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Relationship between the consciousness level and the structural neural connectivity of the medial prefrontal cortex in hypoxic-ischemic brain injury: a pilot study

Sung Ho Jang and Eun Bi Choi

This pilot study investigated the relationship between the consciousness level and the structural neural connectivity of the medial prefrontal cortex (mPFC SNC) in patients with hypoxic-ischemic brain injury (HI-BI), using diffusion tensor tractography (DTT). Twenty-three patients with HI-BI were recruited into the study based on predefined inclusion criteria. Their consciousness levels were evaluated using the Glasgow Coma Scale (GCS) and the Coma Recovery Scale-Revised (CRS-R). Using DTT, the mPFC SNC was reconstructed for each patient. The average of the fractional anisotropy (FA), apparent diffusion coefficient (ADC), and voxel number (VN) for the mPFC SNC in both hemispheres were determined. The GCS score showed moderate positive correlations with the FA value and VN of the mPFC SNC [(FA) $r = 0.439$; (VN) $r = 0.466$; $P < 0.05$], and a strong negative correlation with ADC value ($r = -0.531$; $P < 0.05$). The CRS-R score had a strong positive and negative correlation with the FA and ADC values of the mPFC SNC, respectively, [(FA) $r = 0.540$; (ADC) $r = -0.614$; $P < 0.05$] and a moderate positive correlation with the VN of the mPFC SNC ($r = 0.488$; $P < 0.05$). We found that the severity of the injury to the mPFC SNC was closely related to the consciousness level. Our results suggest that the mPFC SNC appears to be a neural correlate for the control of consciousness in patients with HI-BI. Based on these results, we believe that the mPFC could be a target area for noninvasive neurostimulation therapies for patients with impaired consciousness following HI-BI. *NeuroReport* 33: 750–755 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Hypoxic-ischemic brain injury (HI-BI) is a physiologically significant disruption of brain function as a consequence of a severe reduction in the oxygen and blood supply to the brain. It is a common cause of neurological morbidity across all age groups, and impaired consciousness is a common serious sequela of HI-BI [1]. According to previous studies, of the patients who suffered impairment of consciousness following HI-BI, 27% recovered consciousness within 28 days, 9% remained in an impaired conscious state, and over 50% of the patients died [1]. Detailed knowledge about the neural correlates related to the levels of consciousness in patients with impaired consciousness is clinically important for establishing effective therapeutic strategies including neurorehabilitation or neuromodulation [2–4]. Noninvasive brain stimulation therapies, such as repetitive transcranial magnetic stimulation or transcranial direct current stimulation, can be applied to specific neural correlates relating to the consciousness level to facilitate the recovery of impaired consciousness [2–4].

The neural network for the control of consciousness is not clearly understood thus far. However, it has been reported to be controlled by a complicated network of complex actions involving various neural structures, including the default mode network (DMN), frontoparietal network (FPN), frontostriatal network, and the ascending reticular activating system (ARAS) [5–7]. Previous studies have suggested that among the neural correlates for the control of consciousness, the medial prefrontal cortex (mPFC) in the DMN, plays a crucial role [5,8,9]. Esslen *et al.* [10] reported the mPFC has an important role in self-awareness, which is an important component of consciousness. Especially, they found that prereflective aspects of the self are more related to the ventral mPFC while reflective aspects of the self to the dorsal mPFC [10]. Furthermore, the mPFC also contributes to the recovery of impaired consciousness as a part of the ARAS [11–15].

Several previous studies, using resting-state functional magnetic resonance imaging (rs-fMRI), have demonstrated a relationship between the levels of consciousness and patient outcomes, as well as the role of the mPFC within the DMN and the FPN in various brain pathologies including stroke, traumatic brain injury (TBI), and HI-BI [16–19]. However, rs-fMRI has a limitation in identifying the structural neural connections because the imaging is based on functional connectivity between the brain areas by evaluating coordinated neural activity using the synchronous firing of transient neural signals [20]. By contrast, diffusion tensor tractography (DTT), a recently developed imaging approach derived from diffusion tensor imaging (DTI), allows a three-dimensional visualization and estimation of the structural neural connectivity (SNC) by detecting the translational displacement of water molecules [21]. The state of the structural neural connection of the mPFC can be determined by evaluating DTT parameters, such as fractional anisotropy (FA), apparent diffusion coefficient (ADC), and voxel number (VN) [22]. Several DTT-based case studies have demonstrated that the increased neural connectivity to the mPFC from the thalamus was responsible for the recovery of impaired consciousness in patients with stroke (three patients) and HI-BI (two patients) [11–15]. A recent original study reported that the integrity of the connectivity between the mPFC and thalamus was closely related to the 'obedience-to-command' in patients with TBI [23]. However, no original study involving a large number of patients, on the relationship between the consciousness level (or recovery outcome) and the SNC of the mPFC (mPFC SNC) in HI-BI, has so far been reported.

In this pilot study, we investigated the relationship between the consciousness level and the mPFC SNC in patients with HI-BI, using DTT.

Methods

Twenty-three subjects (15 males and 8 females; mean age 49.30 ± 3.34 years; range: 18–76 years) with HI-BI, who were admitted to the rehabilitation department of a university hospital, were recruited according to the following criteria: (a) an obvious HI-BI history (e.g. cardiac arrest, strangulation, and carbon monoxide intoxication); (b) age at the onset of HI-BI: 18–79 years; (c) an impaired consciousness at the onset of HI-BI; (d) DTI obtained more than 1 month after onset; and (e) no prior history of head trauma and neurological or psychiatric disease. The occupations of patients were unemployment (13.04%), professionals (13.04%), private business owners (8.70%), sales workers (8.70%), clerks (8.70%), farmers (8.70%), students (8.70%), factory workers (4.35%), service workers (4.35%), construction workers (4.35%), and unknown (17.39%). This was a retrospective and explorative study, and the study protocol was approved by the institutional review board of a university hospital.

Clinical evaluation

The consciousness level was evaluated using the Glasgow Coma Scale (GCS) and the Coma Recovery Scale-Revised (CRS-R). The GCS is a representative and validated scale containing three components (eye-opening, verbal, and motor function; range: 3–15) [24]. The CRS-R is a standard neurobehavioral assessment measure for patients with disorders of consciousness and consists of six subscales: auditory, visual, motor, oromotor/verbal, communication, and arousal (range: 0–23) [2]. The CRS-R score can distinguish the state of consciousness from a coma, vegetative state, minimally conscious state, and confusional state [2]. At the time of the DTI scanning, the GCS and the CRS-R scores were an average of 9.70 ± 3.82 and 11.57 ± 7.91, respectively.

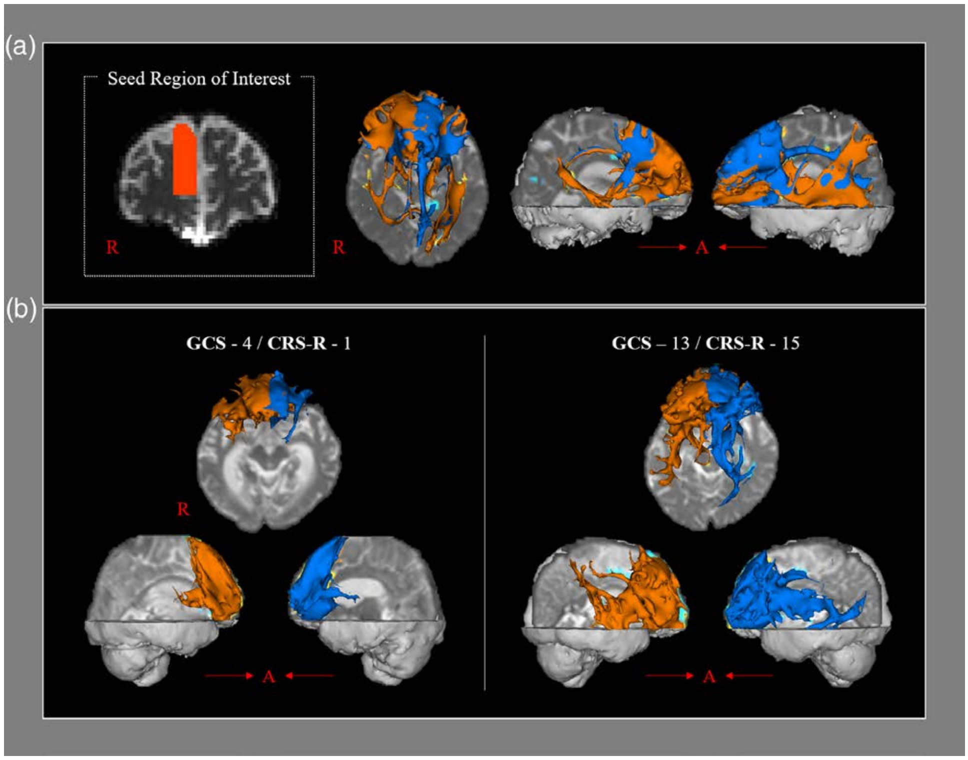
Diffusion tensor imaging

DTI scanning was performed at an average of 8.98 ± 2.17 months after HI-BI using a 1.5T Philips Gyroscan Intera scanner (Hoffman-LaRoche, Best, The Netherlands) with a six-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. The imaging parameters were as follows: acquisition matrix = 96 × 96, reconstructed to matrix = 128 × 128, field of view = 221 × 221 mm^2, 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 (FMRIB) Software Library (FSL: www.fmrib.ox.ac.uk/fsl) was used for the DTI data analysis. Affine multiscale two-dimensional registration was applied to correct for head motion effects and image distortions. A probabilistic tractography method based on a multifiber model in the FMRIB diffusion software was applied using the software routines option (5000 streamline samples, 0.5 mm step lengths, and curvature thresholds = 0.2) for fiber tracking. In each subject, a seed region of interest was placed on the mPFC, which included the subcortical white matter. For the analysis, the results were visualized using a threshold level of two streamlines through each voxel. The average of FA, ADC, and VN for the mPFC SNC in both hemispheres was determined. The DTT of the mPFC SNC with images of a normal person and two representative patients is presented in Fig. 1.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 (SPSS, Chicago, Illinois, USA). The Spearman correlation coefficient was used to determine the correlation between the GCS and CRS-R scores, and the DTT parameters (FA, ADC, and VN) of the mPFC SNC, respectively. The significance of a detected relationship was accepted when the P value of the test was less than 0.05, without applying statistical corrections for multiple comparisons. A correlation coefficient was interpreted as strong when $r \geq 0.50$, as moderate when $0.30 \leq r \leq 0.49$, and weak when $0.10 \leq r \leq 0.29$ [25].

Fig. 1



Diffusion tensor tractography (DTT) of the structural neural connectivity of the medial prefrontal cortex (the mPFC SNC). (a) The seed region of interest is placed on the medial prefrontal cortex including subcortical white matter. The DTT result of the mPFC SNC in a normal subject (58 year-old female). (b) The DTT result of the mPFC SNC of two representative patients are presented [left: 54-year-old male (GCS: 4; CRS-R: 1); severe decrement of the mPFC SNC, and right: 58-year-old female (GCS: 13; CRS-R: 15); mild decrement of the mPFC SNC]. GCS, Glasgow Coma Scale; CRS-R, Coma Recovery Scale-Revised.

Table 1 Correlation between the Glasgow Coma Scale and the Coma Recovery Scale-Revised scores and diffusion tensor tractography parameters for the structural neural connectivity of the medial prefrontal cortex

	Connectivity of mPFC		
Consciousness level	FA	ADC	VN
GCS			
r	0.439	–0.531	0.466
P	0.036*	0.009*	0.025*
CRS-R			
r	0.540	–0.614	0.488
P	0.008*	0.002*	0.018*

*Statistical correlation < 0.05.
ADC, apparent diffusion coefficient; CRS-R, Coma Recovery Scale-Revised; FA, fractional anisotropy; GCS, Glasgow Coma Scale; mPFC, medial prefrontal cortex; VN, voxel number.

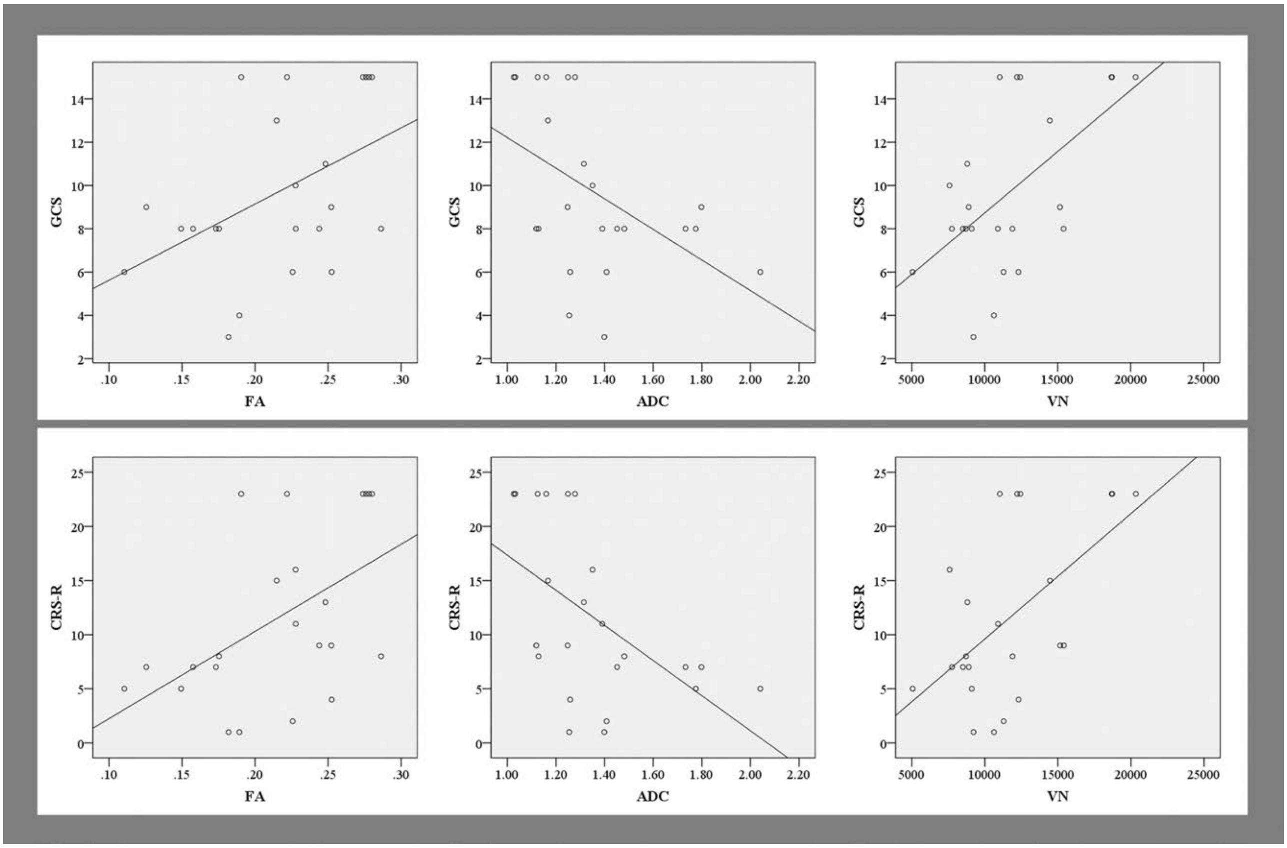
Results

A summary of the correlation between the consciousness state (GCS and CRS-R scores) and DTT parameters (FA, ADC, and VN) of the mPFC SNC is presented in Table 1. The GCS score showed a moderate positive correlation with the FA value and VN of the mPFC SNC [(FA) r = 0.439; (VN) r = 0.466; $P < 0.05$] and a strong negative correlation with the ADC value (r = –0.531; $P < 0.05$). The CRS-R score had a strong positive and negative correlation with the FA and ADC values of the mPFC SNC, respectively [(FA) r = 0.540; (ADC) r = –0.614; $P < 0.05$], and a moderate positive correlation with VN of the mPFC SNC (r = 0.488; $P < 0.05$) (Fig. 2).

Discussion

In this pilot study, we investigated the relationship between the consciousness level and the mPFC SNC in patients with HI-BI. Our results can be summarized as follows: (a) the GCS and the CRS-R scores were positively correlated with the FA and VN of the mPFC SNC,

Fig. 2



Scatter plots showing the correlation of the Glasgow Coma Scale (GCS) and the Coma Recovery Scale-Revised (CRS-R) scores with diffusion tensor tractography (DTT) parameters of the structural neural connectivity of the medial prefrontal cortex [fractional anisotropy (FA), apparent diffusion coefficient (ADC), and voxel number (VN)]. The GCS and the CRS-R scores show a positive correlation with the FA and VN, and a negative correlation with ADC ($P < 0.05$).

and (b) the GCS and the CRS-R scores were negatively correlated with the ADC of the mPFC SNC.

In this pilot study, we estimated the FA, ADC, and VN, which were the most commonly assessed DTT parameters in previous DTT-based studies [22]. The FA value denotes the degree of directionality of water diffusion based on the integrity of the organization of the white matter microstructures (axon, myelin, and microtubule) [22]. A reduced FA value indicates the disintegration of the microneurostructure of the neural fibers [22]. By contrast, the ADC value represents the magnitude of water diffusion in the tissues, and it can increase in some forms of neural pathology such as vasogenic edema or accumulation of cellular debris due to neural injury [22]. The VN indicates the number of voxels within a neural structure, which represents the number of fibers [22]. Hence, the VN can decrease in a neural injury due to the decrement in the number of neural fibers in the neural structure. Therefore, a decrease in the FA value and VN with an increase in the ADC value in a neural structure indicates an injury to the neural structure [22]. The results of our study, indicating the positive correlations of the consciousness level (GCS and CRS-R scores) with the FA value and VN of the mPFC SNC, and the negative correlations of the consciousness level (GCS and CRS-R scores) with the ADC value of the mPFC SNC, suggest that the severity of the impaired consciousness was closely related to the severity of the injury to the mPFC SNC. In other words, the mPFC SNC appeared to be a neural correlate for the control of consciousness in patients with HI-BI.

Several studies have used rs-fMRI, to indicate the link between the consciousness levels and the mPFC in patients with brain injuries [16–19]. In 2010, Vanhaudenhuyse *et al.* [16] reported that the neural connectivity of the DMN areas including the mPFC was negatively correlated with the consciousness level in 14 noncommunicative patients with brain injuries (stroke: five patients; HI-BI: three patients; TBI: two patients; and other pathologies: four patients). In 2015, Silva *et al.* [17] demonstrated that the functional connectivity between the mPFC and the posterior cingulate cortex could predict the recovery outcome of impaired consciousness in 27 patients with coma following a brain injury (TBI: 14 patients and HI-BI: 13 patients). During the same year, Wu *et al*. [18] found that decreased functional connectivity of the mPFC along with the posterior cingulate cortex, precuneus, and lateral parietal cortex was correlated with the consciousness level and outcome in 99 patients with brain injury (TBI: 82 patients, stroke: 14 patients, and other acquired brain pathologies: three patients). In 2017, Liu *et al*. [19] reported that the functional connectivity of the mPFC, primarily related to the DMN, showed a correlation with the consciousness level and outcome in 34 patients with impaired consciousness (TBI: 23 patients, hemorrhage: six patients, and other acquired brain pathologies: five patients).

By using DTT, several case studies have demonstrated that the increased neural connectivity to the mPFC from the thalamic intralaminar nucleus in the ARAS was responsible for the recovery of impaired consciousness in patients with stroke (three patients) and HI-BI (two patients) [11–15]. Recently, Cosgrove *et al*. [23] found that the integrity of the connections between the whole thalamus and the three subregions of the prefrontal cortex (mPFC, anterior cingulate cortex, and orbitofrontal cortex) was associated with the ability to follow commands in 25 patients with severe TBI.

Thus, our results appear to be generally in line with the results of the previous fMRI and DTT-based studies mentioned above [11–19,23]. However, to the best of our knowledge, this is the first study to demonstrate the relationship between the consciousness level and the mPFC SNC in patients with HI-BI. There are, however, some limitations to be considered. First, DTT can result in false-positive or negative results because of the complexity of the neural fibers or the partial volume effect, and analysis conditions such as the curvature threshold [26]. To overcome this limitation and to ensure a more precise and accurate interpretation of the DTT findings, we requested a researcher, Choi EB (corresponding author) with 3 years of experience in DTT analysis to analyze our DTT-related data in this study. Second, we did not divide the mPFC into the dorsal and ventral parts, which have a possibility for different SNCs [10]. Third, we could not determine the connectivity of the mPFC SNC with other important areas, which are known to be of significance in the control of consciousness due to the small number of subjects. Fourth, this is an explorative and preliminary study. Therefore, further studies involving a larger number of subjects should be carried out to overcome the above limitations.

In conclusion, we investigated the relationship between the levels of consciousness and the mPFC SNC in patients with HI-BI and found that the severity of the injury to the mPFC SNC was closely related to the consciousness level. Our results suggest that the mPFC SNC could be a neural correlate for the control of consciousness in patients with HI-BI. We believe that our results have an important implication for the neurorehabilitation of patients with impaired consciousness following HI-BI. In detail, the mPFC could be a target area for noninvasive neurostimulation therapies such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation. Further studies on this topic should be encouraged.

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Conflicts of interest

There are no conflicts of interest.

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