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# CONNECTIVITY OF INFERIOR CEREBELLAR PEDUNCLE IN THE HUMAN BRAIN: A DIFFUSION TENSOR IMAGING STUDY

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**Abstract:** The inferior cerebellar peduncle (ICP) is an important role in motor control, such as coordination of movement control of balance, posture, and gait. In the current study, using diffusion tensor tractography (DTT), we attempted to investigate the connectivity of the ICP in normal subjects. Forty healthy subjects were recruited for this study. DTTs were acquired using a sensitivity-encoding head coil at 1.5 Tesla. A seed region of interest was drawn at the ICP using the FMRIB Software Library. Connectivity was defined as the incidence of connection between the ICP and target brain regions at the threshold of 5, 25, and 50 streamlines. The ICP showed 100 % connectivity to the vestibular nucleus, reticular formation, pontine tegmentum, and posterior lobe of the cerebellum, irrespective of thresholds. In contrast, the ICP showed more than 70 % connectivity with the target brain regions at the threshold of 5 streamlines that is to the thalamus (100 %), anterior lobe of the cerebellum (100 %), pedunclopontine nucleus (95.0 %), red nucleus (92.5 %), primary somatosensory cortex (86.3 %), and primary motor cortex (75.0 %). According to our findings, the ICP had high connectivity, mainly with the sensory-motor related areas. We believe that the methodology and results of this study would be useful in investigation of the neural network associated with the sensory-motor system and brain plasticity following brain injury and other diseases.

Key words: *inferior cerebellar peduncle, restiform body, connectivity, cerebellum, diffusion tensor imaging*

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## 1. Introduction

The cerebellum as a key role of motor coordination and cognitive function communicates cerebrum via cerebellar peduncles [34, 36]. The inferior cerebellar peduncle (ICP, also called the restiform body) is located in the dorsolateral border

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of the medulla oblongata and contains several afferent and efferent tracts (dorsal spinocerebellar tract, cuneocerebellar tract, olivocerebellar tract, reticulocerebellar tract, vestibulocerebellar tract, arcuatocerebellar tract, and trigeminocerebellar tract, cerebellovestibular tract, cerebelloreticular tract, and cerebello-olivary tract) [1, 6, 26, 30-32]. It mainly conveys somatosensory information, such as proprioceptive from muscle spindles and tendons, and vestibular information from vestibular nuclei to cerebellum [1, 6, 26]. Therefore, it has an important role in motor control such as coordination of movement control of balance, posture, and gait [6, 8, 13, 23, 26, 31, 37].

Thorough comprehension of the connectivity of a neural structure would be important for research on normal neurophysiology and neural plasticity, which is based on the unmasking of latent neural connection after brain injury [2, 40, 41]. However, research on the connectivity of a neural structure is difficult because neurons interact with each other in a wide and complicated neural network. On the other hand, recently developed diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), has a unique advantage in estimation and visualization of the connections by detection of water diffusion properties [4, 29]. In particular, the probabilistic tracking method, based on the multi-tensor model, enables calculation of more than one fiber population in each imaging voxel [4, 29, 35]. As a result, many studies using a probabilistic tracking method have reported on connectivity of neural structures in the live human brain [11, 14, 16, 17, 22, 28, 29] and regarding the ICP, many studies have reported on the ICP in terms of tract (or pathway) related to the cerebellum using deterministic tracking method which can trace the only dominant orientation of diffusion in each voxel [7, 9, 18, 21]. However, little is known about connectivity of the ICP in the normal human brain.

In the current study, using probabilistic tracking DTT, we attempted to investigate the ipsilateral connectivity of the ICP in normal subjects.

## 2. Methods

### 2.1 Subjects

We recruited 40 healthy subjects (males: 24, females: 16, mean age: 32.4 years, range: 22–50 years) with no previous history of neurological, physical, psychiatric illness or head trauma. No abnormal lesion in all subjects was observed in brain MRI by a neuroradiologist. All subjects understood the purpose of the study and provided written, informed consent prior to participation. The study protocol was approved by our local Institutional Review Board.

### 2.2 Data acquisition

A 6-channel head coil on a 1.5T Philips Gyroscan Intera (Philips, Ltd, Best, The Netherlands) with single-shot echo-planar imaging (EPI) was used for acquisition of DTI data. 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 =  $96 \times 96$ ;

reconstructed to matrix =  $128 \times 128$ ; field of view =  $221 \times 221$  mm; repetition time (TR) = 10,726 ms; echo time (TE) = 76 ms; parallel imaging reduction factor (SENSE factor) = 2; echo-planar imaging (EPI) factor = 49;  $b = 1000$  s/mm<sup>2</sup>; number of excitations (NEX) = 1; and a slice thickness of 2.3 mm (acquired voxel size  $1.73 \times 1.73 \times 2.3$  mm).

### 2.3 Probabilistic fiber tracking

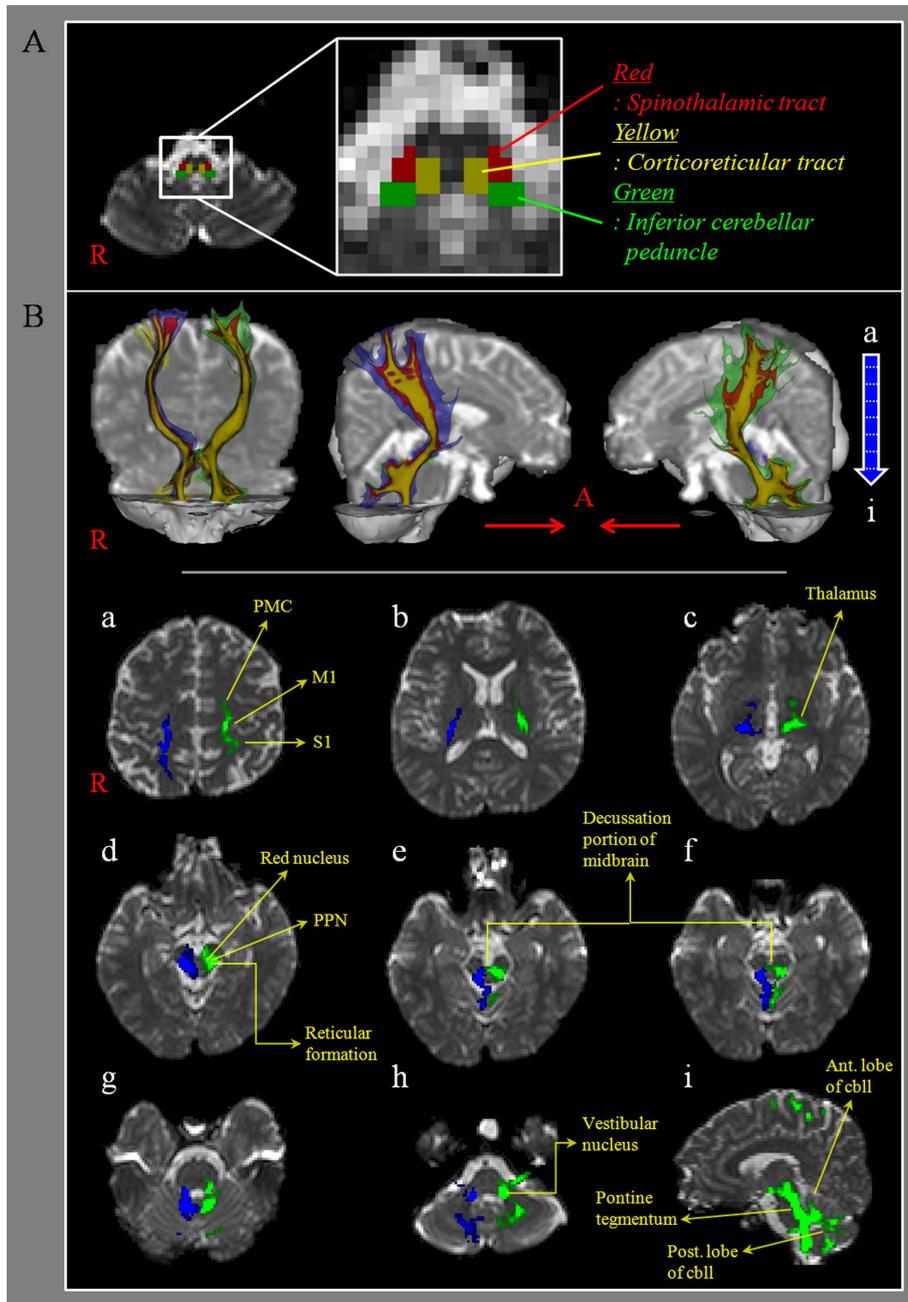
Analysis of DTI data was performed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Head motion effect and image distortion due to eddy current were corrected by affine multi-scale two-dimensional registration. Fiber tracking was performed using a probabilistic tractography method based on a multi-fiber model, and applied in the current study utilizing tractography routines implemented in FMRIB Diffusion (5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2) [4, 35]. For the connectivity of the ICP, a seed region of interest was drawn at the isolated ICP area of the medulla on the axial image [12, 27, 32]. The ICP was identified by reconstructing adjacent structures, that is, the spinothalamic tract (anterior boundary) and the corticoreticular tract (medial boundary). Out of 5000 samples generated from a seed voxel, results were visualized at the threshold of 5, 25, and 50 streamlines through each voxel for analysis (Fig. 1).

### 2.4 Determination of connections between the ICP and target brain regions

Connectivity was defined as the incidence of connection between the ICP and each brain region: primary motor cortex (M1, brodmann area [BA]: 4), primary somatosensory cortex (S1, BA: 1, 2, 3), premotor cortex (PMC, BA: 6), prefrontal cortex (BA: 9, 10, 11, 12), globus pallidus, thalamus, red nucleus, decussation portion of midbrain, pedunculopontine nucleus (PPN), pontine tegmentum, vestibular nucleus, reticular formation, anterior lobe of the cerebellum, posterior lobe of the cerebellum, and flocculonodular lobe of the cerebellum [5]. Incidence of the connectivity was counted the connections from the ICP to each brain region and then the incidence of connectivity calculated as the percentage in all hemispheres of 40 subjects.

### 2.5 Statistical analysis

SPSS software (v.15.0; SPSS, Chicago, IL) was used for the analysis. The chi-square test was used for determination of the incidences of connectivity and differences between incidences of connectivity of the ICP in the right and left hemispheres in each subject and between males and females. Statistical significance was accepted for  $p$  values of  $< 0.05$ .



**Fig. 1** Results of diffusion tensor tractography for the connectivity between the ICP and target brain regions at a threshold of 5 (right: blue left: green), 25 (red), and 50 (yellow). (a: cortex level, b: corona radiata level, c: internal capsule level, d: anterior commissural level, e: upper midbrain level, f: middle midbrain level, g: lower midbrain level, h: upper pons level, i: lower pons level).

### 3. Results

A summary of the connectivity of the ICP is shown in Tab. I. The ICP showed 100 % connectivity with the vestibular nucleus, reticular formation, pontine tegmentum, and posterior lobe of the cerebellum, irrespective of thresholds. In contrast, regarding the threshold of 5, 25, and 50 streamlines, the ICP showed connectivity to the thalamus (100 %, 96.3 %, and 96.3 %), anterior lobe of the cerebellum (100 %, 92.5 %, and 92.5 %), PPN (95.0 %, 91.3 %, and 91.3 %), red nucleus (92.5 %, 83.8 %, and 78.8 %), S1 (86.3 %, 70.0 %, and 58.8 %), M1 (75.0 %, 38.8 %, and 32.5 %), decussation portion of midbrain (66.3 %, 56.3 %, and 53.8 %), globus pallidus (53.8 %, 40.0 %, and 31.3 %), flocculonodular lobe of the cerebellum (32.5 %, 25.0 %, and 13.8 %), prefrontal cortex (15.0 %, 8.8 %, and 6.3 %), and PMC (11.3 %, 5.0 %, and 5.0 %), respectively. According to statistical analysis, no significant differences in connectivity of the ICP were observed between the right and left hemispheres in each subject and between males and females ( $p > 0.05$ ).

Target brain regions	Threshold		
	5 [%]	25 [%]	50 [%]
Vestibular nucleus	100	100	100
Reticular formation	100	100	100
Pontine tegmentum	100	100	100
Posterior lobe of cerebellum	100	100	100
Thalamus	100	96.3	96.3
Anterior lobe of cerebellum	100	92.5	92.5
Pedunculopontine nucleus	95.0	91.3	91.3
Red nucleus	92.5	83.8	78.8
Primary somatosensory cortex	86.3	70.0	58.8
Primary motor cortex	75.0	38.8	32.5
Decussation portion of midbrain	66.3	56.3	53.8
Globus pallidus	53.8	40.0	31.3
Flocculonodular lobe of cerebellum	32.5	25.0	13.8
Prefrontal cortex	15.0	8.8	6.3
Premotor cortex	11.3	5.0	5.0

**Tab. I** Incidence of connectivity [%] between the inferior cerebellar peduncle and target brain regions.

### 4. Discussion

In the current study, using probabilistic tracking DTT, we investigated the connectivity of the ICP in the normal human brain. Our findings showed the following characteristics of connectivity of the ICP: 1) all subjects showed 100 % connectivity with the vestibular nucleus, reticular formation, pontine tegmentum, and posterior lobe of the cerebellum, irrespective of thresholds, 2) the ICP showed more than 70 % connectivity with the sensory-motor function related areas at the threshold

of 5 streamline, that is, the thalamus, posterior lobe of the cerebellum, PPN, red nucleus, S1, and M1.

Many previous studies have reported on the anatomical characteristics of the ICP: the ICP connects the spinal cord and cerebellum and this connection is essential to coordinated movements [1, 6, 8, 26, 30, 31, 33, 37]. In detail, the ICP receives and conveys proprioceptive information from the vestibular nucleus and reticular formation to the cerebellum. By contrast, little is known about the connectivity of the ICP in the human brain. Since the introduction of DTI, to the best of our knowledge, two studies have reported on the reconstruction of ICP or the neural tract which is relevant with ICP [12, 15]. In 2007, Habas and Cabanis reported that the pathway of the ICP ascended and passed through the area between the lateral wall of the fourth ventricle and the middle cerebellar peduncle and then reached the vermis and paravermis of the anterior lobe of the cerebellum in the human brain [12]. In a recent study, using DTT, Jang and Kwon identified the dorsal spinocerebellar tract, which passed through the ICP in 26 normal human subjects [15]. We reported that the dorsal spinocerebellar tract showed 100 % connectivity with the anterior lobe of the cerebellum. Consequently, our results appear to coincide with those of previous studies [12, 15]. On the other hand, although the olivocerebellar tract, which conveys information from the olivary nuclei to the cerebellum, is a major tract of the ICP, we could not find any connectivity to the olivary nuclei, which might be ascribed to the kissing effect, because of the pathway of olivocerebellar tract that originated in the contralateral olivary nucleus, crossed the midline, and then terminated in the cerebellum [3, 19, 26, 31, 32].

Regarding the connectivity with the sensory-motor related areas (thalamus, posterior lobe of the cerebellum, PPN, red nucleus, S1, and M1), previous studies have reported that injury of the ICP could affect motor function with clinical manifestations such as ataxia, hypotonia, and gait disturbance [6, 8, 13, 23, 26, 31, 37]. In 2009, using DTT, Hong et al. recruited six patients with ataxia and demonstrated injury of cerebellar peduncles, including the ICP [13]. Subsequently, Kwon and Jang [2012] reported on a patient who showed hand tremor, gait disturbance, cognitive dysfunction, and truncal ataxia due to injury of the fornix, corticospinal tract, and ICP on DTT following traumatic brain injury [23]. Therefore, in terms of function of the ICP related to the sensory-motor area, our results appear to be compatible with those of previous studies [13, 23].

In conclusion, we found that the ICP has high connectivity, mainly with the sensory-motor related areas, including the vestibular nucleus, reticular formation, pontine tegmentum, thalamus, PPN, red nucleus, primary sensori-motor cortex, and cerebellum. To the best of our knowledge, this is the first study using probabilistic DTI to demonstrate the connectivity of the ICP to each brain region in the human brain. We believe that the results and methodology of this study would be useful in investigation of the neural network associated with the sensory-motor system and brain plasticity following brain injury and other diseases [7, 20, 24]. However, several limitations of this study should be considered [10, 19, 25, 29, 38, 39]. First, due to kissing or partial volume effect, DTI could lead to both false positive and negative results throughout the white matter of the brain [10, 25, 39]. In particular, probabilistic tracking could cause a false positive fiber trajectory [10, 25, 39]. Second, we could not determine the detailed connectivity area, such as the

cerebellar nuclei, because isolation of each cerebellar nucleus is not easy with our resolution. Third, high tesla MRI can provide better resolution and detail anatomical information. Therefore, we think that conduct of further studies to overcome these limitations should be encouraged. In addition, studies for clinical application of our results for patients following brain injury are also invited.

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