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Differences in the thalamocortical tract of the ascending reticular activating system in disorders of consciousness after hypoxic-ischemic brain injury

A pilot study

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Abstract

This study purposed to investigate differences in the thalamocortical tract of the ascending reticular activating system between vegetative state (VS) and minimally conscious state (MCS) patients with hypoxic-ischemic brain injury (HI-BI). Fourteen patients with disorders of consciousness following HI-BI (VS group: 7 patients, MCS group: 7 patients) and 12 normal subjects were recruited. The 5 parts of reconstructed thalamocortical tract were prefrontal cortex (PFC), premotor cortex, primary motor cortex (M1), primary somatosensory cortex (S1), and posterior parietal cortex (PPC). The fractional anisotropy (FA) value and tract volume (TV) in each part of the thalamocortical tract were estimated. The FA values and TV of all parts of the thalamocortical tract in the VS group and the FA values of all parts and TV of PFC, premotor cortex, and PPC parts in the MCS group were lower than the control group ($P < .05$). In addition, the FA values of PFC and PPC parts were significantly lower in the VS group than the MCS group ($P < .05$). The results of our pilot study indicate that PFC and PPC parts of the thalamocortical tract are important areas to assess for differentiation of VS and MCS after HI-BI.

Abbreviations: ARAS = ascending reticular activating system, BA = Brodmann area, CRS-R = Coma Recovery Scale-Revised, DOC = disorders of consciousness, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotropy, HI-BI = hypoxic-ischemic brain injury, M1 = primary motor cortex, MCS = minimally conscious state, PFC = prefrontal cortex, PMC = premotor cortex, PPC = posterior parietal cortex, ROI = region of interest, S1 = primary somatosensory cortex, TV = tract volume, VS = vegetative state.

Keywords: diffusion tensor imaging, diffusion tensor tractography, disorders of consciousness, hypoxic-ischemic brain injury, thalamocortical tract

1. Introduction

Hypoxic-ischemic brain injury (HI-BI), a severe consequence of reductions of the oxygen and blood supply to the brain, can result from cardiac arrest, respiratory arrest, near-hanging, or poisoning.[1,2] Among the various neurological sequelae, disorders of consciousness (DOC) is one of the disabling sequela, occurring in 36% of patients surviving after HI-BI, and many patients with DOC undergo in a vegetative state (VS) or a minimally conscious state (MCS).[1,3] VS is defined by patient unconsciousness without responsiveness or awareness, whereas MCS is characterized by partial preservation of awareness and some responses, such as a nonfunctional and intentional gesture or verbal response to simple questions, sustained visual pursuit, or following a single command.[1,2,4] Therefore, knowledge of differences in brain structures between VS and MCS in patients with DOC is important because that information can be helpful in the development of guidelines for neurorehabilitation.[5,6] For example, recently developed noninvasive brain stimulation therapies such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation can be applied to specific neural structures for recovery of impaired consciousness.[5,6]

DOC can result from damage to various neural structures in the brain. Structures that are critical components of consciousness-related networks include the thalamocortical tract of ascending reticular activating system (ARAS), the lower ARAS, and the

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frontoparietal, frontostriatal, and default mode networks.[7–11] Among these neural networks, the thalamocortical tract of the ARAS, which connects the intralaminar thalamic nuclei to the frontoparietal cortex, has been considered an important neural network related to consciousness, especially awareness.[11,12] Therefore, the status of the thalamocortical tract could be related to differences in impairment of the state of awareness of consciousness (VS or MCS) in patients with DOC. According to a previous study, the thalamocortical tract divide into the 5 parts; the prefrontal cortex (PFC), premotor cortex (PMC), primary motor cortex, primary somatosensory cortex, and posterior parietal cortex (PPC), and the specific parts of the thalamocortical tract could be important for recovery of impaired consciousness.[13,14]

Many studies have reported differences between VS and MCS in patients with DOC based on results obtained by electroencephalography, positron emission tomography, arterial spin labeling, or functional magnetic resonance imaging.[15–20] However, these methods have difficulty in estimating brain regions that include subcortical white matter. By contrast, diffusion tensor tractography (DTT), a recently developed imaging approach derived from diffusion tensor imaging (DTI), has a distinct advantage in discriminating the thalamocortical tract because it facilitates 3-dimensional visualization and estimation of the thalamocortical tract.[21,22] The thalamocortical tract state can be determined by evaluating DTT parameters, including the fractional anisotropy (FA) value, and tract volume (TV).[23,24] The FA value implies the state of white matter organization by indicating the degree of and integrity of white matter microstructures.[23,24] In contrast, the TV indicates the total number of voxels within a neural tract, which is considered representative of the total number of fibers within the tract.[23,24] A few studies have used DTT to demonstrate thalamocortical tract changes associated with the change from VS to MCS in patients with DOC due to brain injury.[25–28] However, regarding HI-BI, only a case study has reported on differences in the state of the thalamocortical tract between VS and MCS patients with DOC after HI-BI.[25]

In this study, the purpose was to investigate differences in the thalamocortical tract of the ARAS between VS and MCS patients with HI-BI.

2. Methods

2.1. Subjects

Fourteen consecutive patients (8 males, 6 females; mean age 48.07 ± 4.18 years, range 18–76 years) with HI-BI who visited the rehabilitation department of a university hospital and 12 normal subjects (7 males, 5 females; mean age 49.00 ± 3.21 years, range 26–66 years) with no neurological and psychiatric history were recruited for this study. The patients were enrolled consecutively according to the following inclusion criteria: an obvious HI-BI history (e.g., cardiac arrest, strangulation, carbon monoxide intoxication, etc); age at onset of HI-BI: 18–79 years; presence of impaired consciousness at HI-BI onset; DTI scans obtained after 1 month following HI-BI (6 weeks–12 months after onset); the patients who underwent comprehensive rehabilitation for recovery DOC at least for 4 weeks at our department, no previous history of head trauma and neurological or psychiatric disease. Based on patients' Coma Recovery Scale-Revised (CRS-R) scores, which were determined at the time of DTI scanning, the patients were assigned to 2 groups[10]: VS group: 7 patients (31.8% of total; 5 males, 2 females; mean age 46.71 ± 7.87 years); MCS group: 7 patients (31.8% of the total; 3 males, 4 females; mean age 49.43 ± 21.56). Demographic data for the VS, MCS, and control groups are summarized in Table 1. There were no significant differences in age or sex among the VS, MCS, and control groups ($P > .05$) or in the duration to DTI between the VS and MCS groups ($P > .05$). However, according to the number of male and female, female was lower in the MCS group compared with the VS and control groups ($P > .05$). In addition, the duration to DTI was lower in the MCS group than in the VS group ($P > .05$). This study was conducted retrospectively and reports the information required by the Strengthening the Reporting of Observational Studies in Epidemiology Statement. The study protocol was approved by the institutional review board of a university hospital, and written informed consent was obtained from each participant of the control group.

Table 1

Demographic data of patients in the vegetative state and minimally conscious state groups and subjects in the control group.

Group	VS (n = 7)	MCS (n = 7)	Control (n = 12)	*P* value
Age (yr)	46.71 ± 7.87	49.43 ± 21.56	49.00 ± 3.21	.80
Sex (male/female)	5/2	3/4	7/5	.54
Duration to DTI (mo)	5.45 ± 3.46	4.29 ± 2.62		.57
CRS-R	3.43 ± 2.88	9.86 ± 2.48		

Values indicate mean ± standard deviation.

CRS-R = Coma Recovery Scale-Revised, DTI = diffusion tensor imaging, MCS = minimally conscious state, VS = vegetative state.

* Significant difference ($P < .05$).

2.2. Clinical evaluation

The consciousness state was evaluated using CRS-R, which is a standard neurobehavioral assessment measure for patients with DOC.[10,29] CRS-R can distinguish the consciousness state according to each score of 6 subscales including auditory, visual, motor, oromotor/verbal, communication, and arousal.[10,29] The classification criteria of 2 groups (VS and MCS groups) were as follows: the VS group: auditory ≤ 2, visual ≤ 1, motor ≤ 2, oromotor/verbal ≤ 2, communication = 0, and arousal ≤ 2; the MCS group: auditory ≥ 3, visual ≥ 2, 3 ≤ motor ≤ 5, oromotor/verbal = 3, or communication = 1.[10,29]

2.3. Diffusion tensor imaging

DTI scanning was performed at an average of 4.29 ± 3.29 months after the onset of HI-BI using a 1.5T Philips Gyroscan Intera scanner (Hoffman-LaRoche, Best, Netherlands) with a 6-channel head coil. A single-shot, spin-echo planar imaging method was used. For each of the 32 noncollinear diffusion sensitizing gradients, 67 contiguous slices were acquired parallel to the anterior commissure–posterior commissure line. Imaging parameters were as follows: acquisition matrix = 96 × 96, reconstructed to matrix = 128 × 128, field of view = 221 mm × 221 mm, repetition time = 10,726 ms, echo time = 76 ms, parallel imaging reduction factor (sensitivity encoding factor) = 2, echo planar imaging factor = 49, b = 1000 s/mm^2, number of excitations = 1, and slice thickness = 2.3 mm. The Oxford Centre for Functional Magnetic Resonance Imaging of Brain Software Library (www.fmrib.ox.ac.uk/fsl) was used for DTI data analysis. Affine multiscale 2-dimensional registration was applied to correct for head motion effects and image distortions. A probabilistic tractography method based on a multifiber model provided in Functional Magnetic Resonance Imaging of Brain diffusion software was applied using the software routines option (5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2) for fiber tracking.

Five parts of the thalamocortical tract (PFC, PMC, primary motor cortex [M1], primary somatosensory cortex [S1], and PPC) were reconstructed following the selection of fibers passing through various regions of interest (ROIs) (Fig.1).[13,30] For reconstruction of the thalamocortical tract, the seed ROI was

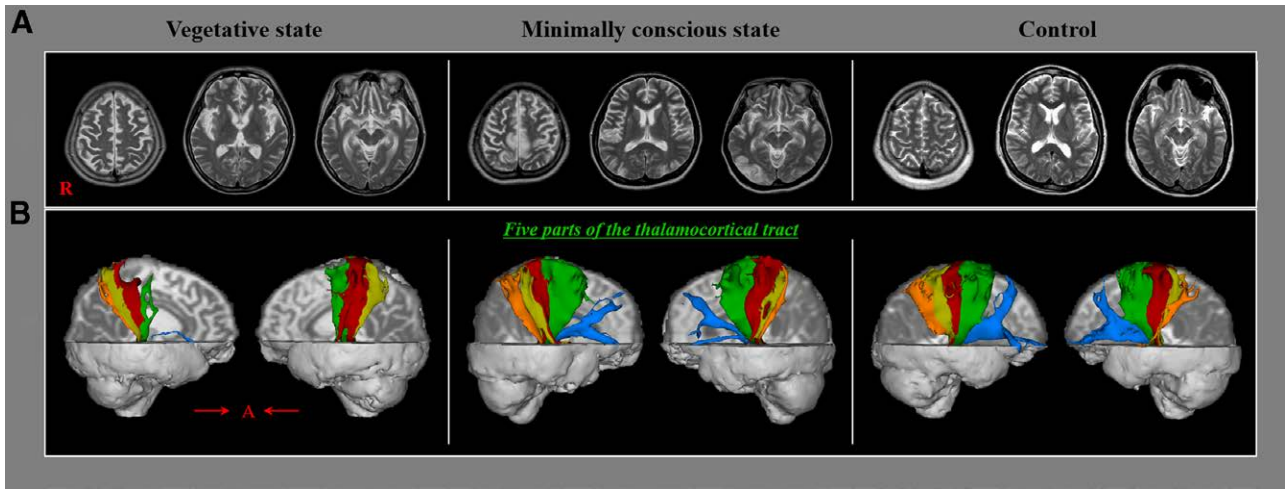

Figure 1. Brain images and diffusion tensor tractography results for representative patients with consciousness in the vegetative state (31-yr-old female) or the minimally conscious state (39-yr-old female) and a control subject (36-yr-old female). (A) T2-weighted brain magnetic resonance images acquired at the time of diffusion tensor imaging scanning. (B) Results of diffusion tensor tractography of 5 parts of the thalamocortical tract (prefrontal cortex, premotor cortex, primary motor cortex, primary somatosensory cortex, and posterior parietal cortex). Narrowing of the thalamocortical tract in the prefrontal cortex (blue color) and posterior parietal cortex (orange color) parts is visible in the vegetative state patient compared with the patient with a minimally conscious state.

placed on the intralaminar thalamic nuclei at the level of the intercommissural plane between the anterior and posterior commissures.[13,31] For the various segments of the PFC part, target ROIs were placed as follows: target ROI of the medial PFC segment was Brodmann area (BA) 32—the boundaries: the midline between the right and left hemisphere (medial boundary), the superior frontal sulcus, (lateral boundary), the frontal pole (anterior boundary), and the anterior margin of BA 6 (posterior boundary); target ROIs of dorsolateral PFC segment were BAs 8, 9, and 46—the boundaries: the superior frontal sulcus (medial boundary), the inferior frontal sulcus (lateral boundary), the frontal pole (anterior boundary), and the anterior margin of BA 6 (posterior boundary); target ROIs of ventrolateral PFC segment were BAs 44, 45, and 47—the boundaries: the inferior frontal sulcus (medial boundary), the sylvian fissure (lateral boundary), the frontal pole (anterior boundary), and the anterior margin of BA 6 (posterior boundary); and the target ROIs of orbitofrontal cortex segment were BAs 10, 11, 12, and 47—the boundaries: the midline between the right and left hemisphere (medial boundary), the cortical margin (lateral boundary), the rostral part of the central orbital region (anterior boundary), and the opercular part of the inferior frontal gyrus (posterior boundary).[13,32–37] For the PMC part of the thalamocortical tract, the boundaries of the target ROI (BA 6) were set as follows—the midline between the right and left hemisphere (medial boundary), the anterior–posterior line passing the lateral margin of the precentral knob (lateral boundary), the anterior margin of BA 6 (anterior boundary), and the precentral sulcus (posterior boundary).[38] The boundaries of the target ROI for the MI part (BA 4) were given as follows: the midline between the right and left hemisphere (medial boundary), the anterior–posterior line passing the lateral margin of the precentral knob (lateral boundary), the precentral sulcus (anterior boundary), and the central sulcus (posterior boundary).[13,35] For the S1 part of the thalamocortical tract, the boundaries of the target ROI (BAs 1, 2, and 3) were the midline between the right and left hemisphere (medial boundary), the anterior–posterior line passing the lateral margin of the precentral knob (lateral boundary), the central sulcus (anterior boundary), and the postcentral sulcus (posterior boundary). The boundaries of the target ROI for the PPC part (BAs 5 and 7) were set as follows: the midline between the right and left hemisphere (medial boundary), the inferior margin of the inferior parietal lobule (lateral boundary), the postcentral sulcus (anterior boundary), and the parieto-occipital sulcus (posterior boundary).[13,35] The seed and target ROIs were acquired by selecting voxels on T2 image (S0 map) of each patient. For analysis, the results were visualized using a threshold level of 2 streamlines through each voxel. The FA value and TV of each part of the thalamocortical tract were determined using MATLAB™ (Matlab R2007b, The Mathworks, Natick, MA, USA).

2.4. Statistical analysis

Statistical analysis was performed by using SPSS 21.0 for Windows (SPSS, Chicago, IL, USA). The chi-squared test was used to examine differences in sex composition of the groups. Mann–Whitney analysis was performed to assess differences in duration to DTI between the VS and MCS groups. Kruskal–Wallis analysis was used to determine age-related differences and assess the significance of differences in the FA values and TV of the 5 parts of the thalamocortical tract (PFC, PMC, M1, S1, and PPC) among the VS, MCS, and control groups. Statistical significance was accepted for $P < .05$. If a significant difference was detected among the 3 groups, a Mann–Whitney U post hoc test was used to elucidate the significance of differences in the DTT parameters between groups. By using Bonferroni method, P values of .017 were considered statistically significant.

3. Results

A summary of the comparison of DTT parameters (FA value and TV) for each of the parts of the thalamocortical tract (PFC, PMC, M1, S1, and PPC) of the VS, MCS, and control groups is presented in Table 2. Significant differences were observed in the FA values and TV of the 5 parts of the thalamocortical tract among the VS, MCS, and control groups ($P < .05$).

3.1. The prefrontal cortex of the thalamocortical tract

The FA values and TV of the PFC part of the thalamocortical tract were significantly different between the VS and control groups, and the MCS and control groups ($P < .017$). In addition, significant difference was observed in the FA value of the PFC part between the VS and MCS groups ($P < .017$). However, the TV of PFC part was not significantly different between the VS and MCS groups ($P > .017$).

Table 2

Comparison of diffusion tensor tractography parameters in the vegetative state, minimally conscious state, and control groups.

Group		VS	MCS	Control	*P* value
Parts of thalamocortical tract					
PFC	FA	0.07 ± 0.09^{a}	0.24 ± 0.13^{b}	0.35 ± 0.06^{c}	<.001*
	TV	42.43 ± 63.76^{ab}	572.79 ± 1010.14^{ab}	1135.63 ± 322.28^{c}	<.001*
PMC	FA	0.18 ± 0.12^{ab}	0.25 ± 0.05^{ab}	0.35 ± 0.06^{c}	.001*
	TV	1210.36 ± 1025.78^{ab}	2091.93 ± 864.91^{ab}	2914.75 ± 564.25^{c}	.003*
MI	FA	0.21 ± 0.11^{ab}	0.26 ± 0.05^{ab}	0.34 ± 0.06^{c}	.001*
	TV	918.00 ± 676.16^{ab}	1659.93 ± 856.84^{abc}	$2009.96 \pm 510.92b^{c}$	.013*
S1	FA	0.20 ± 0.13^{ab}	0.25 ± 0.12^{ab}	0.36 ± 0.06^{c}	.003*
	TV	413.93 ± 341.91^{ab}	657.29 ± 457.98^{abc}	994.33 ± 388.55^{bc}	.021*
PPC	FA	0.08 ± 0.08^{a}	0.22 ± 0.12^{b}	0.38 ± 0.06^{c}	<.001*
	TV	301.50 ± 434.85^{ab}	264.14 ± 249.56^{ab}	700.71 ± 480.32^{c}	.031*

Values indicate mean ± standard deviation.

Kruskal–Wallis analysis with Mann–Whitney *U* post hoc test was used for comparison of diffusion tensor tractography parameter values between VS, MCS, and patient-control groups.

The superscript alphabets a, b, and c denote the results of post-hoc analysis. So, the alphabet a, b, and c mean the VS, MCS, and Control groups, respectively. If one group shared the alphabet of another group, it means that significant differences were not observed between the groups. On the other hand, if one group did not share the alphabet of another group, it means that the groups had significant differences.

Mann–Whitney *U* test result ($P < .017$): a < b < c.

FA = fractional anisotropy, M1 = primary motor cortex, MCS = minimally conscious state, PFC = prefrontal cortex, PMC = premotor cortex, PPC = posterior parietal cortex, S1 = primary somatosensory cortex, TV = tract volume, VS = vegetative state.

*Significant difference ($P < .05$).

3.2. The premotor cortex of the thalamocortical tract

Significant differences were observed in the FA value and TV of the PMC part between the VS and control groups, and the MCS and control groups ($P < .017$). In contrast, the FA value and TV of the PMC part of the thalamocortical tract were not significantly different between the VS and MCS groups ($P > .017$).

3.3. The primary motor cortex of the thalamocortical tract

The FA values of the M1 part of the thalamocortical tract in the VS and MCS groups were significantly different with control group ($P < .017$). In addition, significant difference was observed in the TV of the M1 part between the VS and control groups ($P < .017$). However, there were no significant difference in the FA value of the M1 part between the VS and MCS groups and in the TV of the M1 part between the MCS and control groups, and the VS and MCS groups ($P > .017$).

3.4. The primary somatosensory cortex of the thalamocortical tract

Significant differences were observed in the FA value and TV of the S1 part of the thalamocortical tract between the VS and control groups ($P < .017$). The FA value of the S1 part in the MCS group was significantly different with the control group ($P < .017$); however, there was no significant difference in the TV of the S1 part between the MCS and control groups ($P > .017$). The FA value and TV of the S1 part were not significantly different between the VS and MCS groups ($P > .017$).

3.5. The posterior parietal cortex of the thalamocortical tract

The FA values and TV of the PPC part of the thalamocortical tract were significantly different between the VS and control groups, and the MCS and control groups ($P < .017$). In addition, significant difference was observed in the FA value of the PPC part between the VS and MCS groups ($P < .017$). However, the TV of PPC part was not significantly different between the VS and MCS groups ($P > .017$).

4. Discussion

In this study, by using DTT, differences in the 5 parts of the thalamocortical tract between VS and MCS was investigated in patients with HI-BI and obtained the following results: the FA values of all parts (PFC, PMC, M1, S1, and PPC) of the thalamocortical tract were lower in the VS and MCS group than in the control group; the TV of all parts of the thalamocortical tract in the VS group and the TV of the PFC, PMC, and PPC parts in the MCS group were lower than in the control group; the FA values of the PFC and PPC parts of the thalamocortical tract were lower in the VS group than in the MCS group.

Regarding the significance of the assessed DTT parameters, decrements in the FA value and/or TV of a neural tract indicate an injury to that neural tract.[23,24] These results showed that the FA values and TV of the 5 parts of the thalamocortical tract in the VS group, the FA values of the 5 parts, and the TV of the PFC, PMC, and PPC parts in the MCS group were lower than those in the control group. These results indicate the presence of neural injuries in all parts of the thalamocortical tract in the patients with VS or MCS compared with the normal healthy subjects. In addition, decrements in the FA values of the PFC and PPC parts of the thalamocortical tract in the VS group compared to the MCS group suggest there were more severe injuries in the PFC and PPC parts of the thalamocortical tract in patients with VS than in patients with MCS. This result indicates that the important areas of the thalamocortical tract for differentiating VS from MCS following HI-BI appear to be the PFC and PPC areas. The results appear to be consistent with the results of previous studies, which demonstrated that the PFC and/or PPC were important areas for differentiating VS from MCS.[15–19]

Many studies have reported differences between VS and MCS in patients with DOC based on electroencephalography, positron emission tomography, arterial spin labeling, or functional magnetic resonance imaging results.[15–20] These studies demonstrated that the brain areas helpful in distinguishing MCS from VS are as follows: the PFC, anterior cingulate gyrus, putamen, thalamic region, frontoparietal cortex, salience network, and temporo-parieto-occipital area.[15–20] Regarding HI-BI, 1 study demonstrated differences between patients with persistent VS and those that had recovered from VS.[39] In 2007, Hildebrandt et al investigated differences in brain areas between 13 patients with VS and 8 patients with recovered VS (the precise state of consciousness was not described by the authors) using single-photon emission computed tomography and reported that patients with recovered VS exhibited higher perfusion in the visual cortex and precuneus.[39] Concerning DTT, a few case and a retrospective original studies have reported neural structural

changes in the thalamocortical tract with recovery from VS to MCS in patients with DOC after stroke, traumatic brain injury, or HI-BI.[25–28] According to these case studies, the injured thalamocortical tracts showed increased neural connectivity to the basal forebrain, PFC, thalamus, hypothalamus, anterior cingulate cortex, and parietal cortex concurrent with recovery from VS to MCS.[25–28] Regardless, to the best of authors' knowledge, the present study is the first to report differences in the status of parts of the thalamocortical tract between patients with VS and MCS following HI-BI.

Some limitations of this study should be considered. First, the fiber tracking technique for reconstruction of the thalamocortical tract in DTI analysis is operator-dependent. Second, DTT analysis can overestimate or underestimate neural fiber status in areas with crossing fibers or fiber complexity. Hence, DTT analysis should be performed by an experienced analyzer to minimize the above limitations and an author (E.B.C.: 3-year experience in DTT analysis) analyzed DTT in this study. Third, the balance of male and female, and the duration to DTI was different between VS, MCS, and control groups. Fourth, this study recruited a small number of subjects and patients with early stage after HI-BI were included. Based on these limitations, further prospective and longitudinal studies involving larger numbers of subjects should be encouraged. In addition, because diffuse and multifocal lesions can present throughout the whole brain after HI-BI, further studies which analyze the whole brain or cortical volume would be necessary.

5. Conclusion

In conclusion, differences in the thalamocortical tract between VS and MCS were investigated in patients with DOC following HI-BI and the results observed that the PFC and PPC parts of the thalamocortical tract were important areas for differentiating between VS and MCS. The results of our pilot study suggest that the PFC and PPC parts of the thalamocortical tract could be important assessment areas in patients with DOC after HI-BI and helpful in developing guidelines for their neurorehabilitation. For example, the PFC and PPC parts of the thalamocortical tract could be targets for recovery of impaired consciousness by applying noninvasive brain stimulation therapies such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation in patients with VS following HI-BI.[5,6] Further studies on this topic should be invited.

Author contributions

SHJ: study concept and design, manuscript development, writing, funding, and critical revision of manuscript for intellectual content.
EBC: study design, writing, and critical revision of manuscript for intellectual content.
Conceptualization: Sung Ho Jang.
Formal analysis: Eun Bi Choi.
Funding acquisition: Sung Ho Jang.
Methodology: Eun Bi Choi.
Supervision: Sung Ho Jang.
Writing – original draft: Eun Bi Choi.
Writing – review & editing: Eun Bi Choi, Sung Ho Jang.

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