HHS Public Access

Author manuscript

J Neuroimaging. Author manuscript; available in PMC 2022 November 11.

Published in final edited form as:

J Neuroimaging. 2022 November ; 32(6): 1193–1200. doi:10.1111/jon.13029.

Translingual neural stimulation affects resting-state functional connectivity in mild-moderate traumatic brain injury

Jiancheng Hou[1,2], **Rosaleena Mohanty**[3], **Daniel Chu**[2], **Veena A. Nair**[2], **Yuri Danilov**[4], **Kurt A. Kaczmarek**[4], **Beth Meyerand**[5], **Mitchell Tyler**[4,5], **Vivek Prabhakaran**[2]

[1]Research Center for Cross-Straits Cultural Development, Fujian Normal University, Fuzhou, China

[2]Department of Radiology, School of Medicine and Public Health, University of Wisconsin–Madison, Madison, Wisconsin, USA

[3]Department of Neurobiology, Karolinska Institute, Stockholm, Sweden

[4]Department of Kinesiology, University of Wisconsin–Madison, Madison, Wisconsin, USA

[5]Department of Biomedical Engineering, University of Wisconsin–Madison, Madison, Wisconsin, USA

Abstract

Background and Purpose: Traumatic brain injury (TBI) can lead to movement and balance deficits. In addition to physical therapy, brain-based neurorehabilitation efforts have begun to show promise in improving these deficits. The present study investigated the effectiveness of translingual neural stimulation (TLNS) on patients with mild-to-moderate TBI (mmTBI) and related brain connectivity using a resting-state functional connectivity (RSFC) approach.

Methods: Resting-state images with 5-min on GE750 3T scanner were acquired from nine participants with mmTBI. Paired *t*-test was used for calculating changes in RSFC and behavioral scores before and after the TLNS intervention. The balance and movement performances related to mmTBI were evaluated by Sensory Organization Test (SOT) and Dynamic Gait Index (DGI).

Results: Compared to pre-TLNS intervention, significant behavioral changes in SOT and DGI were observed. The analysis revealed increased RSFC between the left postcentral gyrus and left inferior parietal lobule and left Brodmann Area 40, as well as the increased RSFC between the right culmen and right declive, indicating changes due to TLNS treatment. However, there were no correlations between the sensory/somatomotor (or visual or cerebellar) network and SOT/DGI behavioral performance.

Conclusions: Although the limited sample size may have led to lack of significant correlations with functional assessments, these results provide preliminary evidence that TLNS in conjunction

Correspondence: Vivek Prabhakaran, Department of Radiology, School of Medicine and Public Health, University of Wisconsin–Madison, 600 Highland Ave, Madison, WI 53792, USA. VPrabhakaran@uwhealth.org.
Jiancheng Hou and Rosaleena Mohanty contributed equally to this work.

with physical therapy can induce brain plasticity in TBI patients with balance and movement deficits.

Keywords

Dynamic Gait Index; resting-state functional connectivity; Sensory Organization Test; traumatic brain injuries; translingual neural stimulation

INTRODUCTION

Traumatic brain injury (TBI), as one external acquired impairment to the brain, can generate physical, social, cognitive, and emotional deficits.[1] One of the common deficits due to mild-to-moderate TBI (mmTBI) is balance impairment.[2] Physical therapy that is vestibular based and includes therapeutic exercise that focuses on balance and gait training is a general approach to treating functional deficits due to mmTBI to promote neurological health and reduce negative emotions. This vestibular rehabilitation therapy has, however, generally had limited effectiveness on long-term functional recovery.[3]

Translingual neural stimulation (TLNS) is a relatively new intervention approach that combines superficial electrical stimulation of the facial and trigeminal nerves with physical therapy that is focused on gait and balance deficits.[4] TLNS is delivered by a device called the Portable Neuromodulation Stimulator (PoNS®, Helius Medical Technologies, Newtown, PA), a compact electrical apparatus that delivers comfortable electrical stimulation to the surface of the tongue.[5] The stimuli induce action potentials in the facial and trigeminal nerves that subsequently propagate to the brainstem and cerebellum and may ultimately lead to functional changes in brain structures.[6] Studies on TLNS treatment with mmTBI patients have shown that targeted physical rehabilitation combined with neurostimulation can induce neuroplasticity (eg, the pons, cerebellum, and brainstem in brain) without tissue damage, and lead to overall reduction in symptoms.[4,6] A brain morphometry study found that when TLNS treatment was applied in concert with physical therapy in mmTBI patients, the gray matter volume (GMV) increases in the brain were observed in the temporal and cerebellum, areas that refer to automated processing of balance, gait, visual motion, and motor control. In addition, decreased GMV in the occipital and frontal regions was also observed that involves more effortful processing of balance, gait, vision, motor control, but less automated processing.[7] Overall, this morphometric study indicated the positive brain plasticity changes induced by the TLNS treatment.

However, as far as we know, no study has examined brain functional changes through resting-state functional connectivity (RSFC) following TLNS treatment in mmTBI patients. RSFC is used to investigate the neural activity with low-frequency spontaneous (~0.01-0.1 Hz) fluctuations in brain.[8,9] Compared with the traditional task-related functional MRI (fMRI), an explicit task is not necessary during RSFC scan, which can be used to investigate a wide range of individuals (eg, infants or psychiatric patients).[10,11] Moreover, RSFC can be used to investigate a wide network of brain functional architecture.[12–14] Therefore, the present study examines the RSFC change between the before (pre-) and after (post-) TLNS intervention in mmTBI patients. The changes in RSFC pattern were subsequently correlated

to changes in behavioral testing that refer to gait and balance before and after the TLNS intervention. We particularly focused on three networks involved in sensory/somatomotor, visual, and cerebellar functions.

METHODS

Participants

Nine participants with mmTBI were involved (43-62 years old; mean age was 53.11 ± 6.60; three males and six females). Their mmTBI occurred at least 1 year before enrollment. Participants had previously participated in physical therapy, had reached a plateau in their functional recovery, and still scored at least 16 points below normal (after age adjustment) on the Sensory Organization Test (SOT), a quantitative dynamic postrural posturogrphic analysis system (Neurocom®). Their mmTBI diagnoses were made according to the guidelines established by the Veterans Affairs/Department of Defense.[15] This study was approved by the Institutional Review Board at School of Medicine and Public Health, University of Wisconsin–Madison. All participants in this study were provided informed and voluntary agreements and signed their consent form before the experiments.

All participants could independently walk for at least 20 minutes and had no medication changes for at least 3 months before the experiment. They were without other medical problems such as oral health, diabetes, hypertension, chronic infectious disease, or other potentially confounding neurological disorders. Additionally, participants did not have craniotomy, penetrating head injury, refractory subdural hematoma, or seizures.[5]

Intervention

TLNS was delivered using an experimental PoNS device (version 2.5), which uses 143 electrodes on the tongue array to deliver 19-volt amplitude-controlled, pulse-width-modulated, unbalanced biphasic pulses to the anterior, superior surface of the tongue. The waveform delivers a zero net direct current to minimize the potential for tissue irritation.[16,17] This experimental PoNS device delivered the same electrical stimulation as a commercially available PoNS device (Helius Medical Technologies) that has received regulatory clearance for treating balance and gait disorders arising from mmTBI and multiple sclerosis (MS) in Canada, MS in the United States, and all neurologically based balance and gait disorders in Australia. The 2-week TLNS intervention program (specifically stimulation during focused physical therapy focused on recovery of gait and balance) included twice-daily treatment in the laboratory and the same program at home during the intervening weekend.

Behavioral testing

All participants received both SOT and the Dynamic Gait Index (DGI) testing at baseline (before, or pre-intervention), and after 2 weeks of twice-daily in-lab intervention (post-intervention) as part of the behavioral assessment battery. The SOT is an objective and automated testing of sensory-motor integration that assesses the levels of somatosensory, visual, and vestibular balance. The DGI is a clinician-scored examination of eight facets of gait and is scored from 0 (worst) to 24 (normal). A score change of 3 points is generally considered clinically significant.[5]

MRI acquisition

Both resting-state fMRI and T1 structural MRI data (3T MRI GE750 scanner, GE Healthcare, Waukesha, WI) were acquired before (pre-) and after (post-) TLNS intervention. Each RSFC acquisition took 10 minutes and its parameters were as follows: repetition time (TR) = 2000 ms, echo time (TE) = 22 ms, $\theta = 60°$, field of view (FOV) = 100 × 100 mm, voxel size = 3.5 × 3.5 × 3.5 mm3, and in-plane resolution = 3.5 mm isotropic. The anatomical data scan was acquired using a T1-weighted, 3-dimensional, gradient-echo pulse-sequence (3D Magnetization-Prepared Rapid Gradient Echo) with TR = 8132 ms, TE = 3.18 ms, inversion time = 450 ms, $\theta = 12°$, FOV = 100 × 100 mm, and in-plane resolution = 1 mm isotropic. When lying supine on the scanner bed, the participants were required to keep their heads still, with close eyes and a relaxed body during their scan. Participants' head motion was minimized by MRI compatible foam pads, and all participants reported that their eyes were closed while staying awake during scanning. Each scan of resting-state fMRI and anatomical MRI took 5 minutes.

Region of interests selection

Three brain networks were applied as region of interests (ROIs) from the atlas from Power et al. (composed of 264 ROIs):[18] (1) 35 ROIs in sensory/somatomotor network as illustrated in Table 1 and Figure 1; (2) 31 ROIs in visual network as shown in Table 2 and Figure 2; and (3) four ROIs in cerebellar network in Table 3 and Figure 3. The radius of each spherical ROI was 5 mm, and the spherical ROIs were produced based on the standard Montreal Neurological Institute (MNI) coordinates.

Data preprocessing

RSFC preprocessing was performed using the Data Processing and Analysis of Brain Imaging toolbox version 6.0 (http://rfmri.org/dpabi), which includes the sub-toolbox of Data Processing Assistant for Resting-state fMRI Advanced Edition toolbox (DPARSF V4.5).[19,20] DPARSF is an easy plug-in software that works with Statistical Parametric Mapping (SPM, version 12) (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) integrated in Matlab.[21] The Digital Imaging and Communications in Medicine documents were first arranged, and then the first five volumes were discarded to allow the magnetization to approach a dynamic equilibrium so that the participants could become accustomed to the scanner noise. The parameters (eg, repetition time, slice number, voxel size, etc.) were then set. The preprocessing steps, in order, included slice timing correction, realignment, regressing out head motion parameters (scrubbing with Friston 24-parameter model regression; bad time points were identified using a threshold of frame-wise displacement >0.2 mm, and 1 volume before and 2 volumes after at the individual subject level as well as accounting for head motion at the group-level [ie, covariate analysis]),[18,20,22] normalization (spatial normalization to the MNI template, resampling voxel size of 3.5 × 3.5 × 3.5 mm), and smoothing (a spatial Gaussian filter of 4 mm full width at half maximum was used).[21,23] The temporal correlations as spontaneous neural connectivity was calculated to quantify RSFC and also the symmetric correlation matrixes for a 35 × 35 sensory/somatomotor network, a 31 × 31 visual network, and a 4 × 4 cerebellar network were generated per participant for pre- and post-interventions. Based on these matrices, each participant had a

total of 1225, 961, and 16 unique pairwise functional connectivities that were extracted from the sensory/somatomotor, visual, and cerebellar networks, respectively. Only half of the pairwise functional connectivity with each network was used for further statistical analysis because the top right half and bottom left half are the same in the matrices.

Statistical analysis

The paired *t*-test was used for calculating changes in RSFC and behavioral scores from pre- to post-intervention. RSFC results were generated through multiple comparisons correction by estimating the false discovery rate (FDR) $p < .05$, and the RSFC differences were viewed with the BrainNet Viewer Toolbox (https://www.nitrc.org/projects/bnv/). The correlation analysis between SOT (or DGI; post- minus pre-) and RSFC (post- minus pre-) was corrected at $p < .05$ with IBM SPSS version 23.

RESULTS

Behavioral scores

The paired *t*-test showed that compared to the pre-intervention, the post-intervention had significant increases for both SOT ($t_{(8)} = 2.742$, $p = .028$) and DGI ($t_{(8)} = 2.855$, $p = .024$).

RSFC changes

There was only one significant RSFC change between pre- and post-intervention after FDR correction that was observed within the sensory/somatomotor network. This was an increased RSFC between the left postcentral gyrus and the left inferior parietal lobule and left Brodmann Area 40 (BA 40) (Figure 4 and Table 4) after post-intervention. Moreover, there was only one significant RSFC increase between the post- versus pre-intervention without multiple comparison correction within the cerebellar network, specifically an increased RSFC between the right culmen and right declive after intervention (Figure 5 and Table 4). There is, however, no significant paired *t*-test difference with FDR and without multiple comparison correction within other network regions.

Brain-behavior correlations

Within the sensory/somatomotor and cerebellar networks, the correlations with SOT and DGI testing were not significant, possibly because of the small sample size.

DISCUSSION

There were statistically significant improvements in the behavioral SOT and DGI scores after the intervention. Specific brain regions showed evidence of plastic changes after the intervention.

The present study showed an increase in RSFC in the sensory/somatomotor network between the left postcentral gyrus and the left inferior parietal lobule and left BA 40 in mmTBI patients after TLNS treatment. The function of the postcentral gyrus or primary somatosensory cortex is to processes sensory information and allows for goal-oriented behavior to take place by delivering sensory information to the premotor cortex.[24]

The inferior parietal lobule and its interaction with the nearby supramarginal gyrus are responsible for processing multimodal information, specifically somatosensory and visual inputs[24,25] as well as being related to visual-vestibular interactions[24,26] that are important for gait and balance.[27,28] The increased RSFC in present study indicates the effect of TLNS on the sensory/somatomotor network.

There was increased RSFC in the cerebellar network between the right culmen and right declive, although without using multiple comparison correction, after the post-intervention. The cerebellum can interact with the cerebral cortex, the vestibular system, and also the muscles and joints and is mainly responsible for balance control.[29] The present study found more subregions in the cerebellum, and specifically found significant increased RSFC between the right culmen and right declive after using TLNS intervention, although without multiple comparison correction.

To our knowledge, this is the first study to examine the RSFC changes induced by TLNS intervention. Together with our previous gray matter morphometry study induced by TLNS intervention,[7] these studies have confirmed positive TLNS effects on brain plasticity in mmTBI patients with balance and movement deficits within 2 weeks, but we have not examined whether the effects would be continuous if the intervention was removed. A behavioral study with 26-week TLNS intervention demonstrated positive effects on the balance score in mmTBI patients; these were sustained for 12 weeks after TLNS treatment ended.[17] Another study showed the significant SOT and DGI improvements as well as the reductions in falls and headache disability index scores in mmTBI patients after 2 and 5 weeks, respectively.[30] Therefore, the relatively long-time effects of TLNS intervention and its brain functional changes deserve further study.

One limitation of the present study is a small sample size, although the results merit larger follow-up studies. Additionally, stimulation of the tongue with TLNS can take place with either a high-frequency or low-frequency pulse (HFP or LFP) device, and some studies investigated the efficacy of TLNS in mmTBI patients and compared the outcomes between HFP and LFP with more participants.[17,31,32] Our participant number (also in our previous study[7]) was too small to analyze HFP and LFP subgroups. Finally, in addition to the benefits of TLNS intervention, whether the improved SOT and DGI scores and increased RSFC after intervention could have resulted from physical therapy alone has not been conclusively established so far; therefore, future research is required.[17]

In summary, the present study presents evidence that TLNS effectively improves balance and movement in mmTBI patients accompanied by increased involvement of neural regions associated with gait, balance, and motor control. Therefore, TLNS is an effective approach to treating the symptoms of mmTBI patients.

ACKNOWLEDGEMENTS AND DISCLOSURES

Professional medical writing and editorial assistance were provided by Kelly M. Fahrbach, Ashfield Healthcare Communications, part of UDG Healthcare plc, funded by Helius Medical Technologies. This study is a part of the long-term clinical trial (NCT02158494), which was completed to investigate the efficacy of translingual neural stimulation (cranial nerve noninvasive neuromodulation).

Drs. Tyler, Danilov, and Kaczmarek have a financial interest in Helius Medical Technologies and are also co-founders and co-owners of Advanced NeuroRehabilitation, LLC, which holds the intellectual property rights to the PoNS® technology. Tyler is a board member of Helius Medical Technologies. The other authors declare no conflict of interest.

Funding information

Drs. Tyler, Kaczmarek, Danilov, Hou, and Prabhakaran were being, Grant/Award Number: NHC-TBI-PoNS-RT001; Drs. Hou, Kulkarni, Nair, and Prabhakaran were being, Grant/Award Number: R01AI138647; Drs. Hou and Prabhakaran were being, Grant/Award Numbers: P01AI132132, R01NS105646; Mr. Chu was being supported by MSTP, Grant/Award Number: T32 GM140935; National Center for Research Resources, Grant/Award Number: 1UL1RR025011; Drs. Meyerand, Prabhakaran, and Nair were being, Grant/Award Number: U01NS093650

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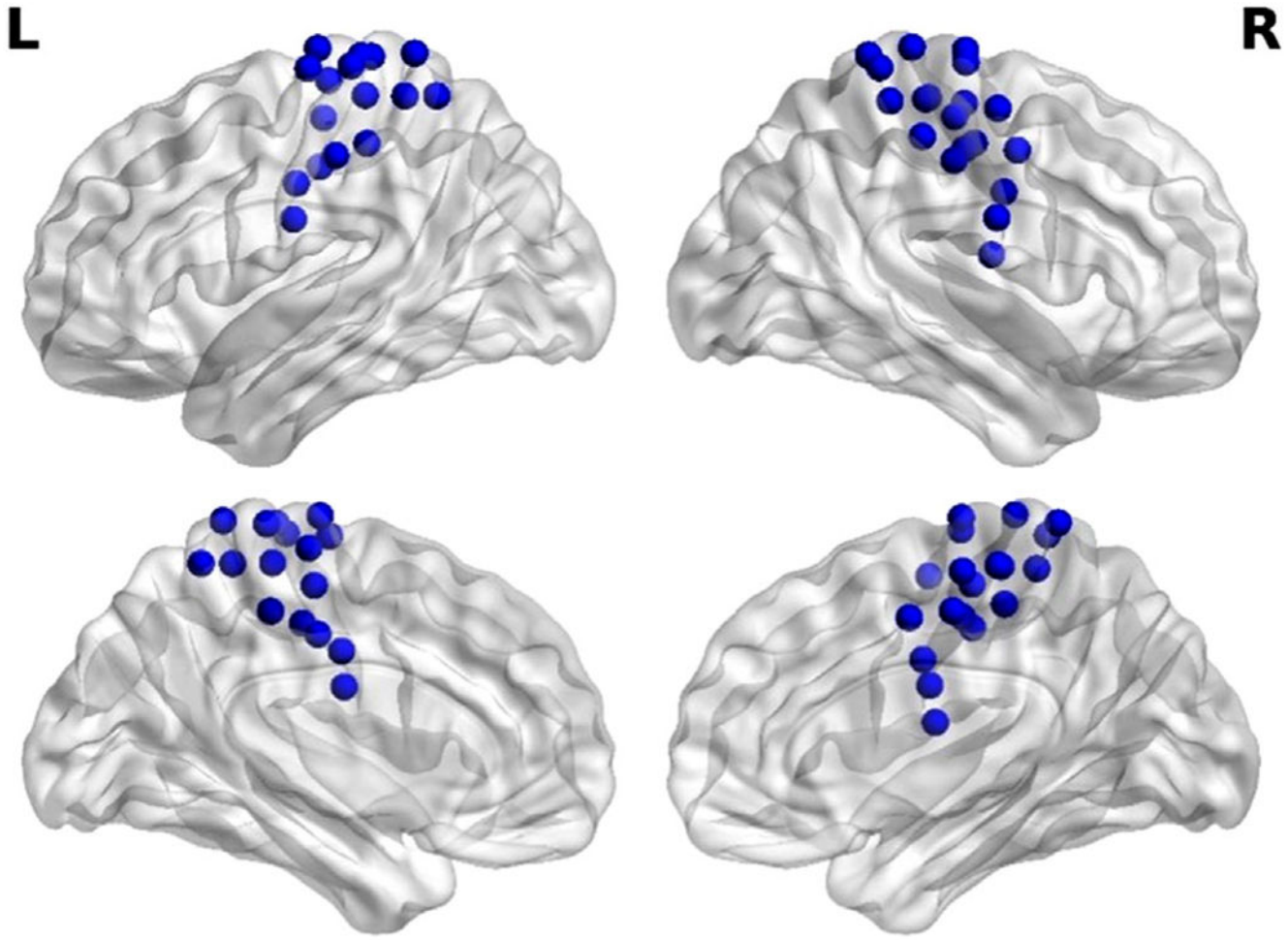

FIGURE 1.
Sensory/somatomotor network seeds. L, left hemisphere; R, right hemisphere

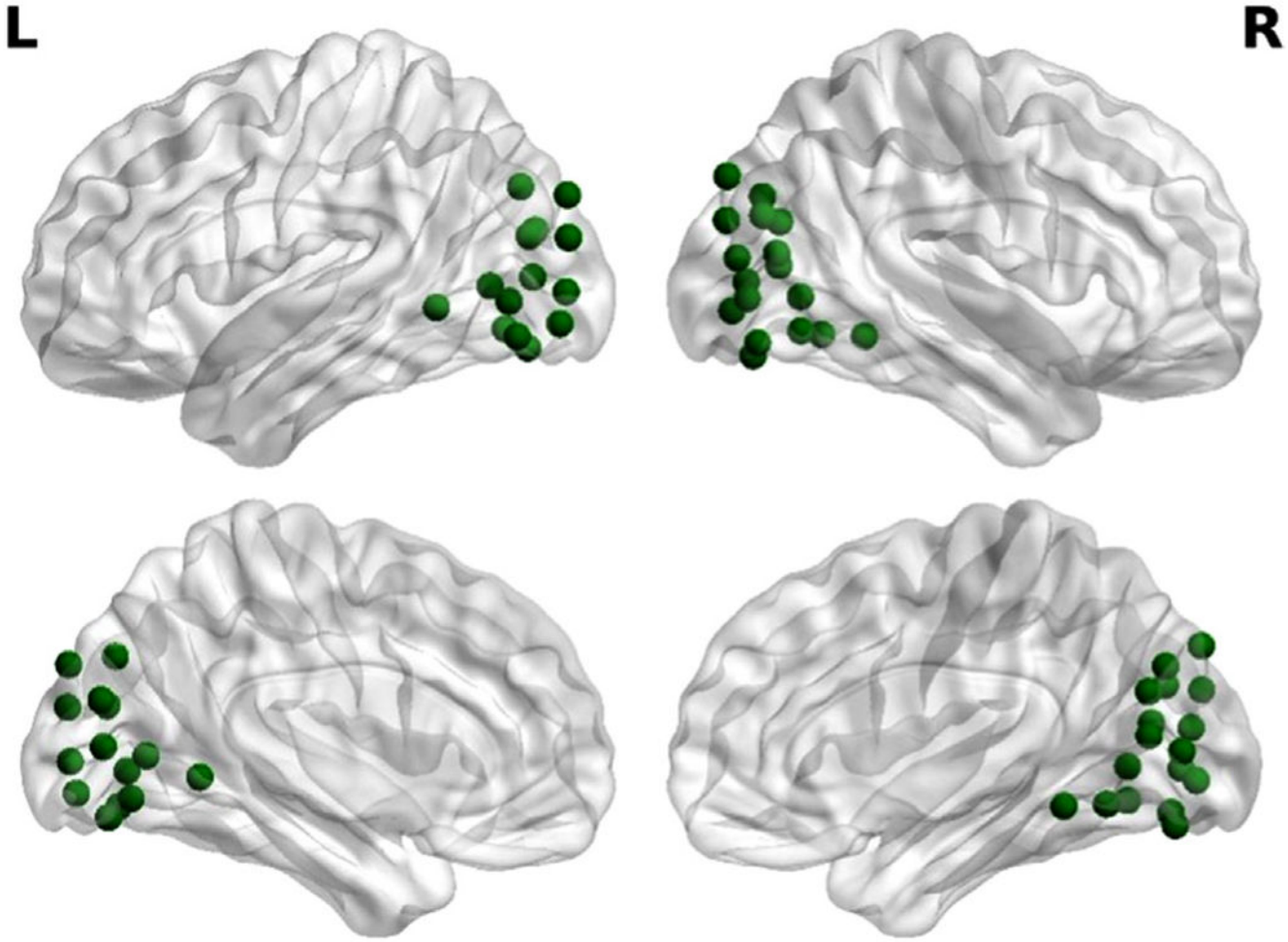

FIGURE 2.
Visual network seeds. L, left hemisphere; R, right hemisphere

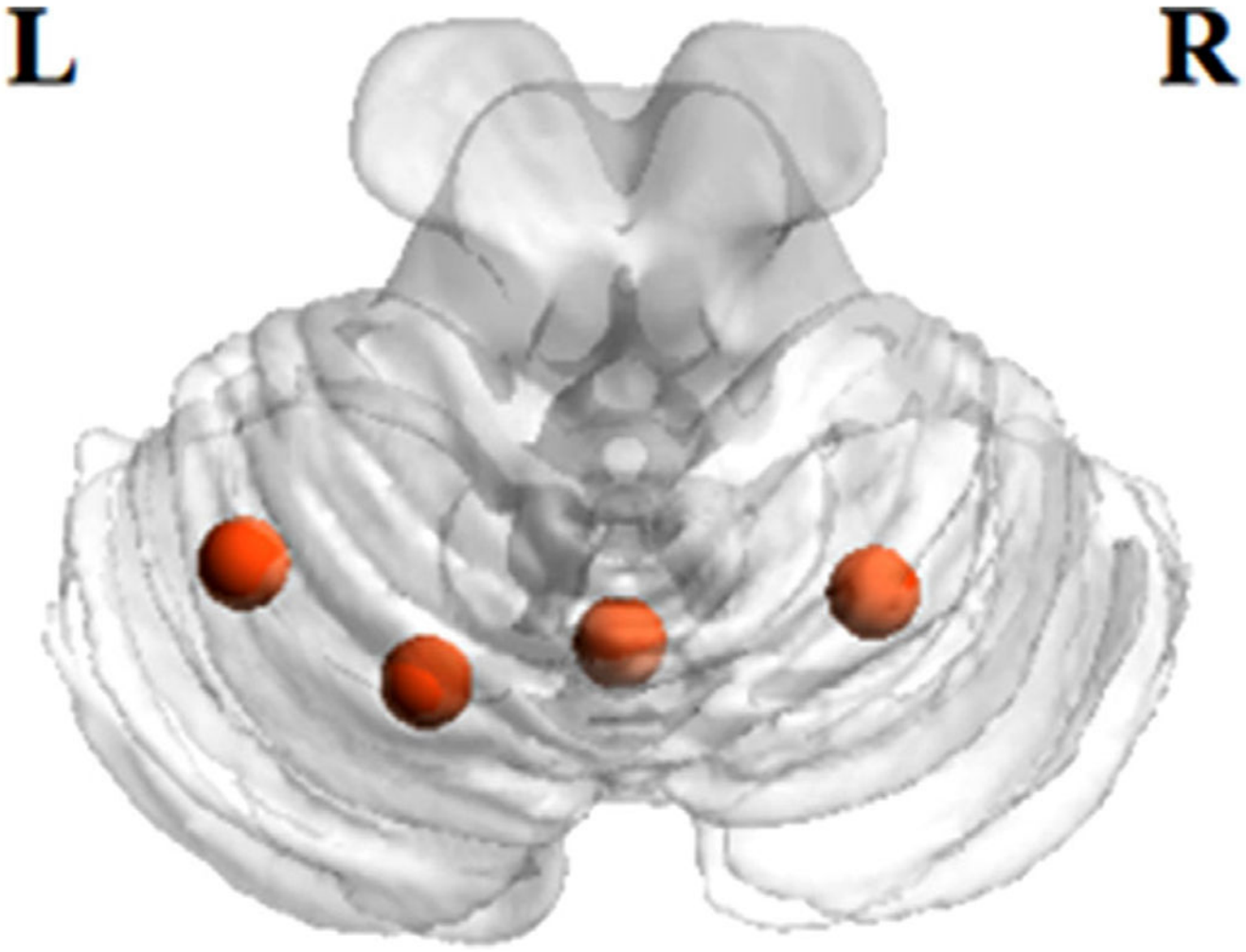

FIGURE 3.
Cerebellar network seeds. L, left hemisphere; R, right hemisphere

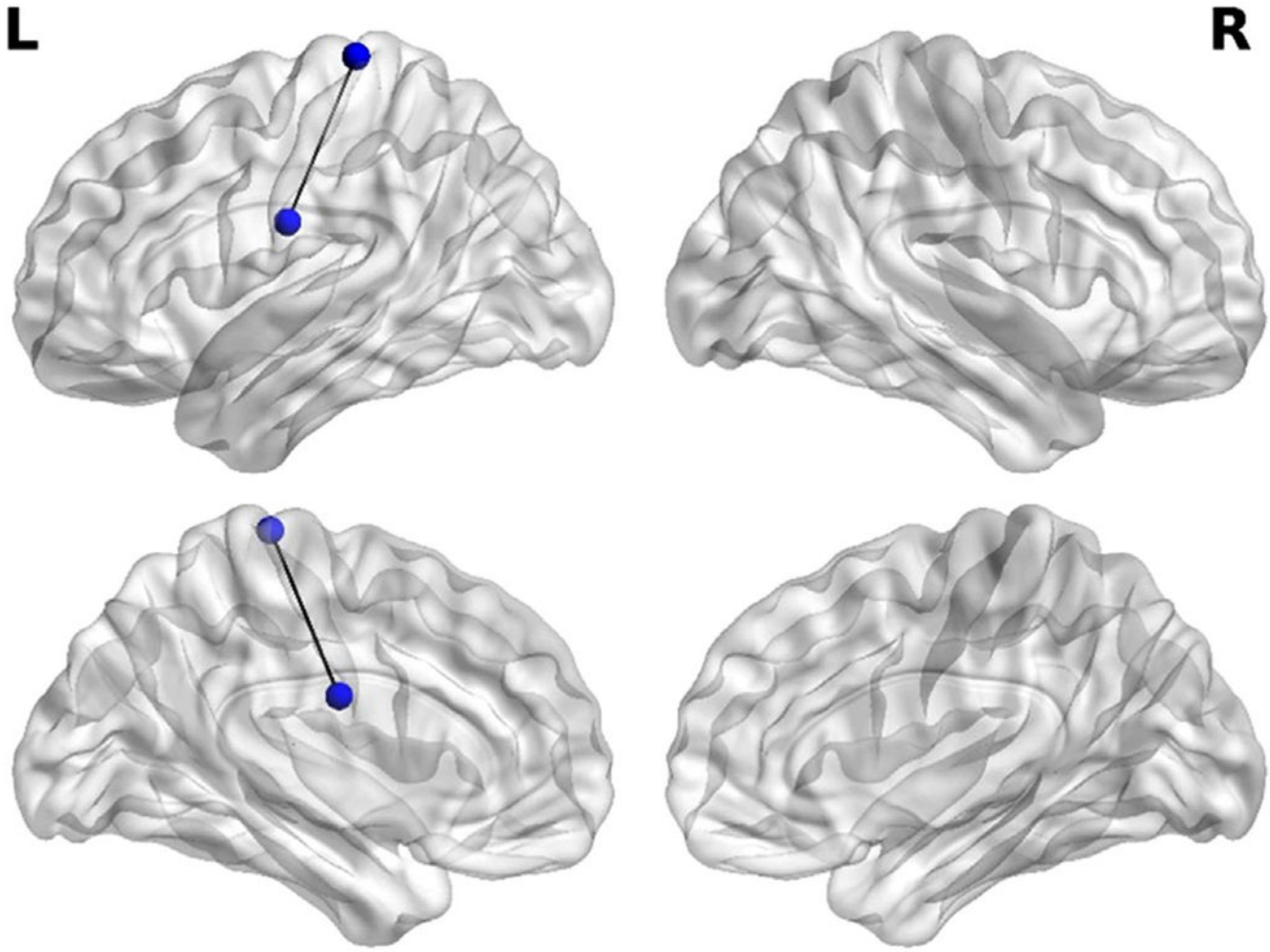

FIGURE 4.
Increased resting-state functional connectivity between the left postcentral gyrus and the left inferior parietal lobule and left BA40 after intervention within the sensory/somatomotor network. L, left hemisphere; R, right hemisphere

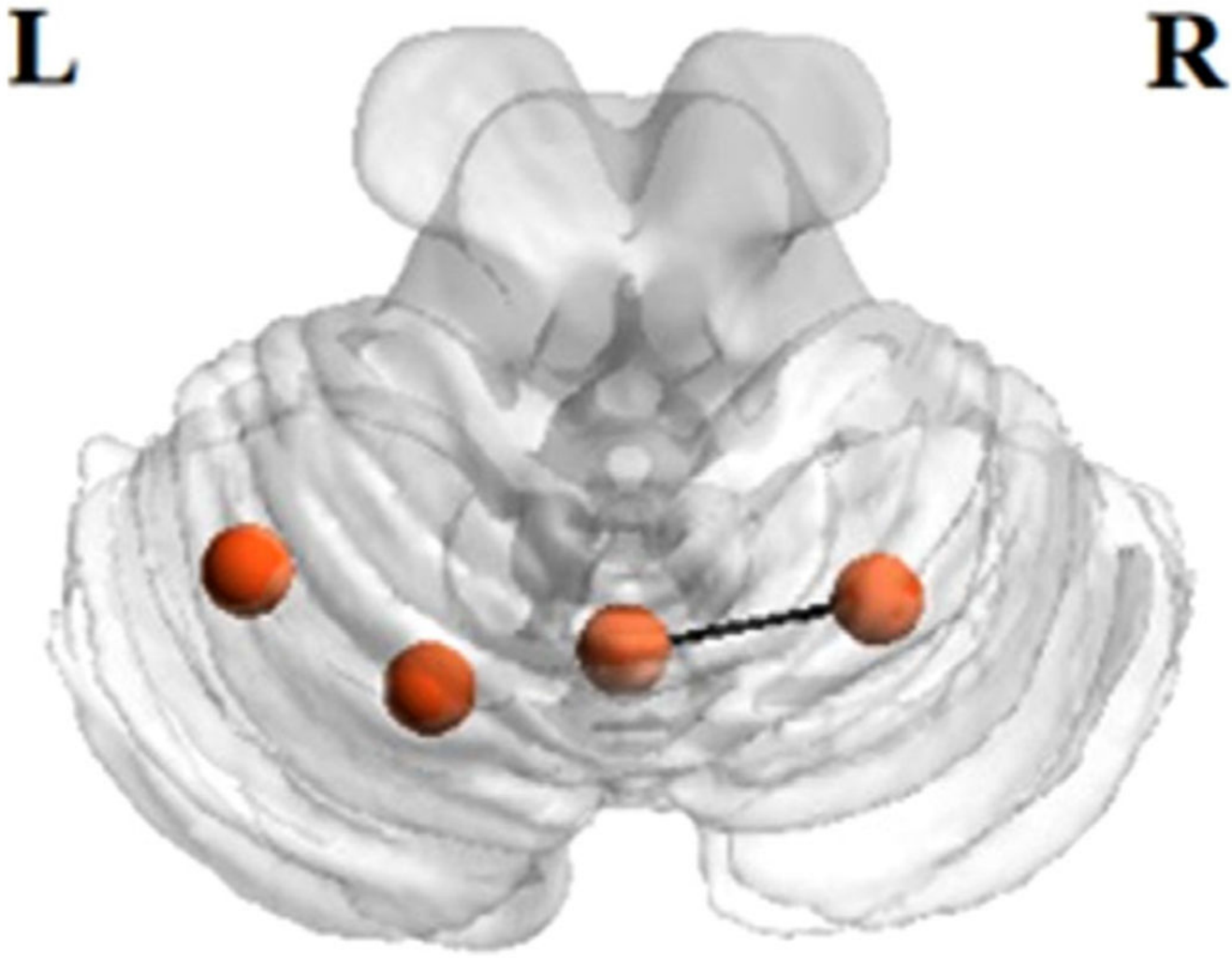

FIGURE 5.
Increased resting-state functional connectivity between the right culmen and the right declive after intervention within the cerebellar network (without multiple comparison correction). L, left hemisphere; R, right hemisphere

TABLE 1

Thirty-five seed regions of the sensory/somatomotor network based on the atlas from Power et al.[18]

MNI				
x	***y***	***z***	**Network**	**Anatomical label**
−7.12	−52.22	60.71	Sensory/somatomotor	Left precuneus
−13.74	−17.95	39.84	Sensory/somatomotor	Left cingulate gyrus
0.05	−14.53	46.74	Sensory/somatomotor	Left paracentral lobule
9.5	−1.84	44.73	Sensory/somatomotor	Right cingulate gyrus and right BA 24
−6.9	−20.59	65.21	Sensory/somatomotor	Left medial frontal gyrus
−6.79	−33.09	72.27	Sensory/somatomotor	Left paracentral lobule
13.19	−32.82	74.98	Sensory/somatomotor	Right postcentral gyrus
−53.52	−22.54	43.1	Sensory/somatomotor	Left postcentral gyrus
28.88	−16.95	70.55	Sensory/somatomotor	Right precentral gyrus
9.94	−45.52	72.63	Sensory/somatomotor	Right postcentral gyrus
−22.5	−30.1	72.44	Sensory/somatomotor	Left postcentral gyrus
−39.63	−19.04	54.21	Sensory/somatomotor	Left precentral gyrus and left BA 4
28.54	−39.24	59.17	Sensory/somatomotor	Right postcentral gyrus and right BA 5
50.24	−20.37	41.74	Sensory/somatomotor	Right postcentral gyrus
−38.28	−27.17	69.45	Sensory/somatomotor	Left precentral gyrus
20.21	−28.8	59.8	Sensory/somatomotor	Right postcentral gyrus and right BA 3
44.34	−7.55	56.98	Sensory/somatomotor	Right precentral gyrus
−29.1	−43	60.66	Sensory/somatomotor	Left postcentral gyrus and left BA 5
10.09	−17.1	74.14	Sensory/somatomotor	Right superior frontal gyrus
22.45	−42.29	68.99	Sensory/somatomotor	Right postcentral gyrus
−45.1	−31.85	46.63	Sensory/somatomotor	Left inferior parietal lobule and left BA 40
−20.66	−31.33	60.85	Sensory/somatomotor	Left postcentral gyrus
−12.96	−17.34	74.66	Sensory/somatomotor	Left paracentral lobule
42.14	−20.24	54.59	Sensory/somatomotor	Right postcentral gyrus and right BA 3
−38.24	−14.57	68.72	Sensory/somatomotor	Left precentral gyrus
−16.25	−45.8	73.22	Sensory/somatomotor	Left postcentral gyrus
2.4	−27.94	60.15	Sensory/somatomotor	Right paracentral lobule

MNI			Network	Anatomical label
x	*y*	*z*		
3.45	−17.44	58.45	Sensory/somatomotor	Right medial frontal gyrus
37.74	−17.3	45.01	Sensory/somatomotor	Right precentral gyrus and right BA 4
47.21	−29.75	48.7	Sensory/somatomotor	Right postcentral gyrus
−49.47	−11.06	34.95	Sensory/somatomotor	Left precentral gyrus
36.04	−9.44	13.95	Sensory/somatomotor	Right insula and right BA 13
51.14	−5.8	32.42	Sensory/somatomotor	Right precentral gyrus and right BA 6
−52.84	−10.23	24.41	Sensory/somatomotor	Left postcentral gyrus
65.64	−7.88	24.83	Sensory/somatomotor	Right precentral gyrus

Note: MNI is the Montreal Neurological Institute coordinates.

TABLE 2

Thirty-one seed regions of the visual network based on the atlas from Power et al.[18]

MNI				
x	*y*	*z*	Network	Anatomical label
17.53	−46.86	−9.88	Visual	Right culmen
39.98	−72.49	14.36	Visual	Right middle occipital gyrus
8.45	−71.84	10.79	Visual	Right cuneus and right BA 23
−8.43	−80.5	7.44	Visual	Left cuneus
−28.07	−79.45	19.43	Visual	Left middle occipital gyrus and left BA 19
19.81	−65.56	1.72	Visual	Right lingual gyrus
−23.94	−90.98	18.96	Visual	Left middle occipital gyrus
26.93	−59.37	−9.36	Visual	Right fusiform gyrus
−15.02	−72.42	−7.68	Visual	Left lingual gyrus
−17.87	−68.03	4.81	Visual	Left lingual gyrus
42.52	−78.17	−11.78	Visual	Right fusiform gyrus
−46.54	−75.95	−9.95	Visual	Left middle occipital gyrus and left BA 19
−14.22	−90.66	31.4	Visual	Left cuneus
15.27	−87.09	36.89	Visual	Right cuneus and right BA 19
28.68	−76.62	25.42	Visual	Right superior occipital gyrus
19.64	−85.62	−2.39	Visual	Right lingual gyrus
15.18	−76.68	31	Visual	Right cuneus and right BA 19
−15.85	−52.34	−1.43	Visual	Left lingual gyrus and left BA 19
41.6	−65.5	−8.27	Visual	Right middle occipital gyrus
24.41	−87.21	24.01	Visual	Right cuneus
5.59	−71.65	23.52	Visual	Right precuneus and right BA 31
−42.1	−73.62	0.38	Visual	Left middle occipital gyrus
25.66	−79.47	−15.56	Visual	Right declive
−16.21	−76.97	33.82	Visual	Left precuneus and left BA 7
−2.88	−81.25	21.1	Visual	Left cuneus and left BA 18
−40.21	−88.44	−6.19	Visual	Left inferior occipital gyrus and left BA 18
36.76	−84.11	12.99	Visual	Right middle occipital gyrus and right BA 19

MNI			Network	Anatomical label
x	*y*	*z*		
6.21	−81.41	6.11	Visual	Right cuneus and right BA 17
−26.39	−90.23	3.12	Visual	Left middle occipital gyrus
−33	−79.02	−13.24	Visual	Left fusiform gyrus and left BA 19
36.51	−81.16	1.2	Visual	Right middle occipital gyrus

Note: MNI is the Montreal Neurological Institute coordinates.

TABLE 3

Four seed regions of the cerebellar network based on the atlas from Power et al.[18]

MNI				
x	***y***	***z***	**Network**	**Anatomical Label**
−16.31	−65.28	−19.69	Cerebellar	Left declive
−32.12	−55.03	−25.22	Cerebellar	Left culmen
22.43	−57.55	−23.11	Cerebellar	Right culmen
0.51	−61.91	−18.14	Cerebellar	Right declive

Note: MNI is the Montreal Neurological Institute coordinates.

TABLE 4

Resting-state functional connectivity difference between post- vs. pre-intervention

Network	Seed 1	Seed 2	Post (mean ± SD)	Pre (mean ± SD)	*t*	*p*
						(FDR-corrected)
Sensory/somatomotor network	Left postcentral gyrus	Left inferior parietal lobule and left BA 40	0.648 (0.192)	0.484 (0.133)	10.800**	.0027
						(Without multiple correction)
Cerebellar network	Right culmen	Right declive	0.483 (0.159)	0.245 (0.254)	3.216*	.0123

Note: Positive paired *t*-test indicates increased resting-state functional connectivity after post-intervention comparison to pre-intervention.

Abbreviations: FDR, false discovery rate; Post, post-intervention; Pre, pre-intervention; SD, standard deviation.

** $p < .005$;

* $p < .05$.