Injury of thalamocortical connection between the mediodorsal nucleus of the thalamus and the orbitofrontal cortex in a patient with traumatic brain injury

The prefrontal cortex (PFC) is responsible for personality expression and various cognitive functions, including working memory, recognition memory, decision making, attention, and motivation (Frey and Petrides, 2000, 2002; Mesulam, 2000; Clarke et al., 2010). Anatomical tract-tracing studies have demonstrated that the PFC receives many afferent fibers from the mediodorsal nucleus (MD) of the thalamus through the thalamocortical connection (Fuster, 2008; Jang and Yeo, 2014).

Recently, diffusion tensor tractography (DTT), which is derived from diffusion tensor imaging (DTI), has enabled three-dimensional visualization and estimation of the thalamocortical connections between the MD and the PFCs in the human brain (Jang and Yeo, 2014). However, little is known about injury of the thalamocortical connections between the MD and the PFC.

In the current study, we reported on a patient with traumatic brain injury (TBI), who showed injury of the thalamocortical connections between the MD and the PFC, which was demonstrated by DTT.

The patient is a 55-year-old male patient who suffered from a traffic accident. He underwent hematoma removal for an intracerebral hemorrhage in both frontotemporal lobes and an epidural hemorrhage in the left occipital lobe at the Department of Neurosurgery in Yeungnam University Hospital (**Figure 1A**). He complained of memory impairment since the onset of TBI. Brain MRI taken at two weeks after onset showed resolved hematoma and leukomalactic lesion in both PFCs. Eight age-matched right-handed control subjects (four males; mean age: 50.5 years, range: 47–56) with no history of neurologic disease (Mini-Mental State Examination (MMSE): 30) participated in this study. All subjects provided signed informed consent, and the study protocol was approved by the institutional review board of Yeungnam University Hospital (YUH-15-07-064).

Two scales were used for evaluation of cognitive function at nine weeks after onset; the MMSE and the Memory Assessment Scale (MAS) (Ross et al., 2003; Han et al., 2008). With a score of 25 on MMSE, the patient did not show severe cognitive impairment. However, the patient showed memory impairment in verbal memory (64: 1%ile) and global memory (62: 1%ile), and other

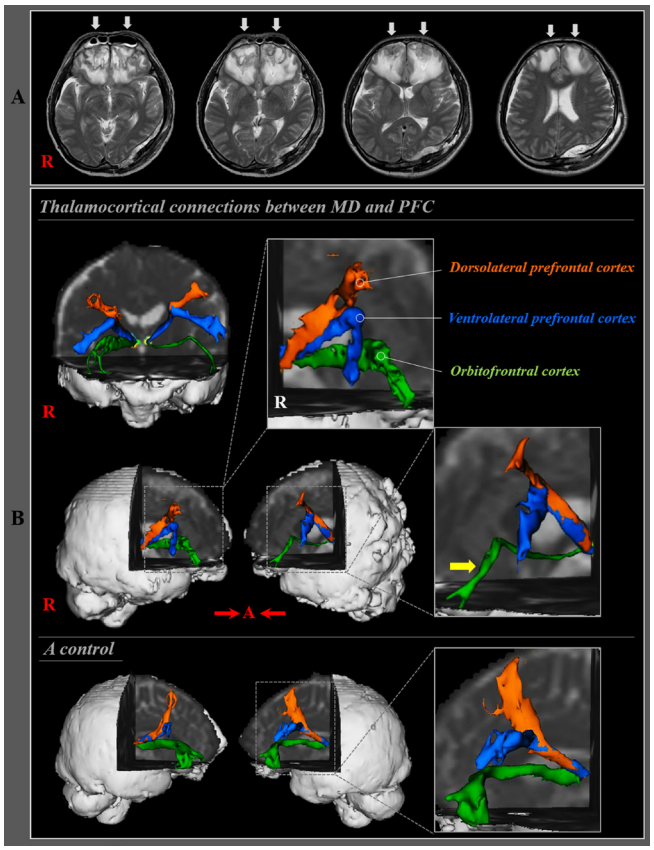

Figure 1 MRI and diffusion tensor tractography images of a 55-year-old male patient with traumatic brain injury and a control subject.
(A) Brain MRI at two weeks after onset shows severe injury (arrows) on both prefrontal cortices. (B) Results of diffusion tensor tractography of the thalamocortical connections to each prefrontal cortex region in the patient and a control subject. The integrities of the thalamocortical connections to the ventrolateral and dorsolateral prefrontal cortex were preserved, however, the thalamocortical connection to the orbitofrontal cortex shows that the patient's left side is thinner than the right side and that of the control subject (arrow).

MAS subscales were within borderline range: short-term memory (81: 10%ile) and visual memory (73: 4%ile).

DTI data were acquired at two weeks after onset using a 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Best, The Netherlands) and single-shot echo-planar imaging. For each of the 32 non-collinear diffusion sensitizing gradients, we acquired 67 contiguous slices parallel to the anterior commissure-posterior commissure line. Imaging parameters were as follows: acquisition matrix = 96 × 96; reconstructed matrix = 192 × 192; field of view = 240 × 240 mm^2; repetition time (TR) = 10,726 ms; echo time (TE) = 76 ms; parallel imaging reduction factor (SENSE factor) = 2; EPI factor = 49; b = 1000 s/mm^2; number of excitation (NEX) = 1; and a slice thickness of 2.5 mm.

Diffusion-weighted imaging data were analyzed using software from the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB)

Table 1 DTI parameters of thalamocortical connections between the medial nucleus of the thalamus and the prefrontal cortex in the patient and control subjects

	Rt hemisphere			Lt hemisphere			Control subjects		
	FA	MD	TV (number of voxels)	FA	MD	TV (number of voxels)	FA	MD	TV (number of voxel)
DLPFC	0.36	0.79	679.00	0.31	0.83	725.00	0.33±0.02	0.86±0.06	1073.31±395.58
VLPFC	0.35	0.75	890.00	0.35	0.83	921.00	0.33±0.03	0.83±0.05	1276.06±462.57
OFC	0.24*	1.14**	647.00	0.30	1.02**	140.00*	0.32±0.03	0.84±0.06	2327.38±1079.45

DTI parameters are presented as the mean ± standard deviation. DLPFC: Dorsolateral prefrontal cortex; VLPFC: ventrolateral prefrontal cortex; OFC: orbitofrontal cortex; FA: fractional anisotropy; MD: mean diffusivity; TV: tract volume. *: when the diffusion tensor imaging parameters were decreased two standard deviations below those of controls. **: when the diffusion tensor imaging parameters were increased two standard deviations over those of controls.

Software Library (FSL v5.0; www.fmrib.ox.ac.uk/fsl). In all cases, a seed region of interest (ROI) was placed at the thalamic MD on a coronal image; location of MD was defined as previous studies (Klein et al., 2010; Jang and Yeo, 2014). For thalamocortical connections to the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC), we defined the DLPFC as Brodmann areas (BAs) 8, 9, and 46, and the VLPFC as BAs 44, 45, and 47, and manually drew target ROIs on each cortex on the coronal images, respectively (Klein et al., 2010; Jang and Yeo, 2014). For thalamocortical connection between the MD and the orbitofrontal cortex (OFC), we defined the OFC as BAs 47/12, 10, 11, and 13, and manually drew the target ROI on the OFC on an axial image (Klein et al., 2010; Jang and Yeo, 2014). In addition, for analysis of the fornix, we placed the seed ROI on the mammillary body on the axial image, and the target ROI was placed on the crus of the fornix on the coronal image (Yeo et al., 2013). Of 5,000 samples generated from the seed voxel, contact results were visualized at a threshold minimum of 1 streamline through each voxel for analysis. Fractional anisotropy (FA), mean diffusivity, and tract volume in the three thalamocortical connections to each PFC were then measured. DTT parameter values showing a deviation of more than two standard deviations from normal control values were defined as abnormal.

A summary of the DTI parameters of the thalamocortical connections to each PFC in the patient and normal control subjects is shown in **Table 1**. No difference in the DTI parameters of the thalamocortical connections to the DLPFC and VLPFC in terms of the FA, mean diffusivity, and fiber volume was observed between the patient and control subjects. By contrast, the values of FA and mean diffusivity in the right thalamocortical connection to the OFC in the patient were decreased and increased by more than two standard deviations of those of normal control subjects, respectively. In addition, the values of mean diffusivity and fiber volume of the left thalamocortical pathway to the OFC were increased and decreased by more than two standard deviations of those of normal control subjects. The right DTT for the thalamocortical pathway to the OFC in the patient was thinner compared with that of the right hemisphere and those of control subjects (**Figure 1B**). By contrast, the integrity of the reconstructed fornix was preserved between the hippocampal formation and the mammillary body.

In the current study, we investigated injury of the thalamocortical connections between the thalamic MD and the PFCs in a patient with TBI. Result of reconstructed thalamocortical connections to the DLPFC and VLPFC showed no definite injury on the pathway. By contrast, the thalamocortical connection to the OFC showed significantly decreased values of FA in the right hemisphere and fiber volume in the left hemisphere. In addition, significantly increased values of mean diffusivity were observed in both hemispheres. The FA value represents the degree of directionality of microstructures (*e.g.*, axons, myelin, and microtubules) and the mean diffusivity value indicates the magnitude of water diffusion (Assaf and Pasternak, 2008). By contrast, the voxel volume is determined by the number of voxels contained within the neural tract (Pagani et al., 2008). Therefore, the decrement of the FA value and fiber volume, and the increment of the mean diffusivity value appeared to indicate neural injury of the thalamocortical connection to the OFC. In contrast, result of estimation of the fornix showed no definite injury, even though the patient showed memory impairment. Consequently, this patient's memory impairment (verbal and global memory deficit with borderline range of short-term and visual memory) appears to be related to injury of the thalamocortical connection to the OFC.

A few studies have reported on the specific functional contribution of the OFC in the human brain (Frey and Petrides, 2000, 2002). In 2000, using positron emission tomography (PET), Frey and Petrides demonstrated involvement of the rostral orbitofrontal region in the process of encoding of new information (Frey and Petrides, 2000). Subsequently, using PET, Frey and Petrides (2002) also reported that the region of OFC showed

gradual increment of the blood flow along with change of encoding control conditions (minimal to maximal) for the different memory conditions (Frey and Petrides, 2002). Based on these previous studies, the region of OFC has a major role in the processing of new information for memory function (Frey and Petrides, 2000, 2002). Due to the functional characteristic of the OFC, the thalamocortical connection between MD of the thalamus and the OFC might have a similar functional contribution to the memory system, because patients with injury of the thalamic MD can exhibit similar clinical manifestations to those associated with PFC injury (Liebermann et al., 2013). As a result, injury of the thalamocortical connection between the thalamic MD and the OFC is related to memory impairment of patients with TBI.

In conclusion, we reported on a patient who showed injury of the thalamocortical connection to the OFC following TBI. It appears that memory impairment in this patient was related to injury of the thalamocortical connection between the thalamic MD and the OFC. Therefore, we suggest that evaluation of the thalamocortical connection to the OFC would be useful for patients with memory impairment due to injury of the OFC. To the best of our knowledge, this is the first DTI study demonstrating injury of the thalamocortical connections to the OFC in a patient with TBI. In addition, results of the current study will be helpful for the investigation of brain plasticity and neural regeneration after injury of thalamocortical connections to the OFC. However, limitations of this study should be considered. First, despite being a powerful anatomic imaging tool, which can demonstrate gross fiber architecture, DTI may underestimate or overestimate the fiber tracts because regions of fiber complexity and crossing can prevent full reflection of the underlying fiber architecture by DTI (Parker and Alexander, 2005). Second, because it is case report, this study is limited. Therefore, larger-scale complementary studies with more detailed evaluation of memory function should be performed in future.

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