inversion recovery (FLAIR) imaging was applied to exclude subjects who had visible brain abnormalities, the parameters were: 20 axial slices with a slice thickness = 5 mm, repetition time = 8000 ms, echo time = 94 ms, field of view = 240 × 240 mm^2. Then, high-resolution three-dimensional (3D) structural T1-weighted images were obtained in sagittal orientation using a 3D magnetization-prepared rapid gradient-echo sequence. The following were the parameters: repetition time = 1800 ms, echo time = 2.13 ms, inversion time = 1100 ms, field of view = 256 × 256 mm^2, matrix size = 256 × 256, flip angle = 9°, number of slices = 192, slice thickness = 1 mm, and voxel size = 1 × 1 × 1 mm^3.

2.3. MI training protocol

After the MRI data scanning, all the participants and their parents/guardians were required to familiarize themselves with the procedure of the next one-week MI training. First, our rehabilitation physicians distributed and explained the VAS questionnaire and the standard body map, followed by an explanation and demonstration of the entire MI training. Subsequently, all participants and their parents/guardians practiced the entire process. To ensure that all parents/guardians and children could understand and accurately conduct the MI training, the training process was repeated three times. Then, each participant was asked to performan the MI training over 7 days at home. The MI training involved an MI task that was performed once a day for seven consecutive days. The MI task consisted of imagining right ankle dorsiflexion for 3 min and imagining left ankle dorsiflexion for 3 min alternately, lasting for 30 min in total. During this process, parents/guardians timed and reminded the pediatric CSCI patients to alternate their ankle dorsiflexion every 3 min. If they experienced pain during MI training, each of the pediatric CSCI patients was asked to describe the intensity and the location of their evoked pain, and then their parents/guardians recorded the intensity of pain, and drew the region of pain on a standard body map. After 7 days of MI training, according to the information obtained from the telephone interview, we obtained the impact of MI on pain, affected location, and the degree of pain impacted by MI training. Then, all participants were divided into different groups according to the effect of MI training on NP in pediatric CSCI patients.

2.4. Data preprocessing

By using the MRICRON software routine dcm2nii (https://www.mtrc.org/projects/mricron), raw DICOM images of the participants were converted to Neuroimaging Informatics Technology Initiative (NIfTI) format for further processing. Next, the preprocessing steps were conducted using the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.uni-jena.de/cat/) implemented in MATLAB 2013b (Math Works, Natick, MA, USA). 3D T1-weighted imaging scans were normalized with an affine, followed by nonlinear registration, corrected for biasfield inhomogeneities. Then, all images were segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) components, using the tissue probability templates of Chinese pediatric atlases that were built from the MRI data of 328 normal Chinese children aged 6 to 12 (https://www.nitrc.org/projects/chn-pd). After that, the segmented scans were normalized into the same template (from the CHN-PD atlases) using the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra algorithm [22]. Multiplied by the nonlinear part of the deformation field, the normalized GM component was modulated to generate the relative GMV. Then, a Gaussian kernel with an 8 mm full-width at half-maximum was applied to smooth the normalized GM images.

2.5. Statistical analysis

All clinical data were analysed using SPSS version 22.0 (IBM, Armonk, NY, USA). Continuous variables, including age, injury duration, and motor and sensory scores, were tested using independent t tests, while gender differences were examined by a chi-square tests. Continuous variables were first analysed for normality and homogeneity of variance, and then independent t tests were employed to compare differences for data with normal distribution and homogeneous variances, if not, the Mann–Whitney *U* test was used. A *P*-value <0.05 was considered to be statistically significant.

Analysis for GMV values was conducted using SPM12 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm) based on MATLAB 2013b. Independent t tests were performed, with age and gender as covariates (uncorrected voxel-wise $P < 0.001$, FWE-corrected cluster-level $P < 0.05$).

Then, the receiver operating characteristic (ROC) analysis was performed using SPSS 22.0 to evaluate the sensitivity and specificity of imaging biomarkers to predict the effect of MI on NP in pediatric CSCI. The ROC curve was created by plotting the true positive rates against false-positive rates at various thresholds. A *P*-value <0.05 was considered statistically significant.

Finally, to explore the correlations between the GMV values in brain regions with significant group differences and the VAS scores of pediatric CSCI patients, Spearman correlation analyses were calculated using SPSS 22.0. The *P*-value <0.05 was considered statistically significant.

3. Results

3.1. General information and the characteristics of the participants

Excluding three participants who did not insist on the MI training, thirty pediatric CSCI patients were included in this study, and all of them were thoracic CSCI and had no NP (the VAS score was 0) before the MI training. When performing the MI training, out of the remaining 30 participants, 12 subjects (40 %) experienced NP below the lesion level during MI (CSCI-NP) (12 females, with a mean age of 8.50 ± 1.624 years and an age range of 6–11 years, the injury duration ranged from 8 to 42 months), and 18 subjects (60 %) did not experience NP during MI (CSCI-NNP) (16 females and 2 males, with a mean age of 7.94 ± 2.043 years and an age range of 6–12 years, the injury duration ranged from 3 to 108 months). According to the VAS questionnaire, the NP intensity of the pediatric CSCI-NP group ranged from 1.5 to 4 score. Pain was reported mostly as numbness (paraesthesia) or aching sensation. Pain in the feet was reported by all patients, and some of them also reported pain in additional locations, such as the thigh, shin or knee (Fig. 1). Table 1 presents the detailed information of the two groups (CSCI-NP and CSCI-NNP).

The two groups did not differ in age (Mann-Whitney Test, $P = 0.254$), gender (Chi-square test, $P = 0.503$), injury duration (Mann-Whitney Test, $P = 0.299$), KVIQ-10 score (Two-sample *t*-test, $P = 0.830$), motor score (Mann-Whitney Test, $P = 1.000$), or sensory score (Mann-Whitney Test, $P = 0.267$).

3.2. Difference in brain GMV between the two groups before MI training

To find possible predictive indicators and to explore the possible neural mechanism of NP evoked by MI, using a two-sample *t*-test,

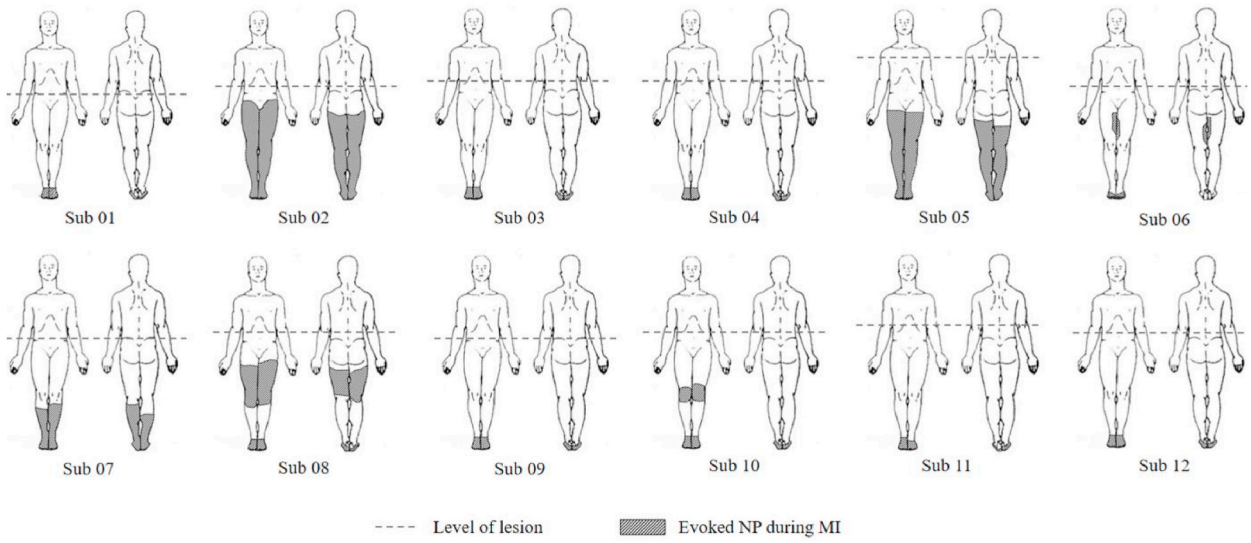

Fig. 1. The distribution of pain evoked by MI in pediatric CSCI patients. The dotted line represents the neurological level of injury. The slash regions indicate the distribution of NP that evoked by MI. MI: motor imagery, CSCI: complete spinal cord injury, NP: neuropathic pain.

Table 1
Clinical data of pediatric CSCI patients.

Subjects	Age (years)	Gender	Etiology	Duration (months)	Level of lesion	ASIA	Motor (0–100)	Sensory (0–224)	KVIQ-10 (0–50)	Mean VAS score during one-week MI training
Pediatric CSCI patients with below-level NP during MI										
1	10	F	Backbend[a]	36	T11	A	50	152	28	4
2	8	F	Backbend	21	T10	A	50	144	36	4
3	11	F	Accident	36	T8	A	50	112	30	4
4	7	F	Backbend	11	T8	A	50	104	38	1.5
5	8	F	Backbend	42	T2-3	A	50	80	43	2
6	10	F	Backbend	26	T9	A	50	144	36	2
7	8	F	Backbend	19	T10	A	50	138	39	4
8	8	F	Backbend	25	T9	A	50	136	37	3
9	11	F	Backbend	21	T10	A	50	132	30	1.5
10	7	F	Backbend	9	T9	A	50	138	38	2
11	8	F	Backbend	8	T8	A	50	126	42	3
12	6	F	Fall	20	T9	A	50	144	39	2
Pediatric CSCI patients without below-level NP during MI										
13	6	F	Backbend	14	T9	A	50	128	35	0
14	9	F	Backbend	47	T9	A	50	120	43	0
15	9	F	Backbend	8	T10	A	50	140	38	0
16	7	F	Backbend	24	T5	A	50	112	32	0
17	11	F	Backbend	12	T8-9	A	50	128	29	0
18	7	F	Backbend	16	T9	A	50	128	34	0
19	6	F	Backbend	14	T10	A	50	120	43	0
20	6	F	Backbend	11	T6	A	50	104	35	0
21	9	F	Backbend	31	T9	A	50	128	34	0
22	7	F	Fall	28	T7	A	50	112	41	0
23	9	F	Backbend	14	T9	A	50	128	33	0
24	7	F	Backbend	3	T8	A	50	112	32	0
25	6	F	Fall	7	T9	A	50	176	36	0
26	7	M	Stab	9	T9	A	50	128	29	0
27	6	F	Backbend	4	T8	A	50	120	31	0
28	12	F	Fall	108	T10	A	50	140	40	0
29	12	M	Accident	84	T2	A	50	128	45	0
30	7	F	Backbend	12	T11	A	50	140	37	0

Note: The level of lesion refers to the neurological level. ASIA: American Spinal Injury Association, ASIA impairment scale: A: complete—no sensory or motor function is preserved in sacral segments S4–S5, Sensory score: sum of segmental light touch and pinprick classifications. Backbend[a]: pediatric patients had a clear traumatic history after backbend during dance practice. CSCI: complete spinal cord injury, KVIQ: Kinesthetic and Visual Imagery Questionnaire, VAS: visual analogue scale, NP: neuropathic pain, MI: motor imagery.

we compared the brain GMV of the two groups scanned before MI training. Our results found that compared with the pediatric CSCI-NNP group, the GMV values of the right insula and primary sensorimotor cortex (PSMC) in the pediatric CSCI-NP group were larger (Fig. 2, Table 2).

3.3. GMV values of the right insula and PSMC combined as a predictor

To perform the ROC analysis, a binary classifier was employed to distinguish pediatric CSCI-NP from pediatric CSCI-NNP using a high to low discrimination threshold. The result of the ROC curve analysis for the combination of GMV values in the right insula and the right PSMC is shown in Fig. 3, which indicates a sensitivity of 83.3 %, a specificity of 75 %, and an area under the curve of 0.824 at the cut-off value of 0.583 ($P = 0.003$).

3.4. Correlation analyses between the GMV values and the VAS scores in pediatric CSCI patients

No significant associations were detected between the GMV values of the right insula, PSMC and the VAS scores of pediatric CSCI patients ($P > 0.05$).

4. Discussion

The present study demonstrates that MI can evoke a below-level NP in some, but not all, pediatric CSCI patients without NP. The different results were related to individual differences in pediatric brain reorganization (such as the GMV values of the right PSMC and insula) before MI training. In addition, the combination of the GMV values in the right insula and PSMC showed potential to be used as an indicator to predict whether MI evokes NP in pediatric CSCI patients, which could be used to screen patients before the MI training therapy.

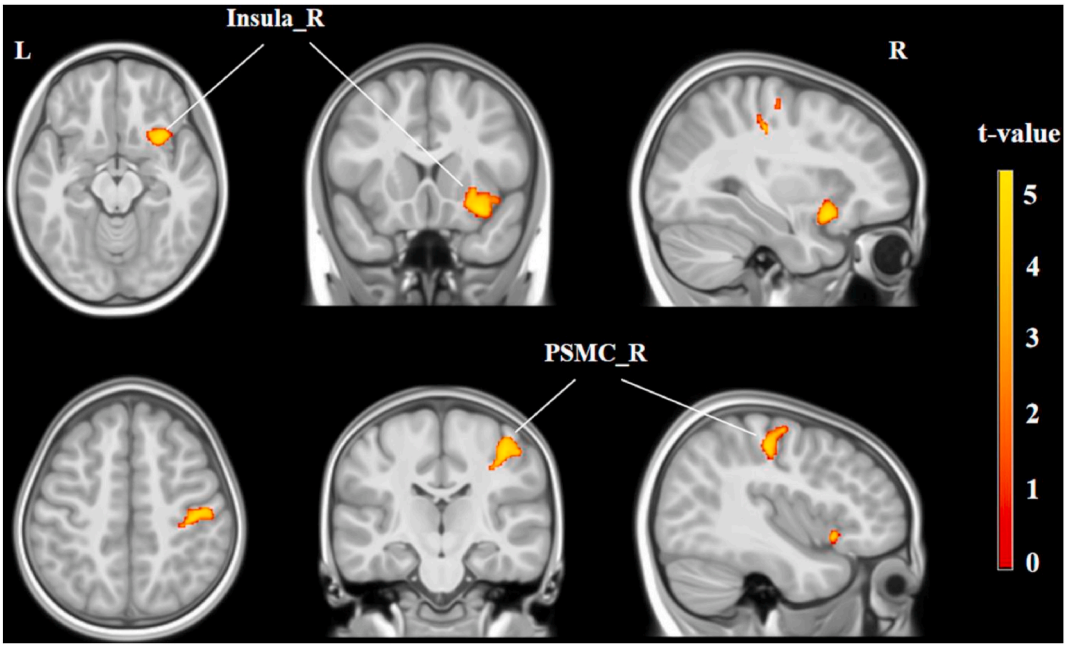

Fig. 2. Brain regions showing intergroup differences in GMV between pediatric CSCI-NP and pediatric CSCI-NNP. Compared with pediatric CSCI-NNP, the pediatric CSCI-NP subjects showed larger GMV in the right insula and PSMC. GMV: gray matter volume, CSCI-NP: complete spinal cord injury patients who experienced neuropathic pain during motor imagery, CSCI-NNP: complete spinal cord injury patients who did not experience neuropathic pain during motor imagery, PSMC: primary sensorimotor cortex.

Table 2
Brain regions with larger GMV in pediatric CSCI patients who experience NP during MI.

Brain regions	MNI coordinate			Cluster size (voxels)	Peak T value
	x	y	z		
Insula_R	36	19.5	−9	590	5.3665
PSMC_R	42	−21	49.5	499	5.1234

Note: GMV: gray matter volume, CSCI: complete spinal cord injury, NP: neuropathic pain, MI: motor imagery, MNI: Montreal Neurological Institute, PSMC: primary sensorimotor cortex, R: right.

4.1. NP evoked by MI

Some studies have reported that MI is an effective method to reduce pain in spinal cord injury patients through distraction [23], correction of the incongruency between motor output and sensory feedback [19,24], or reversing/modulating the somatosensory neural reorganization [25]. However, our study proved that MI training could evoke below-level NP in some pediatric CSCI patients without NP. Below-level NP arises from more than three dermatomes below the dermatome of the neurological level of injury [26] and is mainly caused by the reorganization of the cerebral cortex [27,28]. MI may evoke NP in some pediatric spinal cord injury patients by stimulating brain areas associated with the below-level NP, such as the anterior cingulate cortex, dorsolateral prefrontal cortex, anterior insula, supplementary motor area and premotor cortex, similar to the mechanism of MI causing NP in adult spinal cord injury patients [14]. However, in another group of pediatric CSCI patients in our study, MI did not evoke NP. To explore whether the different effects of MI on NP are related to the individual differences in pediatric brain reorganization after CSCI, the alterations in the GMV values in each group before MI training were analysed.

4.2. Larger GMV in right insula and PSMC of pediatric CSCI-NP

Previous studies have shown that the degree of pain intensity change is closely associated with brain activities related to peripherally evoked pain, which may involve the PSMC, insula, anterior cingulate cortex, prefrontal cortex and thalamus [14,29]. In our study, compared with pediatric CSCI-NNP patients, larger GMV values in the right anterior insula and PSMC of pediatric CSCI-NP patients were found. These brain regions are not only involved in MI but also participated in NP in spinal cord injury patients [7,14,30,31].

Several studies have shown a correlation between NP and sensorimotor cortex reorganization [31,32], and the GMV changes in the

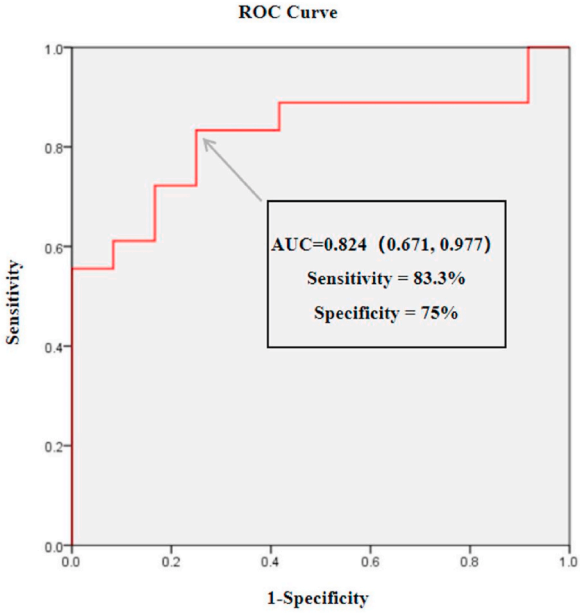

Fig. 3. ROC curve between pediatric CSCI-NP and pediatric CSCI-NNP when using the GMV values of the right PSMC and insula in combination as an indicator. The area under the curve for the ROC was 0.824 (95 % confidence intervals: 0.671 to 0.977), with a sensitivity of 83.3 %, specificity of 75 %. ROC: receiver operating characteristic, AUC: area under the curve, CSCI-NP: complete spinal cord injury patients who experienced neuropathic pain during motor imagery, CSCI-NNP: complete spinal cord injury patients who did not experience neuropathic pain during motor imagery, GMV: gray matter volume, PSMC: primary sensorimotor cortex.

primary sensory cortex (S1) and primary motor cortex (M1) were correlated with the degree of NP in spinal cord injury patients [31]. Increased activity in S1 not only produces the perception of pain but also results in changes in relevant cortical representation [33]. While the brain regions involved in pain processing usually do not involve M1, a previous functional MRI study has demonstrated that the presence of NP in spinal cord injury patients causes increased activation in M1 during MI [14]. In various chronic pain syndromes, M1 regulates pain in a top-down manner, sending signals toward the cingulate gyrus, prefrontal cortex, thalamocortical and peri-aqueductal gray, and plays an important role in pain modulation [34,35]. Moreover, previous studies have found that MI of CSCI patients could evoke strong activation of the PSMC, and the activation level of the PSMC in CSCI patients was even higher than that of healthy people during MI [7,36]. This indicates that MI can strongly activate PSMC even in CSCI patients who have completely disconnected efferent motor and afferent sensory pathways, which is enough to induce pain.

As a part of the paralimbic system, the insula is not only involved in cognitive functions such as memory, drive and emotion, but also associated with the basal ganglia, thalamus and participates in regulating pain perception [37,38]. An increasing amount of evidence indicates that the insula contains nociceptive regulatory networks [37] and that the electrical stimulation in the insula can cause a pain experience [39]. As a key node of the salience network, the anterior insula encodes unhappiness associated with olfaction, vision, and pain, and forms part of the interoceptive cortex that monitors the body's internal state [14,40,41]. The right anterior insula may be involved in the emotional state changes related to pain stimulation [14]. In addition, the activation magnitude of the anterior insula in spinal cord injury patients was significantly related to the pain intensity during MI [14]. We speculate that the larger GMV of the PSMC and insula may cause more activation during MI, resulting in the occurrence of NP.

4.3. Imaging biomarker for screening pediatric CSCI patients before MI training

When the combination of GMV values of the right PSMC and insula was used as a potential predictor, the area under the curve (AUC) reached 0.824, with a sensitivity of 83.3 % and a specificity of 75 %. This result demonstrates that the combination of GMV values of the right PSMC and insula has potential to be used as a helpful imaging indicator for pediatric spinal cord injury patients, screening before MI training, and predicting whether MI can evoke NP.

4.4. Limitations

There are some limitations in our study. First, all patients enrolled in this study did not have NP, and the effect of MI on pediatric spinal cord injury patients with NP is still unclear. Second, a relatively small sample size was used in this study. Moreover, the majority of the subjects in this study were girls, and most of them had a clear traumatic history after backbend during dance practice. Therefore, more patients need to be recruited in future studies to further validate these findings.

5. Conclusions

Our study demonstrated that MI may evoke NP in some pediatric CSCI patients without NP. The different effects of MI on NP in pediatric CSCI patients may be related to individual differences in pediatric brain reorganization after CSCI. The right PSMC and insula may be involved in the regulation of MI on the NP in pediatric patients after CSCI. In addition, the GMV values of the right PSMC and insula in combination may be an indicator that can be used to predict prognoses in pediatric CSCI patients and to screen patients before the MI training therapy.

Data availability statement

The authors do not have permission to share data.

Ethics approval and consent to participate

The acquisition of data reported here was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University (Ethics No: [2020] 003). And informed consents were obtained from the parents/guardians of all pediatric participants.

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CRediT authorship contribution statement

Ling Wang: Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Formal analysis, Validation. **Xin Chen:** Conceptualization, Data curation, Formal analysis. **Weimin Zheng:** Formal analysis, Methodology, Writing – review & editing. **Yanhui Yang:** Methodology, Software. **Beining Yang:** Methodology, Software, Visualization. **Qian Chen:** Methodology, Writing – review & editing, Formal analysis, Validation. **Xuejing Li:** Data curation, Methodology. **Tengfei Liang:** Methodology, Software. **Baowei Li:** Methodology, Software. **Yongsheng Hu:** Data curation, Resources. **Jubao Du:** Data curation, Investigation, Resources. **Jie Lu:** Investigation, Supervision. **Nan Chen:** Conceptualization, Data curation, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Z. Zou, A. Teng, L. Huang, et al., Pediatric spinal cord injury without radiographic abnormality: the Beijing experience, Spine 46 (20) (2021) E1083–E1088, https://doi.org/10.1097/BRS.0000000000004030.
[2] A. Mcintyre, C. Sadowsky, A. Behrman, et al., A systematic review of the scientific literature for rehabilitation/habilitation among individuals with pediatric-onset spinal cord injury, Top. Spinal Cord Inj. Rehabil. 28 (2) (2022) 13–90, https://doi.org/10.46292/sci21-00046. Epub 2022 Apr 12.
[3] L. Wang, W.M. Zheng, T.F. Liang, et al., Brain activation evoked by motor imagery in pediatric patients with complete spinal cord injury, AJNR Am J Neuroradiol 44 (5) (2023) 611–617, https://doi.org/10.3174/ajnr.A7847.
[4] Z. Zou, S. Kang, Y. Hou, et al., Pediatric spinal cord injury with radiographic abnormality: the Beijing experience, Spine J. 23 (3) (2022) 403–411, https://doi.org/10.1016/j.spinee.2022.08.023.
[5] G. Cuomo, V. Maglianella, G.S. Ghanbari, et al., Motor imagery and gait control in Parkinson's disease: techniques and new perspectives in neurorehabilitation, Expert Rev. Neurother. 22 (1) (2022) 43–51, https://doi.org/10.1080/14737175.2022.2018301.Epub2021Dec28.
[6] N. Cederstrom, S. Graner, G. Nilsson, et al., Effect of motor imagery on enjoyment in knee-injury prevention and rehabilitation training: a randomized crossover study, J. Sci. Med. Sport 24 (3) (2021) 258–263, https://doi.org/10.1016/j.jsams.2020.09.004.
[7] L. Wang, X. Li, W. Zheng, et al., Motor imagery evokes strengthened activation in sensorimotor areas and its effective connectivity related to cognitive regions in patients with complete spinal cord injury, Brain Imaging Behav 16 (5) (2022) 2049–2060, https://doi.org/10.1007/s11682-022-00675-0.
[8] K.G. Sharp, R. Gramer, L. Butler, et al., Effect of overground training augmented by mental practice on gait velocity in chronic, incomplete spinal cord injury, Arch. Phys. Med. Rehabil. 95 (4) (2014) 615–621, https://doi.org/10.1016/j.apmr.2013.11.016.
[9] V. Moro, M. Corbella, S. Ionta, et al., Cognitive training improves disconnected limbs' mental representation and peripersonal space after spinal cord injury, Int. J. Environ. Res. Publ. Health 18 (18) (2021) 9589, https://doi.org/10.3390/ijerph18189589.
[10] Z.F. Guerra, A. Lucchetti, G. Lucchetti, Motor imagery training after stroke: a systematic review and meta-analysis of randomized controlled trials, J. Neurol. Phys. Ther. 41 (4) (2017) 205–214, https://doi.org/10.1097/NPT.0000000000000200.
[11] E. Sarasso, F. Agosta, N. Piramide, et al., Action observation and motor imagery improve dual task in Parkinson's disease: a clinical/fMRI study, Mov. Disord. 36 (11) (2021) 2569–2582, https://doi.org/10.1002/mds.28717.

[12] S. Tinaz, S. Kamel, S.S. Aravala, et al., Neurofeedback-guided kinesthetic motor imagery training in Parkinson's disease: randomized trial, Neuroimage Clin 34 (2022) 102980, https://doi.org/10.1016/j.nicl.2022.102980.
[13] S.M. Gustin, P.J. Wrigley, S.C. Gandevia, et al., Movement imagery increases pain in people with neuropathic pain following complete thoracic spinal cord injury, Pain 137 (2) (2008) 237–244, https://doi.org/10.1016/j.pain.2007.08.032.
[14] S.M. Gustin, P.J. Wrigley, L.A. Henderson, et al., Brain circuitry underlying pain in response to imagined movement in people with spinal cord injury, Pain 148 (3) (2010) 438–445, https://doi.org/10.1016/j.pain.2009.12.001.
[15] P.W. Hodges, R.J. Smeets, Interaction between pain, movement, and physical activity: short-term benefits, long-term consequences, and targets for treatment, Clin. J. Pain 31 (2) (2015) 97–107, https://doi.org/10.1097/AJP.0000000000000098.
[16] P. Pozeg, E. Palluel, R. Ronchi, et al., Virtual reality improves embodiment and neuropathic pain caused by spinal cord injury, Neurology 89 (18) (2017) 1894–1903, https://doi.org/10.1212/WNL.0000000000004585.
[17] G. Misra, S.A. Coombes, Neuroimaging evidence of motor control and pain processing in the human midcingulate cortex, Cerebr. Cortex 25 (7) (2015) 1906–1919, https://doi.org/10.1093/cercor/bhu001.
[18] M.S. Volz, V. Suarez-Contreras, A.L. Portilla, et al., Mental imagery-induced attention modulates pain perception and cortical excitability, BMC Neurosci. 16 (2015) 15, https://doi.org/10.1186/s12868-015-0146-6.
[19] E. Opsommer, O. Chevalley, N. Korogod, Motor imagery for pain and motor function after spinal cord injury: a systematic review, Spinal Cord 58 (3) (2020) 262–274, https://doi.org/10.1038/s41393-019-0390-1.
[20] H. Keenan, A. Clark, R. Holubkov, et al., Psychosocial and executive function recovery trajectories one year after pediatric traumatic brain injury: the influence of age and injury severity, J. Neurotrauma 35 (2) (2018) 286–296, https://doi.org/10.1089/neu.2017.5265.
[21] F. Malouin, C.L. Richards, P.L. Jackson, et al., The Kinesthetic and Visual Imagery Questionnaire (KVIQ) for assessing motor imagery in persons with physical disabilities: a reliability and construct validity study, J. Neurol. Phys. Ther. 31 (1) (2007) 20–29, https://doi.org/10.1097/01.npt.0000260567.24122.64.
[22] J. Ashburner, A fast diffeomorphic image registration algorithm, Neuroimage 38 (1) (2007) 95–113, https://doi.org/10.1016/j.neuroimage.2007.07.007.
[23] V. Lambert, P. Boylan, L. Boran, et al., Virtual reality distraction for acute pain in children, Cochrane Database Syst. Rev. 10 (2020) D10686, https://doi.org/10.1002/14651858.CD010686.pub2.
[24] L.G. Moseley, Using visual illusion to reduce at-level neuropathic pain in paraplegia, Pain 130 (3) (2007) 294–298, https://doi.org/10.1016/j.pain.2007.01.007.
[25] M.D. Soler, H. Kumru, R. Pelayo, et al., Effectiveness of transcranial direct current stimulation and visual illusion on neuropathic pain in spinal cord injury, Brain 133 (9) (2010) 2565–2577, https://doi.org/10.1093/brain/awq184.
[26] T.N. Bryce, F. Biering-Sorensen, N.B. Finnerup, et al., International spinal cord injury pain classification: part I. Background and description. March 6-7, 2009, Spinal Cord 50 (6) (2012) 413–417, https://doi.org/10.1038/sc.2011.156.
[27] T.B. Mole, K. Maciver, V. Sluming, et al., Specific brain morphometric changes in spinal cord injury with and without neuropathic pain, Neuroimage Clin 5 (2014) 28–35, https://doi.org/10.1016/j.nicl.2014.05.014.
[28] E. Opsommer, N. Korogod, Mental practice for chronic pain in people with spinal cord injury: a systematic review protocol, JBI Database System Rev Implement Rep 15 (8) (2017) 2004–2012, https://doi.org/10.11124/JBISRIR-2016-003149.
[29] M. Kocot-Kepska, R. Zajaczkowska, J. Mika, et al., Peripheral mechanisms of neuropathic pain-the role of neuronal and non-neuronal interactions and their implications for topical treatment of neuropathic pain, Pharmaceuticals 14 (2) (2021) 77, https://doi.org/10.3390/ph14020077.
[30] R. Kumari, H. Gibson, M. Jarjees, et al., The predictive value of cortical activity during motor imagery for subacute spinal cord injury-induced neuropathic pain, Clin. Neurophysiol. 148 (2023) 32–43, https://doi.org/10.1016/j.clinph.2023.01.006.
[31] C.R. Jutzeler, E. Huber, M.F. Callaghan, et al., Association of pain and CNS structural changes after spinal cord injury, Sci. Rep. 6 (2016) 18534, https://doi.org/10.1038/srep18534.
[32] G. Ziegler, P. Grabher, A. Thompson, et al., Progressive neurodegeneration following spinal cord injury: implications for clinical trials, Neurology 90 (14) (2018) e1257–e1266, https://doi.org/10.1212/WNL.0000000000005258.
[33] S.M. Gustin, C.C. Peck, L.B. Cheney, et al., Pain and plasticity: is chronic pain always associated with somatosensory cortex activity and reorganization? J. Neurosci. 32 (43) (2012) 14874–14884, https://doi.org/10.1523/JNEUROSCI.1733-12.2012.
[34] J. Islam, E. Kc, B.H. Oh, et al., Optogenetic stimulation of the motor cortex alleviates neuropathic pain in rats of infraorbital nerve injury with/without CGRP knock-down, J. Headache Pain 21 (1) (2020) 106, https://doi.org/10.1186/s10194-020-01174-7.
[35] K. Pacheco-Barrios, X. Meng, F. Fregni, Neuromodulation techniques in phantom limb pain: a systematic review and meta-analysis, Pain Med. 21 (10) (2020) 2310–2322, https://doi.org/10.1093/pm/pnaa039.
[36] H. Alkadhi, P. Brugger, S.H. Boendermaker, et al., What disconnection tells about motor imagery: evidence from paraplegic patients, Cerebr. Cortex 15 (2) (2005) 131–140, https://doi.org/10.1093/cercor/bhh116.
[37] D.J. Denis, R. Marouf, P. Rainville, et al., Effects of insular stimulation on thermal nociception, Eur. J. Pain 20 (5) (2016) 800–810, https://doi.org/10.1002/ejp.806.
[38] C.C. Liu, S. Moosa, M. Quigg, et al., Anterior insula stimulation increases pain threshold in humans: a pilot study, J. Neurosurg. (2021) 1–6, https://doi.org/10.3171/2020.10.JNS203323.
[39] L. Mazzola, J. Isnard, R. Peyron, et al., Stimulation of the human cortex and the experience of pain: wilder Penfield's observations revisited, Brain 135 (Pt 2) (2012) 631–640, https://doi.org/10.1093/brain/awr265.
[40] L.Q. Uddin, Salience processing and insular cortical function and dysfunction, Nat. Rev. Neurosci. 16 (1) (2015) 55–61, https://doi.org/10.1038/nrn3857.
[41] R.R. Bhatt, A. Gupta, E.A. Mayer, et al., Chronic pain in children: structural and resting-state functional brain imaging within a developmental perspective, Pediatr. Res. 88 (6) (2020) 840–849, https://doi.org/10.1038/s41390-019-0689-9.