The neural connectivity of the inferior olivary nucleus in the human brain: A diffusion tensor tractography study

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HIGHLIGHTS

► We attempted to neural connectivity of the inferior olivary nucleus (ION) in the human.
► The ION showed high connectivity with motor function-related areas.
► In conclusion, the ION is closely related to motor function in the human brain.

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ABSTRACT

Objectives: Many animal studies have reported on the neural connectivity of the inferior olivary nucleus (ION). However, the neural connectivity of the ION has not been clearly elucidated in the human brain. In this study, the neural connectivity of the ION in the human brain was investigated by diffusion tensor imaging (DTI).

Methods: Forty healthy subjects were recruited. DTIs were acquired using a sensitivity-encoding head coil at 1.5 T. Connectivity was defined as the incidence of connection between the ION and regions of interest (ROIs) in the brain.

Results: In these subjects, the ION showed higher connectivity to the reticular formation (100%), the posterior limb of internal capsule (100%), the red nucleus (93.75%), the cerebral peduncle of midbrain (91.25%), the primary motor cortex (86.25%), the primary somatosensory cortex (85%), the periaqueductal gray matter (81.25%), the globus pallidus (81.25%), the anterior limb of internal capsule (62.5%), the pontine basis (62.5%), and the posterior parietal cortex (60%).

Conclusions: The ION shows high connectivity with motor function-related areas, such as, the posterior limb of internal capsule, the red nucleus, the cerebral peduncle of midbrain, the primary motor cortex, and the pontine basis. These results indicate that the ION is closely related to motor function in the human brain.

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1. Introduction

The inferior olivary nucleus (ION) is located at the medulla oblongata and consists of three nuclei: the principle olivary nucleus, the medial accessory olivary nucleus, and the dorsal accessory olivary nucleus [1,4,11,12,18,25,34]. The ION is known to be involved in motor learning, motor control, movement coordination, sensory processing, and cognitive function and to be connected to the sensori-motor cortex, basal ganglion, red nucleus, periaqueductal gray, reticular formation, and cerebellum [1,2,4,8–15,17–20,22,24–26,29–31,33,34,36–38]. Many animal studies have reported on the neural connectivity of the ION [2,8,10,13,15,25,26,30,31,33,36–38], however, little is known about the topic in the human brain [14,17,20,22], and as a result, connectivities of the ION with whole brain areas have not been clearly elucidated so far.

Diffusion tensor imaging (DTI) has a unique advantage in terms of the evaluation of white matter due to its ability to visualize water diffusion characteristics [5]. Recently developed multi-tensor model DTI allows multiple dominant diffusion orientations to be estimated within imaging voxels, and results obtained to date suggest that probability corresponds with multiple fiber population [3,6,21,28]. Several studies have been reported on neural connectivity using multi-tensor model DTI in normal subjects [7,16,17,20,22,23,28,39], and a small number of studies have
addressed connection between the ION and the red nucleus or cerebellum, but no study has previously addressed connectivity with whole brain areas [14,17,20,22].

Accordingly, in the current study, we attempted to investigate in neural connectivity of the ION in the human brain using DTI Fig. 1.

2. Subjects and methods

2.1. Subjects

We recruited 40 healthy subjects (males: 26, females: 14, mean age: 30.5 years, range: 20–48 years) with no previous history of neurological, physical, or psychiatric illness. 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

DTI data were acquired using a 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Best, Netherlands) with 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 = 128 × 128; field of view = 221 mm × 221 mm; TR = 10,726 ms; TE = 76 ms; parallel imaging reduction factor (SENSE factor) = 2; EPI factor = 49; b = 1000 s/mm²; NEX = 1; and a slice thickness of 2.3 mm (acquired isotropic voxel size 2.3 mm × 2.3 mm × 2.3 mm).

Fig. 1. Neural connectivity of the inferior olivary nucleus (ION) in a normal subject (25 year-old man). (A) A seed ROI was placed on the isolated ION (green) of the medulla on the color map. The ION was identified by reconstructing adjacent structures: corticospinal tract (anterior boundary, orange), medial lemniscus (medial boundary, white-lined rectangular). (B) Diffusion tensor tractography results regarding connectivity of the ION. (C) Connectivity is shown at each brain level.
2.3. Probabilistic fiber tracking

The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl) was used to analyze diffusion-weighted imaging data. Head motion and image distortion (due to eddy currents) effects 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 utilizing tractography routines implemented in FMRIB diffusion (5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2) [6,32]. For the connectivity of the ION, a seed region of interest (ROI) was placed on the isolated ION of the medulla on a color map [1,27]. The ION was identified by reconstructing adjacent structures, that is, the corticospinal tract (anterior boundary) and the medial lemniscus (medial boundary). Out of 5000 samples generated from a seed voxel, contact results were visualized with the threshold at 5 streamline through each voxel for analysis.

2.4. Determination of connections between the ION and other brain regions

Connectivity was defined as the incidence of connection between the ION and each ROI: primary motor cortex (M1), primary somatosensory cortex (S1), premotor cortex (PMC), prefrontal cortex, posterior parietal cortex, globus pallidus, anterior and posterior limb of internal capsule, red nucleus, cerebral peduncle of midbrain, periaqueductal gray matter, hypothalamus, occipital lobe, medial and lateral temporal lobe, pontine basis, reticular formation, ipsilateral and contralateral vermis of cerebellum, and ipsilateral and contralateral hemisphere of cerebellum.

2.5. Statistical analysis

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

3. Results

Connectivity of the ION is summarized in Table 1. In all subjects, the ION showed more than 60% connectivity to the reticular formation (100%), the posterior limb of internal capsule (100%), the red nucleus (93.75%), the cerebral peduncle of midbrain (91.25%), M1 (86.25%), S1 (85%), periaqueductal gray matter (81.25%), the globus pallidus (81.25%), the anterior limb of the internal capsule (62.5%), the pontine basis (62.5%), and the posterior parietal cortex (60%). In contrast, the other ROIs showed less than 40% connectivity in all subjects, that is, the PMC (40%), the hypothalamus (33.75%), the prefrontal cortex (32.5%), the contralateral vermis of cerebellum (30%), the medial temporal lobe (26.25%), the ipsilateral hemisphere of cerebellum (18.75%), the ipsilateral vermis of cerebellum (17.5%), the occipital lobe (12.5%), the contralateral hemisphere of cerebellum (12.5%), and the lateral temporal lobe (11.25%).

In all ROIs, no significant differences were observed between connectivities with right and left hemispheres (p > 0.05).

4. Discussion

In the current study, we investigated the neural connectivity of the ION in the normal human brain using diffusion tensor tractography (DTT). We found high connectivity between the ION and motor function-related areas, that is, the posterior limb of internal capsule (100%), the red nucleus (93.75%), the cerebral peduncle of midbrain (91.25%), M1 (86.25%), the globus pallidus (81.25%), and the pontine basis (62.5%). However, connectivities between IONs and cerebellar areas were lower than connectivities with motor areas; the contralateral vermis of cerebellum (30%), the ipsilateral hemisphere of cerebellum (18.75%), the ipsilateral vermis of cerebellum (13.75%), the contralateral hemisphere of cerebellum (12.5%).

Many previous animal studies and textbooks have reported that the ION is connected to various motor areas [1,2,4,10–13,25,31,33,36,37]. Animal studies can be classified into four groups: (1) studies that demonstrated connectivity with the motor cortex, for example, Walberg (1956) with the sensorimotor area via the pyramidal tract in the cat [37]; Sousa-Pinto and Brodal (1969) with the motor portion of the cortex in the cat [33]; (2) studies that demonstrated connectivity with the red nucleus; Edwards (1972) with the red nucleus in the cat [13], Walberg (1974) with the caudal part of red nucleus in the cat [36], Martin (1975) with the red nucleus in the rat [25]; (3) Studies that demonstrated connectivity with the cerebellum; Armstrong (1966) with the contralateral paramedian lobule of the cerebellum in the cat [2], Martin et al. (1975) with deep cerebellar nuclei in the rat [25], Sugihara (2001) with the cerebellar cortex via the inferior cerebellar peduncle in the rat [35]; (4) studies that demonstrated connectivity with the basal ganglia; Walberg (1956) with the caudate nucleus in the cat [37], Walberg (1974) with the globus pallidus in the cat [36].

With regard to the human brain, several studies have reported on connections of the ION [14,17,20,22]. To our best knowledge, three studies have demonstrated the pathway of the rubro-olivary tract between the red nucleus and the ION using DTT [17,20,22]. On the other hand, Granziera et al. (2009) reconstructed and visualized the olivo-dentate-olivary loop in four normal subjects by diffusion spectrum imaging tractography [14]. Our results appear to coincide with those of previous animal studies, which reported that the ION is mainly connected with motor areas, excepting the cerebellum [2,10,13,25,31,33,36,37]. In this study, we found that connectivities between the ION and cerebellar region were low as compared with connectivities to other brain regions. Neural fibers from the ION cross midline and then enter the contralateral cerebellum via the inferior cerebellar peduncle [4,11]. In DTT, regions of fiber complexity and crossing can prevent comprehensive visualization of

Table 1 Incidence of connectivity between the inferior olivary nucleus and regions of interest.

<table>
<thead>
<tr>
<th>Region of interest</th>
<th>Inferior olivary nucleus</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
</tr>
<tr>
<td>Reticular formation</td>
<td>100%</td>
</tr>
<tr>
<td>Posterior limb of internal capsule</td>
<td>100%</td>
</tr>
<tr>
<td>Red nucleus</td>
<td>95%</td>
</tr>
<tr>
<td>Cerebral peduncle of midbrain</td>
<td>95%</td>
</tr>
<tr>
<td>Primary motor cortex</td>
<td>92.5%</td>
</tr>
<tr>
<td>Primary somatosensory cortex</td>
<td>95%</td>
</tr>
<tr>
<td>Globus pallidus</td>
<td>80%</td>
</tr>
<tr>
<td>Periaqueductal gray matter</td>
<td>82.5%</td>
</tr>
<tr>
<td>Anterior limb of internal capsule</td>
<td>67.5%</td>
</tr>
<tr>
<td>Pontine basis</td>
<td>61.25%</td>
</tr>
<tr>
<td>Posterior parietal cortex</td>
<td>67.5%</td>
</tr>
<tr>
<td>Premotor cortex</td>
<td>40%</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>32.5%</td>
</tr>
<tr>
<td>Prefrontal cortex</td>
<td>35%</td>
</tr>
<tr>
<td>Contralateral vermis of cerebellum</td>
<td>32.5%</td>
</tr>
<tr>
<td>Medial temporal lobe</td>
<td>25%</td>
</tr>
<tr>
<td>Ipsilateral hemisphere of cerebellum</td>
<td>15%</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>15%</td>
</tr>
<tr>
<td>Ipsilateral vermis of cerebellum</td>
<td>12.5%</td>
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<tr>
<td>Contralateral hemisphere of cerebellum</td>
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<tr>
<td>Lateral temporal lobe</td>
<td>12.5%</td>
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</table>
the underlying fiber architecture, and therefore, we believe that crossing fibers, such as, between the medial lemniscus with the ION probably obscure tractographic reconstructions between the ION and the cerebellum [23,28,39]. Although we used the multi-fiber model to overcome this limitation, our results of low connectivity between the ION and cerebellar areas could be due to this effect [6,18].

Summarizing, we found that ION has high connectivity with motor areas, such as, the posterior limb of the internal capsule, the red nucleus, the cerebral peduncle of midbrain, M1, and the pontine basis. This result indicates that ION is closely related to motor function in the human brain. To the best of our knowledge, this is the first DTT study to demonstrate connectivities between the ION and various brain regions in human brain. The methods used and the results of this study provide useful information to clinicians and to researchers investigating the ION. However, as mentioned above, this study is limited by technical uncertainties regarding connectivity between the ION and cerebellum. Further studies are required to address this limitation.

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References