Difference in the ascending reticular activating system between vegetative and minimally conscious states following traumatic brain injury

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Objectives **We investigated differences in the ascending reticular activating system (ARAS) between vegetative state (VS) and minimally conscious state (MCS) in patients with traumatic brain injury (TBI) by using diffusion tensor tractography.**

Methods **We recruited TBI patients and normal subjects. We reconstructed the lower ARAS and five parts of upper ARAS [prefrontal cortex (PFC), premotor cortex, primary motor cortex, primary somatosensory cortex, and posterior parietal cortex].**

Results **Significant differences were observed in the fractional anisotropy (FA) and fiber number (FN) values of the five parts of upper ARAS between the VS and control groups and between the MCS and control groups ($P < 0.05$), but no differences were detected in the lower ARAS ($P > 0.05$). The FA and FN values of the PFC in the upper ARAS were significantly different between the VS and MCS groups ($P < 0.05$). No other significant differences in FA and FN values were detected among the other segments of the upper ARAS or in the lower ARAS ($P > 0.05$).**

Conclusion **The results indicate that the prefrontal portion of the upper ARAS is the critical area for distinguishing between VS and MCS in patients with TBI.** *NeuroReport* **32: 1423–1427 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Traumatic brain injury (TBI) is a major cause of disorders of consciousness (DOC) [1]. Based on the severity of the consciousness impairment, DOC can be categorized as coma, vegetative state (VS), minimally conscious state (MCS), confusional state, and normal consciousness [2]. The VS is characterized by an absence of responsiveness and awareness, whereas the MCS is characterized by some evidence of awareness of the self and/or the environment [2]. Therefore, clarification of differences in brain structures between VS and MCS in patients with DOC is important, and such information can be useful for prognosis prediction and guideline development for neurorehabilitation or neurointervention for patients with DOC.

The ascending reticular activating system (ARAS) is a major neural network for control of consciousness along with the frontoparietal network, frontostriatal network, and default mode network [3–6]. Consciousness is mainly controlled by the actions of the ARAS. Therefore, analysis of the ARAS is required for the identification of potential differences in the brain structures of VS and MCS in patients with DOC. Diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), has a unique advantage in investigating the ARAS because it can provide a three-dimensional reconstruction of the ARAS [7–9]. However, previous studies have not elucidated differences in the ARAS between VS and MCS in patients with DOC [9–11].

In the current study, by using DTT, we investigated differences in the ARAS of VS and MCS in patients with TBI.

Methods

Subjects

Twenty-three consecutive patients (8 males, 15 females; mean age 47.12 ± 16.19 years, range 20–72) with TBI who had visited the rehabilitation department of a university hospital and 12 normal subjects with no history of neurological, physical, or psychiatric illness (5 males, 7 females; mean age 40.87 ± 11.25 years, range 21–65) were included in the study. The patients were recruited consecutively according to the following inclusion criteria: (1) age at the time of head trauma: 20–75 years; (2) no history of previous head trauma or neurologic or psychiatric disease; (3)

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Table 1 Demographic data of patients in the vegetative state, minimally conscious state, and control groups

Group	VS	MCS	Control
Patient number (male:female)	10 (3:7)	13 (5:8)	12 (5:7)
Mean age (years)	45.36 ± 13.85	48.61 ± 18.37	40.87 ± 11.25
GCS	8.09 ± 3.80	11.92 ± 2.53	
CRS-R	9.63 ± 4.41	16.69 ± 4.60	
Mean duration to DTI (months)	4.18 ± 4.23	6.61 ± 6.41	

Values indicate mean ± SD.
CRS-R, Coma Recovery Scale-Revised; DTI, diffusion tensor imaging; GCS, Glasgow Coma Scale; MCS, minimally conscious state; VS, vegetative state.

a chronic stage of TBI: more than 1 month had elapsed after onset; and (4) the presence of impaired consciousness. Patients with VS and MCS were classified according to their Coma Recovery Scale-Revised (CRS-R) scores and were assigned to one of two groups: (1) the VS group: 10 patients (43.47% of total; three males, seven females; mean age 45.36 ± 13.85 years) and (2) the MCS group: 13 patients (56.52%, five males, eight females; mean age 48.61 ± 18.37 years) (Table 1). This study was conducted retrospectively, and the study protocol was approved by the institutional review board of a university hospital. The participants provided written informed consent.

Diffusion tensor imaging and tractography

DTI data were acquired at an average of 5.51 ± 5.54 months after the onset of TBI by using a 1.5T Philips Gyroscan Intera (Hoffmann-LaRoche, Best, the Netherlands) with 32 noncollinear diffusion-sensitizing gradients by performing single-shot echo-planar imaging. For each of the 32 noncollinear diffusion-sensitizing gradients, 67 contiguous slices were acquired parallel to the anterior commissure–posterior commissure line.

In each subject, six parts of the ARAS [lower ARAS, prefrontal cortex (PFC)-upper ARAS, premotor cortex-upper ARAS, primary motor cortex-upper ARAS, primary somatosensory cortex-upper ARAS, and posterior parietal cortex-upper ARAS] were reconstructed by selection of fibers passing through various regions of interest (ROIs) [12]. For analysis of the lower ARAS, the seed ROI was placed on the pontine reticular formation, and the target ROI with an option of termination was placed on the thalamic intralaminar nucleus [3]. For the thalamocortical fibers between the intralaminar thalamic nuclei and the frontoparietal cortex, the seed ROI was placed on the intralaminar thalamic nuclei at the level of the intercommissural plane between the anterior and posterior commissures [12]. For reconstruction of the various segments of the PFC-upper ARAS, target ROIs were placed on the medial prefrontal cortex, dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and orbitofrontal cortex. Boundaries of each target ROI was set as follows [12–17]: the medial PFC [Brodmann areas (BAs) 10 and 12] - the medial boundary: the midline between the right and left hemisphere, the lateral boundary: the superior frontal sulcus, the anterior boundary: the frontal pole, the posterior boundary: the anterior margin of BA 6; the dorsolateral PFC (BAs 8, 9, and 46) - the medial boundary: the superior frontal sulcus, the lateral boundary: the inferior frontal sulcus, the anterior boundary: the frontal pole, the posterior boundary: the anterior margin of BA 6; the ventrolateral PFC (BAs 44, 45, and 47) - medial boundary: the inferior frontal sulcus, the lateral boundary: the sylvian fissure, the anterior boundary: the frontal pole, the posterior boundary: the anterior margin of BA 6; the orbitofrontal cortex (BAs 10, 11, 12, 13, and 47) - the medial boundary: the midline between the right and left hemisphere, the lateral boundary: the cortical margin, the anterior boundary: rostral part of the central orbital region, the posterior boundary: opercular part of the inferior frontal gyrus. For reconstruction of the premotor cortex-upper ARAS, the target ROI was given on the premotor cortex (BA 6): the medial boundary: the midline between the right and left hemisphere, the lateral boundary: the anterior-posterior line passing the lateral margin of the precentral knob, the anterior boundary: the anterior margin of BA 6, the posterior boundary: the precentral sulcus [18]. For reconstruction of the primary motor cortex-upper ARAS, the target ROI was placed on the primary motor cortex (BA 4); the medial boundary: the midline between the right and left hemisphere, the lateral boundary: the anterior-posterior line passing the lateral margin of the precentral knob, the anterior boundary: the precentral sulcus, the posterior boundary: the central sulcus. For reconstruction of the primary somatosensory cortex-upper ARAS, the target ROI was placed on the primary somatosensory cortex (BAs 1, 2, and 3); the medial boundary: the midline between the right and left hemisphere, the lateral boundary: the anterior-posterior line passing the lateral margin of the precentral knob, the anterior boundary: the central sulcus, the posterior boundary: the postcentral sulcus. For reconstruction of the posterior parietal cortex-upper ARAS, the target ROI was set on the posterior parietal cortex (BAs 5, 7, 39, and 40) - the medial boundary: the midline between the right and left hemisphere, the lateral boundary: the inferior margin of the inferior parietal lobule, the anterior boundary: the postcentral sulcus, the posterior boundary: the parieto-occipital sulcus [12]. The thalamocortical projections between the intralaminar thalamic nuclei and the frontoparietal cortex were determined by selection of fibers passing through the seed ROI and each target ROI.

Statistical analysis

SPSS software (version 18.0, SPSS; Chicago, Illinois, USA) was used for data analysis. One-way analysis of

Table 2 Comparison of diffusion tensor tractography parameters in the vegetative state, minimally conscious state, and control groups

Group	VS		MCS		Control	
Five parts of upper ARAS						
PFC						
FA	0.31 ± 0.04		0.35 ± 0.04		0.36 ± 0.02	
P value	VS-control	0.00*	MCS-control	0.39*	VS-MCS	0.03*
FN	315.38 ± 269.21		592.44 ± 280.51		1481.35 ± 259.01	
P value	VS-control	0.00*	MCS-control	0.00*	VS-MCS	0.01*
PMC						
FA	0.32 ± 0.05		0.34 ± 0.04		0.36 ± 0.02	
P value	VS-control	0.01*	MCS-control	0.03*	VS-MCS	0.57
FN	1055.69 ± 558.27		1151.40 ± 403.47		2244.81 ± 784.25	
P value	VS-control	0.00*	MCS-control	0.00*	VS-MCS	0.48
M1						
FA	0.33 ± 0.05		0.33 ± 0.03		0.36 ± 0.02	
P value	VS-control	0.04*	MCS-control	0.03*	VS-MCS	0.96
FN	1247.67 ± 650.30		1140.56 ± 636.02		2057.48 ± 776.07	
P value	VS-control	0.00*	MCS-control	0.00*	VS-MCS	0.69
S1						
FA	0.34 ± 0.05		0.35 ± 0.03		0.38 ± 0.03	
P value	VS-control	0.00*	MCS-control	0.02*	VS-MCS	0.58
FN	672.76 ± 455.81		718.94 ± 449.03		1336.95 ± 659.89	
P value	VS-control	0.00*	MCS-control	0.00*	VS-MCS	0.72
PPC						
FA	0.34 ± 0.05		0.34 ± 0.04		0.38 ± 0.03	
P value	VS-control	0.01*	MCS-control	0.00*	VS-MCS	0.99
FN	709.93 ± 528.70		753.33 ± 550.15		1145.95 ± 706.37	
P value	VS-control	0.03*	MCS-control	0.04*	VS-MCS	0.83
Lower ARAS						
FA	0.35 ± 0.05		0.34 ± 0.05		0.35 ± 0.04	
P value	VS-control	0.98	MCS-control	0.51	VS-MCS	0.38
FN	356.37 ± 146.85		367.58 ± 140.06		511.82 ± 182.10	
P value	VS-control	0.01*	MCS-control	0.02*	VS-MCS	0.81

Values indicate mean ± SD.
ARAS, ascending reticular activating system; FA, fractional anisotropy; FN, fiber number; M1, primary motor cortex; MCS, minimally conscious state; PFC, prefrontal cortex; PMC, premotor cortex; PPC, posterior parietal cortex; S1, primary somatosensory cortex; VS, vegetative state.
*Significant difference between the persistent vegetative state and minimally conscious state groups, $P < 0.05$.

variance (ANOVA) was performed for the determination of significant differences in the lower ARAS and the five reconstructed parts of ARAS for each of the DTT parameters among the VS, MCS, and control groups. When using ANOVA, if a significant difference was detected among the three groups, a least significant difference post-hoc test was performed to elucidate the significance of differences in the DTT parameters between groups. Statistical significance was accepted for *P* values of <0.05.

Results

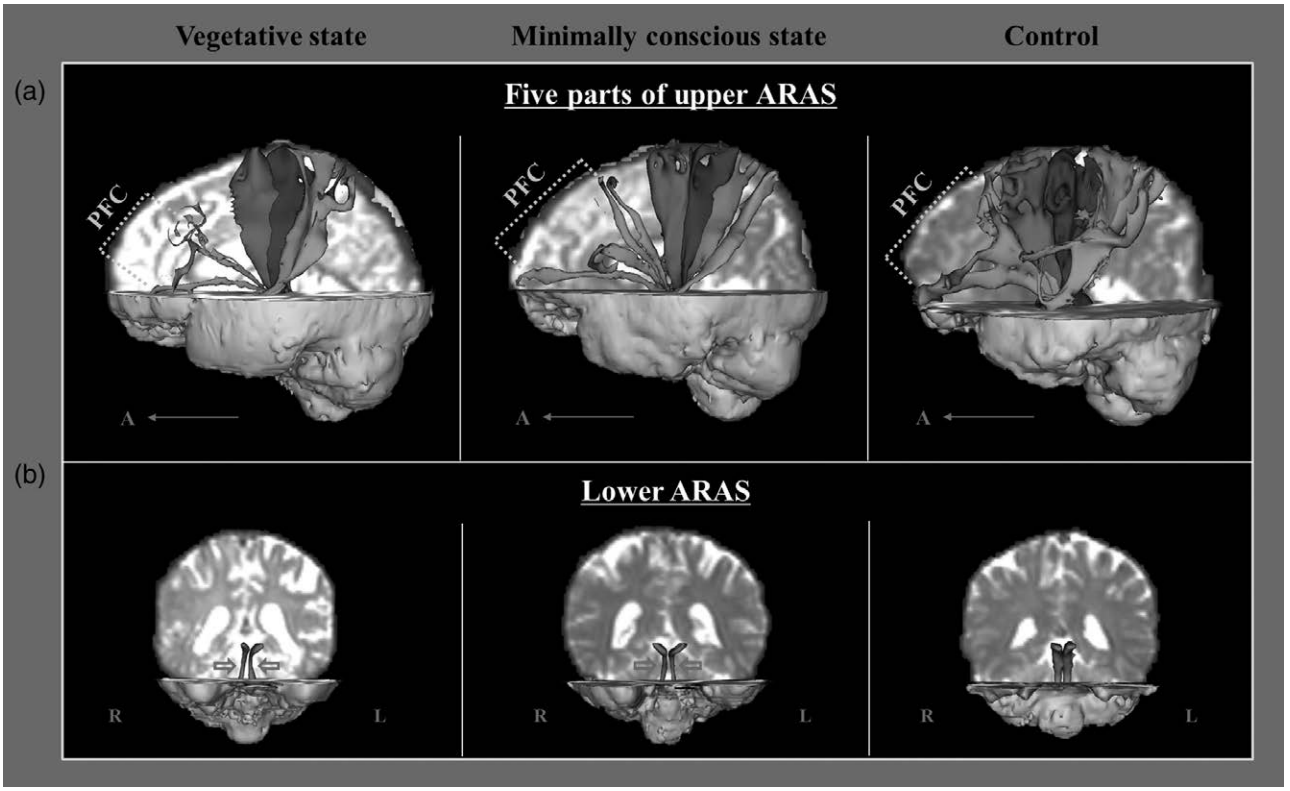
A summary of the mean values of the fractional anisotropy (FA) and fiber number (FN) DTT parameters for the lower ARAS and each of the five segments of the upper ARAS in the VS, MCS, and control groups is presented in Table 2. Significant differences were observed in both the FA and the FN values in each of the five parts of the upper ARAS between the VS and control, the MCS and control groups ($P > 0.05$) (Fig. 1a). In addition, the FN value of the lower ARAS was significantly different between the VS and control groups, the MCS and control groups ($P > 0.05$) (Fig. 1b). However, there were no significant differences in the FA values of the lower ARAS between the VS and control groups or between the MCS and control groups ($P > 0.05$).

Comparison of DTT parameters between the VS and MCS groups revealed that both the FA and FN values of the PFC-upper ARAS were significantly different between the two DOC groups ($P < 0.05$). No other significant differences in FA and FN values were detected among the other segments of the upper ARAS or in the lower ARAS ($P > 0.05$).

Discussion

The FA value indicates the degree of directionality of water diffusion, and the FN value is determined by counting the number of voxels within a neural tract. Thus, decrements in FA and/or FN values can indicate injury of a neural tract. Our results showing that the FA and FN values in the five parts of upper ARAS, as well as the FN value in the lower ARAS, were lower in the VS and MCS groups compared with the control group indicate injuries in the upper and lower ARAS in the VS and MCS groups. Furthermore, the results showing that the FA and FN values of the PFC-upper ARAS were lower in the VS group than those in the MCS group suggest the presence

Fig. 1



(a) Results of diffusion tensor tractography (DTT) for the prefrontal cortex (PFC)-upper ascending reticular activating system (ARAS) (orange color), premotor cortex-upper ARAS (blue color), primary motor cortex-upper ARAS (red color), primary somatosensory cortex-upper ARAS (green color), and posterior parietal cortex-upper ARAS (yellow color) in representative subjects from each group (vegetative state: 41-year-old female, minimally conscious state: 48-year-old female, and control: 46-year-old female). Narrowing of the PFC-upper ARAS is observed in the vegetative state (orange dotted line) compared with that in the minimally conscious state (orange dotted line). (b) Results of DTT for the lower ARAS show narrowing in the vegetative and minimally conscious states (red arrows) compared with control.

of more severe PFC-upper ARAS injuries in the VS group than those in the MCS group. That result indicates that the critical ARAS area distinguishing the VS from the MCS following TBI is the prefrontal area [3,9,10].

Several studies have used DTT to demonstrate structural changes in the ARAS during recovery of impaired consciousness in patients with DOC [9,10,19]. Among these studies, a few case studies have demonstrated changes in the ARAS of patients with DOC that were concurrent with the changes from a VS to an MCS [9,10]. In 2015, Jang and Lee reported a patient with HI-BI who showed recovery from VS to MCS concurrent with increased neural connectivity of the injured upper ARAS to the basal forebrain and PFC [3]. In 2016, Jang *et al*. reported on a patient with stroke who showed recovery from a VS to an MCS concurrent with increased neural connectivity in both prefrontal cortices and the right thalamus [9]. During the same year, Jang *et al*. demonstrated a change in the upper ARAS that was concurrent with recovery from a VS to an MCS in a patient with hypoxic-ischemic brain injury and TBI [10]. As a result, to the best of our knowledge, the present DTT-based study is the first to include a large number of patients in an investigation of differences in the ARAS between VS and MCS in patients with TBI. However, the limitations of this study should be considered. First, this study included a relatively small number of subjects. Second, although DTT is a powerful anatomic imaging tool that can demonstrate gross fiber architecture, it may underestimate fiber tracts due to regions of fiber complexity and fiber crossing.

In conclusion, neural tract reconstruction via DTT indicated that the prefrontal portion of the upper ARAS is the critical area for distinguishing between VS and MCS. Our results suggest that the PFC area of the upper ARAS could be an important target area for neurorehabilitation or neurointervention therapy in patients with VS after TBI.

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Conflicts of interest

There are no conflicts of interest.

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