Neuroscience Letters 579 (2014) 140–144

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

# The neural connectivity of the intralaminar thalamic nuclei in the human brain: A diffusion tensor tractography study

Sung Ho Jang [a], Hyoung Won Lim [b], Sang Seok Yeo [b,*]

[a] Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Republic of Korea
[b] Department of Physical Therapy, College of Health Sciences, Dankook University, Republic of Korea

## HIGHLIGHTS

- We found high connectivity between intralaminar nucleus and arousal-related areas.
- Intralaminar nucleus showed high connectivity with brain areas for the attention.
- Intralaminar nucleus showed high connectivity with sensorimotor area.

## ARTICLE INFO

*Article history:*
Received 30 April 2014
Received in revised form 19 June 2014
Accepted 11 July 2014
Available online 22 July 2014

*Keywords:*
Thalamus
Intralaminar nuclei
Neural connectivity
Diffusion tensor imaging
Ascending reticular activating system

## ABSTRACT

Research on the neural connectivity of the intralaminar thalamic nuclei (ILN) has been limited. Since the introduction of diffusion tensor imaging (DTI), many probabilistic DTI studies have reported on neural connectivity of neural structures in normal subjects. However, no study on the neural connectivity of the ILN has been reported so far. In this study, using probabilistic DTI, we investigated the neural connectivity of the ILN in normal subjects. A total of 40 healthy subjects were recruited for this study. A seed region of interest was placed on the ILN of the thalamus using the FMRIB Software Library. Connectivity was defined as the incidence of connection between the ILN and target brain areas. We found high connectivity between the ILN and arousal-related areas (prefrontal cortex 100%, reticular formation 100%, pedunculopontine nucleus 97.5%, basal forebrain 95%, and hypothalamus 92.5% at threshold 5), attention related area (prefrontal cortex 100% at threshold 5), and sensori-motor function related areas (primary motor cortex 100%, globus pallidus 100%, putamen 98.8%, premotor cortex 96.3%, primary somatosensory cortex 95.0%, caudate nucleus 92.5%, and posterior parietal cortex 90.0% at threshold 5). Findings of this study showed that ILN has high connectivity with brain areas related to arousal, attention, and sensorimotor function. This result indicates a close association of ILN with these functions in the human brain.



## 1. Introduction

The intralaminar thalamic nuclei (ILN) belong to the nonspecific thalamic nuclei along with midline nuclei, and reticular nuclei, which constitute the dorsal pathway of the ascending reticular activating system with reticular formation (RF) of the brainstem and cerebral cortex [7,18]. It is involved in the arousal system with RF, basal forebrain, hypothalamus, and prefrontal cortex (PFC) [18,25,28,32]. It is regarded as a common locus in vegetative state and has been a main target for neuromodulation such as deep brain stimulation [29]. It is also involved in control of attention by interaction with the PFC and sensori-motor function by interaction with the fronto-parietal cortex [18,25,28,31]. Therefore, clarification of the neural connectivity of the ILN would be important in control of consciousness, attention, and sensori-motor function in the human brain. However, due to the shortage of neuroimaging techniques for neural connectivity, research on this topic has been limited.

Diffusion tensor imaging (DTI) enables the evaluation of white matter tracts by virtue of its ability to image water diffusion characteristics [21]. Probabilistic tractography, which is a multi-tensor model, estimates multiple dominant diffusion orientations within an imaging voxel and results suggest that probability corresponds with multiple fiber population [3,24]. Therefore, it is adequate for research on the neural connectivity of a neural tract. Since the introduction of DTI, many probabilistic tractography studies have

* Corresponding author at: 119, Dandae-ro, Dongnam-gu, Cheonan-si, Chungnam 330-714, Republic of Korea. Tel.: +82 53 620 4098; fax: +82 53 625 3508.
*E-mail address:* eangbul@hanmail.net (S.S. Yeo).

http://dx.doi.org/10.1016/j.neulet.2014.07.024
0304-3940/

reported on neural connectivity using this technique in normal subjects [11,13,22]. However, little is known about the neural connectivity of the ILN in the human brain.

In the current study, using probabilistic DTI tractography, we attempted to investigate neural connectivity of the ILN in normal subjects.

## 2. Subjects and methods

### 2.1. Subjects

We recruited 40 healthy subjects (males: 23, females: 17, mean age: 37.2 years, range: 20–58 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 the Institutional Review Board of a University Hospital.

### 2.2. Data acquisition

Acquisition of DTI data was performed 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 = $96 \times 96$; reconstructed matrix = $192 \times 192$; field of view = $240 \times 240\,mm^2$; TR = 10,726 ms; TE = 76 ms; parallel imaging reduction factor (SENSE factor) = 2; EPI factor = 49; b = $1000\,s/mm^2$; NEX = 1; and a slice thickness of 2.5 mm with no gap (acquired isotropic voxel size $1.3 \times 1.3 \times 2.5\,mm^3$).

### 2.3. Probabilistic fiber tracking

The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl) was used for analysis of diffusion-weighted imaging data. Head motion and image distortion (due to eddy currents) effects were corrected using 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) [3,4,30]. For the connectivity of the ILN of the thalamus, the seed region of interest (ROI) was placed on the ILN at the level of the inter-commissural plane between the anterior and posterior commissures [20,39]. 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. Connectivity was defined as the incidence of connection between the ILN and any neural structure of the brain.

### 2.4. Determination of connection between the intralaminar nucleus and target brain areas

Connectivity was measured as the incidence of connection between the ILN and target brain areas: anterior cingulate cortex (ACC) (Brodmann areas (BA) 24, 32, 33), PFC (BA 8, 9, 10, 11, 12, 46), premotor cortex (PMC) (BA 6), primary motor cortex (M1) (BA 4), primary somatosensory cortex (S1) (BA 1,2,3), posterior parietal cortex (PPC) (BA 5,7), caudate nucleus (CN), globus pallidus (GP), putamen, basal forebrain, hypothalamus, pedunculopontine nucleus (PPN), and RF [5] (Fig. 1A).

## 3. Results

A summary of the connectivity of the ILN is shown in Fig. 1. According to our findings, the ILN showed four kinds of connectivity to other brain regions: (1) the cerebral cortex (PFC, PMC, M1, S1, and PPC), (2) the basal ganglia (CN, GP, and putamen), (3) the limbic system (ACC, basal forebrain, and hypothalamus), and (4) brain stem (PPN and RF).

At the threshold of 5, 25, and 50, the ILN of the thalamus showed more than 90% connectivity to the PFC (100%, 98.8%, and 98.8%) and GP (100%, 95.0%, and 98.8%). In addition, RF (100%, 91.3%, and 88.8%), M1 (100%, 90.0%, and 87.5%), PPN (97.5%, 90.0%, and 87.5%), PMC (96.3%, 87.5%, and 83.8%), hypothalamus (92.5%, 88.8%, and 82.5%), CN (92.5%, 85.0%, and 82.5%), and basal forebrain (95.0%, 85.0%, and 81.3%) showed more than 80% connectivity with the ILN of the thalamus. By contrast, the other ROIs showed less than 80% connectivity at the threshold of 50, that is, S1 (95.0%, 77.5%, and 71.3%), putamen (98.8%, 82.5%, and 70.0%), PPC (90.0%, 62.5%, and 50.0%), and ACC (20.0%, 11.3%, and 7.5%) (Fig. 1B).

## 4. Discussion

In the current study, we investigated the neural connectivity of the ILN in the normal human brain using probabilistic DTI tractography. We found high connectivity between the ILN and arousal-related areas (PFC 100%, RF 100%, PPN 97.5%, basal forebrain 95%, and hypothalamus 92.5% at threshold 5), attention-related area (PFC 100% at threshold 5), and sensori-motor function related areas (M1 100%, GP 100%, putamen 98.8%, PMC 96.3%, S1 95.0%, CN 92.5%, and PPC 90.0% at threshold 5). These results indicate a close link between the ILN and arousal, attention, and sensori-motor function. By contrast, connectivity to the ACC was very low (20.0% at threshold 5) (Fig. 2).

Many previous studies and have reported that the ILN is connected to various areas of the brain [11,13–15,20,21,24]. In addition, many studies have suggested that individual ILN have the connection with particular regions of cortex and sub-cortical area; the centromedian–parafascicular complex – basal ganglia, medial temporal lobe, RF, PMC, M1 and S1; central lateral nuclei – basal ganglia, RF, PFC and PPC; and paracentral nuclei – RF, PFC, PMC, M1 and S1 [14,15,19,26,27,32–35]. By contrast, in the human brain, Schiff classified these areas according to three systems: arousal system, fronto-parietal system, and brainstem attentional capture areas [28]. Although there is some controversy, the brain connection areas of the ILN can be classified according to the diverse function of the ILN as follows: (1) arousal; basal forebrain, PFC, hypothalamus and RF of brainstem, (2) attention; PFC and ACC, (3) motor planning and execution; PMC, M1, basal ganglia, and (4) polysensory integration; S1 and PPC [17,18,28,31]. Considering our results, in general, the connectivity to the basal forebrain, cerebral cortex, basal ganglia, sensori-motor cortex, and hypothalamus appears to be compatible with the results of previous studies [12,16–18,25,28,31]. However, the connectivity to the ACC was very low, 20.0% at threshold 5. The ACC is known be involved in cognition and emotional control: in detail, error detection, motivation, attention, and emotional modulation [1,6]. Previous animal studies have reported that the ACC receives thalamic afferents mainly from the midline and ILN [2,36]. Considering the location of the ACC, it is not an area that can be significantly affected by crossing fiber [37,38]. Therefore, we believe that conduct of further studies on this topic should be encouraged.

Since introduction of DTI, several studies have reported on the ILN in normal subjects or patients with brain injury [9,10,39,40]. In 2010, using intrathalamic DTT, Zarei et al. found that the internal medullary lamina was significantly smaller in 16 patients with

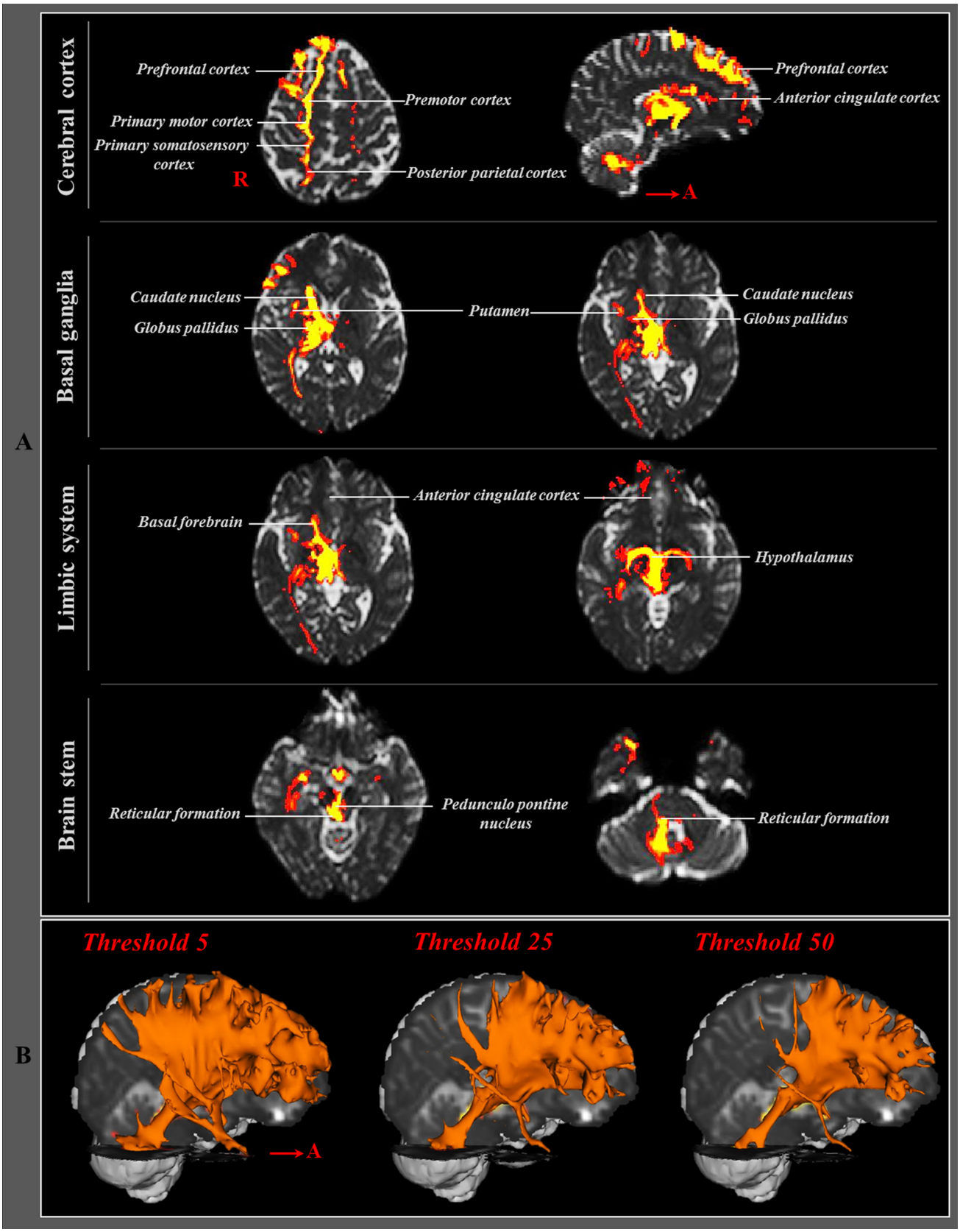


**Fig. 1.** (A) Neural connectivity of the intralaminar nuclei of the thalamus; cerebral cortex:, prefrontal cortex, premotor cortex, primary motor cortex, primary somatosensory cortex, posterior parietal cortex; basal ganglia: caudate nucleus, globus pallidus, putamen; limbic system; anterior cingulate cortex, basal forebrain, hypothalamus; brain stem: pedunculopontine nucleus, reticular formation. (B) Diffusion tensor tractography results regarding connectivity of the intralaminar nucleus at a threshold of 5, 25, and 50.

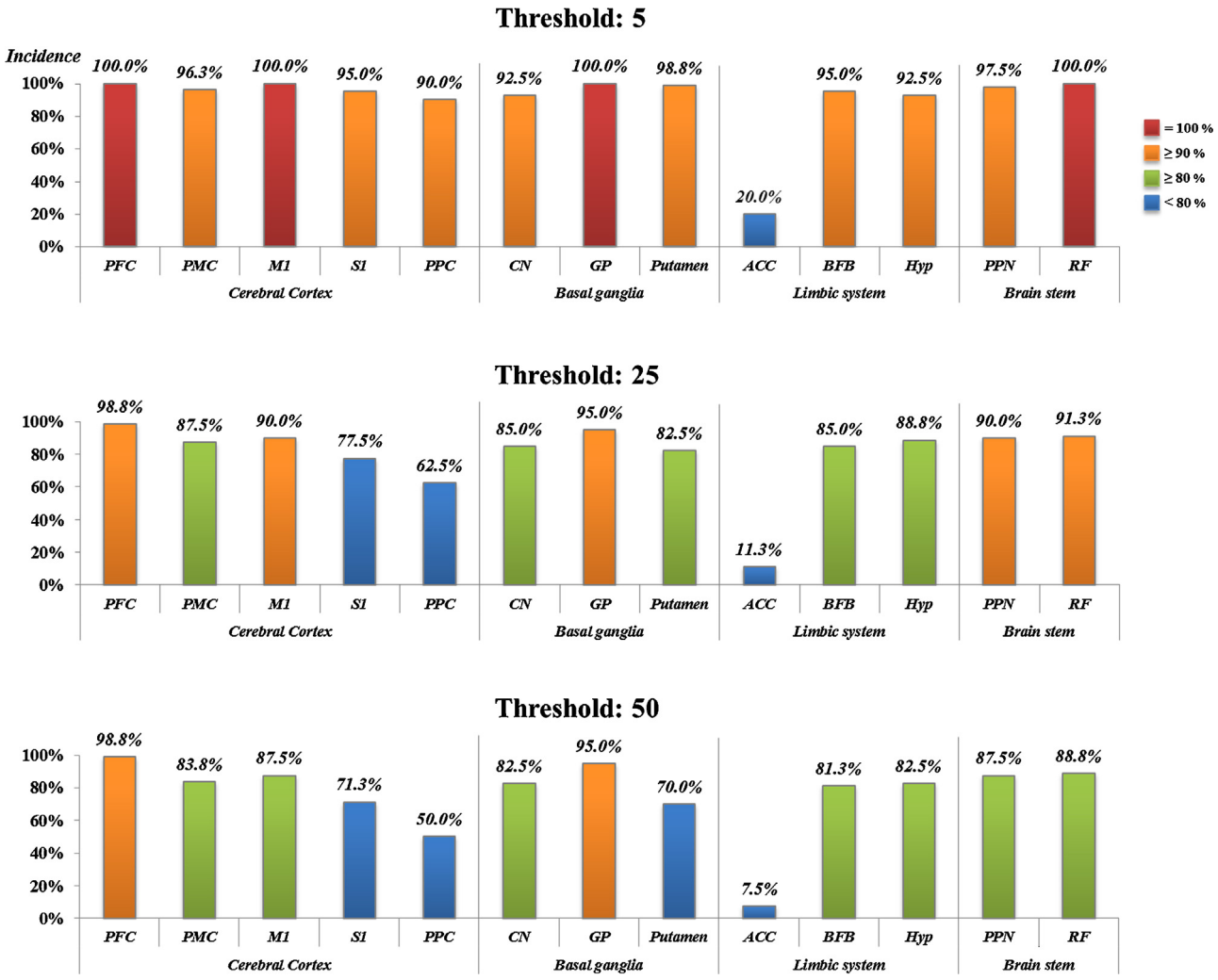


**Fig. 2.** Incidence of connectivity between the intralaminar nuclei of the thalamus and brain regions. Cerebral cortex: prefrontal cortex (PFC), premotor cortex (PMC), primary motor cortex (M1), primary somatosensory cortex (S1), posterior parietal cortex (PPC); basal ganglia: caudate nucleus (CN), globus pallidus (GP), putamen; limbic system; anterior cingulate cortex (ACC), basal forebrain (BFB), hypothalamus (Hyp); brain stem: pedunculopontine nucleus (PPN), reticular formation (RF).

Alzheimer's disease [40]. They suggested that this change could be attributed to degeneration of the ILN. In 2012, using high angular resolution diffusion imaging, Edlow et al. reconstructed the ARAS connecting the brainstem to the thalamus, hypothalamus, and the basal forebrain in three adult human brains [10]. Subsequently, Yeo et al. reconstructed the lower component of the ARAS between the ILN and the pontine reticular formation in normal healthy subjects [39]. In 2003, using Tract-Based Spatial Statistics, Osoba et al. reported that the patient with depressive disorder showed positive correlation with increment of fractional anisotropy value in the centromedian nucleus of the ILN [23]. In 2003, Edlow et al. reported on a patient with coma who showed complete disruption of white matter pathways connecting brainstem arousal nuclei to the basal forebrain and thalamic intralaminar and reticular nuclei, and partial disruption of the pathways connecting the thalamus and basal forebrain to the cerebral cortex following traumatic brain injury [9]. In a recent study, Eckert et al. found that the centromedian–parafascicular complex, a part of the ILN, showed stronger connection with hippocampus, amygdala, pallidum, putamen, and anterior insula cortex, compared with the mediodorsal thalamic nuclei. By contrast, we placed ROIs in the whole ILN and our results showed that high connectivity of the ILN with brain areas related to arousal, attention, and sensorimotor function [8]. These different results appear to be related to difference of the selected ROI. Therefore, to the best of our knowledge, this is the first study using DTI to investigate the neural connectivity of the whole ILN in the human brain. However, limitations of DTI should be considered. First, DTI is a powerful anatomic imaging tool, which can demonstrate gross fiber architecture; however, regions of fiber complexity and crossing can prevent comprehensive visualization of the underlying fiber architecture [37,38], Second, use of a probabilistic approach of DTI can produce false positive results throughout the white matter of the brain [3,24,38].

## 5. Conclusion

In conclusion, findings of this study showed that the ILN has high connectivity with brain areas related to arousal, attention, and sensorimotor function. This result indicates that ILN is closely related to consciousness and attention and sensori-motor function in the human brain. The methods used and the results of this study provide useful information for use by clinicians and researchers investigating the ILN and cerebral cortex, especially consciousness for the connectivity to the basal forebrain and PFC. However, as mentioned above, conduct of further studies will be required in order to address this limitation.

## Acknowledgements

This research was supported by Basic Science Research Program through the National Research Foundation of Korea NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A4A01001873).

## References

[1] J.M. Allman, A. Hakeem, J.M. Erwin, E. Nimchinsky, P. Hof, The anterior cingulate cortex – the evolution of an interface between emotion and cognition, Ann. N.Y. Acad. Sci. 935 (2001) 107–117.
[2] C. Baleydier, F. Mauguiere, The duality of the cingulate gyrus in monkey. Neuroanatomical study and functional hypothesis, Brain: J. Neurol. 103 (1980) 525–554.
[3] T.E. Behrens, H.J. Berg, S. Jbabdi, M.F. Rushworth, M.W. Woolrich, Probabilistic diffusion tractography with multiple fibre orientations: what can we gain? Neuroimage 34 (2007) 144–155.
[4] T.E.J. Behrens, H. Johansen-Berg, M.W. Woolrich, S.M. Smith, C.A.M. Wheeler-Kingshott, P.A. Boulby, G.J. Barker, E.L. Sillery, K. Sheehan, O. Ciccarelli, A.J. Thompson, J.M. Brady, P.M. Matthews, Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging, Nat. Neurosci. 6 (2003) 750–757.
[5] K. Brodmann, L.J. Gary, Brodmann's Localization in the Cerebral Cortex: The Principles of Comparative Localisation in the Cerebral Cortex based on Cytoarchitectonics, vol. xv, Springer, New York, NY, 2006, 298 pp.
[6] G. Bush, P. Luu, M.I. Posner, Cognitive and emotional influences in anterior cingulate cortex, Trends Cogn. Sci. 4 (2000) 215–222.
[7] J.R. Daube, Medical Neurosciences: An Approach to Anatomy, Pathology, and Physiology by Systems and Levels, vol. x, 2nd ed., Little, Brown and Co., Boston, 1986, 450 pp.
[8] U. Eckert, C.D. Metzger, J.E. Buchmann, J. Kaufmann, A. Osoba, M. Li, A. Safron, W. Liao, J. Steiner, B. Bogerts, M. Walter, Preferential networks of the mediodorsal nucleus and centromedian–parafascicular complex of the thalamus – a DTI tractography study, Hum. Brain Mapp. 33 (2012) 2627–2637.
[9] B.L. Edlow, R.L. Haynes, E. Takahashi, J.P. Klein, P. Cummings, T. Benner, D.M. Greer, S.M. Greenberg, O. Wu, H.C. Kinney, R.D. Folkerth, Disconnection of the ascending arousal system in traumatic coma, J. Neuropathol. Exp. Neurol. 72 (2013) 505–523.
[10] B.L. Edlow, E. Takahashi, O. Wu, T. Benner, G. Dai, L. Bu, P.E. Grant, D.M. Greer, S.M. Greenberg, H.C. Kinney, R.D. Folkerth, Neuroanatomic connectivity of the human ascending arousal system critical to consciousness and its disorders, J. Neuropathol. Exp. Neurol. 71 (2012) 531–546.
[11] M. Guye, G.J. Parker, M. Symms, P. Boulby, C.A. Wheeler-Kingshott, A. Salek-Haddadi, G.J. Barker, J.S. Duncan, Combined functional MRI and tractography to demonstrate the connectivity of the human primary motor cortex in vivo, Neuroimage 19 (2003) 1349–1360.
[12] S.N. Haber, R. Calzavara, The cortico-basal ganglia integrative network: the role of the thalamus, Brain Res. Bull. 78 (2009) 69–74.
[13] S.H. Jang, P.H. Chang, H.G. Kwon, The neural connectivity of the inferior olivary nucleus in the human brain: a diffusion tensor tractography study, Neurosci. Lett. 523 (2012) 67–70.
[14] S.S. Kaitz, R.T. Robertson, Thalamic connections with limbic cortex. II. Corticothalamic projections, J. Comp. Neurol. 195 (1981) 527–545.
[15] E.F. Kaufman, A.C. Rosenquist, Afferent connections of the thalamic intralaminar nuclei in the cat, Brain Res. 335 (1985) 281–296.
[16] K.E. Krout, R.E. Belzer, A.D. Loewy, Brainstem projections to midline and intralaminar thalamic nuclei of the rat, J. Comp. Neurol. 448 (2002) 53–101.
[17] S. Laureys, M.E. Faymonville, A. Luxen, M. Lamy, G. Franck, P. Maquet, Restoration of thalamocortical connectivity after recovery from persistent vegetative state, Lancet 355 (2000) 1790–1791.
[18] U. Leon-Dominguez, A. Vela-Bueno, M. Froufe-Torres, J. Leon-Carrion, A chronometric functional sub-network in the thalamo-cortical system regulates the flow of neural information necessary for conscious cognitive processes, Neuropsychologia 51 (2013) 1336–1349.
[19] C.D. Metzger, Y.D. van der Werf, M. Walter, Functional mapping of thalamic nuclei and their integration into cortico-striatal-thalamo-cortical loops via ultra-high resolution imaging-from animal anatomy to in vivo imaging in humans, Front. Neurosci. 7 (2013) 24.
[20] A. Morel, Stereotactic Atlas of the Human Thalamus and Basal Ganglia, Informa Healthcare, New York, 2007, 149 pp., 148 p. of plates.
[21] S. Mori, B.J. Crain, V.P. Chacko, P.C. van Zijl, Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging, Ann. Neurol. 45 (1999) 265–269.
[22] K.A. Muthusamy, B.R. Aravamuthan, M.L. Kringelbach, N. Jenkinson, N.L. Voets, H. Johansen-Berg, J.F. Stein, T.Z. Aziz, Connectivity of the human pedunculopontine nucleus region and diffusion tensor imaging in surgical targeting, J. Neurosurg. 107 (2007) 814–820.
[23] A. Osoba, J. Hanggi, M. Li, D.I. Horn, C. Metzger, U. Eckert, J. Kaufmann, K. Zierhut, J. Steiner, K. Schiltz, H.J. Heinze, B. Bogerts, M. Walter, Disease severity is correlated to tract specific changes of fractional anisotropy in MD and CM thalamus – a DTI study in major depressive disorder, J. Affect. Disord. 149 (2013) 116–128.
[24] G.J. Parker, D.C. Alexander, Probabilistic anatomical connectivity derived from the microscopic persistent angular structure of cerebral tissue, Philos. Trans. R. Soc. Lond. Ser. B: Biol. Sci. 360 (2005) 893–902.
[25] T. Paus, Functional anatomy of arousal and attention systems in the human brain, Prog. Brain Res. 126 (2000) 65–77.
[26] M. Peschanski, J.M. Besson, A spino-reticulo-thalamic pathway in the rat: an anatomical study with reference to pain transmission, Neuroscience 12 (1984) 165–178.
[27] S.T. Sakai, D. Tanaka Jr., Contralateral corticothalamic projections from area 6 in the raccoon, Brain Res. 299 (1984) 371–375.
[28] N.D. Schiff, Central thalamic contributions to arousal regulation and neurological disorders of consciousness, Ann. N.Y. Acad. Sci. 1129 (2008) 105–118.
[29] N.D. Schiff, J.T. Giacino, K. Kalmar, J.D. Victor, K. Baker, M. Gerber, B. Fritz, B. Eisenberg, T. Biondi, J. O'Connor, E.J. Kobylarz, S. Farris, A. Machado, C. McCagg, F. Plum, J.J. Fins, A.R. Rezai, Behavioural improvements with thalamic stimulation after severe traumatic brain injury, Nature 448 (2007) 600–603.
[30] S.M. Smith, M. Jenkinson, M.W. Woolrich, C.F. Beckmann, T.E.J. Behrens, H. Johansen-Berg, P.R. Bannister, M. De Luca, I. Drobnjak, D.E. Flitney, R.K. Niazy, J. Saunders, J. Vickers, Y.Y. Zhang, N. De Stefano, J.M. Brady, P.M. Matthews, Advances in functional and structural MR image analysis and implementation as FSL, Neuroimage 23 (2004) S208–S219.
[31] J. Smythies, The functional neuroanatomy of awareness: with a focus on the role of various anatomical systems in the control of intermodal attention, Conscious. Cogn. 6 (1997) 455–481.
[32] Y.D. Van der Werf, M.P. Witter, H.J. Groenewegen, The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness, Brain Res. Brain Res. Rev. 39 (2002) 107–140.
[33] R.P. Vertes, A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat, J. Comp. Neurol. 313 (1991) 643–668.
[34] R.P. Vertes, G.F. Martin, Autoradiographic analysis of ascending projections from the pontine and mesencephalic reticular formation and the median raphe nucleus in the rat, J. Comp. Neurol. 275 (1988) 511–541.
[35] L. Villanueva, C. Desbois, D. Le Bars, J.F. Bernard, Organization of diencephalic projections from the medullary subnucleus reticularis dorsalis and the adjacent cuneate nucleus: a retrograde and anterograde tracer study in the rat, J. Comp. Neurol. 390 (1998) 133–160.
[36] B.A. Vogt, D.L. Rosene, D.N. Pandya, Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey, Science 204 (1979) 205–207.
[37] V.J. Wedeen, R.P. Wang, J.D. Schmahmann, T. Benner, W.Y. Tseng, G. Dai, D.N. Pandya, P. Hagmann, H. D'Arceuil, A.J. de Crespigny, Diffusion spectrum magnetic resonance imaging (DSI) tractography of crossing fibers, Neuroimage 41 (2008) 1267–1277.
[38] K. Yamada, K. Sakai, K. Akazawa, S. Yuen, T. Nishimura, MR tractography – a review of its clinical applications, Magn. Reson. Med. Sci. 8 (2009) 165–174.
[39] S.S. Yeo, P.H. Chang, S.H. Jang, The ascending reticular activating system from pontine reticular formation to the thalamus in the human brain, Front. Hum. Neurosci. 7 (2013) 416.
[40] M. Zarei, B. Patenaude, J. Damoiseaux, C. Morgese, S. Smith, P.M. Matthews, F. Barkhof, S.A. Rombouts, E. Sanz-Arigita, M. Jenkinson, Combining shape and connectivity analysis: an MRI study of thalamic degeneration in Alzheimer's disease, Neuroimage 49 (2010) 1–8.