INVITED REVIEW

Perspectives on the neural connectivity of the fornix in the human brain

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Abstract

The fornix is involved in the transfer of information on episodic memory as a part of the Papez circuit. Diffusion tensor imaging enables to estimate the neural connectivity of the fornix. The anterior fornical body has high connectivity with the anterior commissure, and brain areas relevant to cholinergic nuclei (septal forebrain region and brainstem) and memory function (medial temporal lobe). In the normal subjects, by contrast, the posterior fornical body has connectivity with the cerebral cortex and brainstem through the splenium of the corpus callosum. We believe that knowledge of the neural connectivity of the fornix would be helpful in investigation of the neural network associated with memory and recovery mechanisms following injury of the fornix.

Key Words: *fornix; neural connectivity; diffusion tensor imaging; anterior commissure; corpus callosum; cholinergic nucleus*

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The fornix is involved in the transfer of information on episodic memory as a part of the Papez circuit (Wolk and Budson, 2010). The fornix has long been known to be connected to the septal region through the precommissural fornix anteriorly, the mammillary body through the postcommissural fornix anteriorly, and the hippocampus through the crus of the fornix posteriorly (Concha et al., 2005; Jones et al., 2013; Nolte and Angevine, 2013; Yeo et al., 2013). However, recent studies have suggested that the neural connectivity of the fornix is much wider and more complicated than the classical concept of the fornix anatomy (Jang and Kwon, 2013; Yeo and Jang, 2013a, b; Jang and Kwon, 2014).

Accurate assessment of the fornix using conventional brain CT and MRI has been difficult in the past, therefore, the neural connectivity of the fornix in the human brain has not been clearly elucidated (Tucker et al., 1988; Gaffan et al., 1991; Hodges and Carpenter, 1991; Thomas et al., 2011). The introduction of diffusion tensor imaging (DTI) has enabled three-dimensional visualization and estimation of the fornix (Concha et al., 2005; Sugiyama et al., 2007; Hong et al., 2012). In detail, streamline DTI based on the single-tensor model estimates only a dominant direction of the fiber in a voxel. This fiber tracking method is known to have limitation in crossing fiber effect. By contrast, probabilistic DTI based on the multi-tensor model estimates both dominant and non-dominant directions of the fiber in a voxel. Therefore, it has advantage to reduce the problem of the crossing fiber effect and investigate the neural connectivity of neural structure (Behrens et al., 2003, 2007). Several studies have reported on the neural connectivity of the fornix in normal subjects and the mechanisms for recovery of an injured fornix. In addition, these studies on the mechanisms for recovery of an injured fornix coincided with the results of studies on the neural connectivity of the anterior and posterior bodies of the fornix in normal subjects (Jang and Kwon, 2013, 2014; Yeo and Jang, 2013a, b).

Recent clinical studies using DTI have suggested that clarification of the neural connectivity of the fornix is important in terms of mechanisms for recovery of an injured fornix (Yeo and Jang, 2013a, b). Results of these studies indicate that the mechanisms for recovery of an injured fornix might be based on the involvement of the neural connectivity of the fornix and the basic mechanisms of brain plasticity in detail: 1) unmasking of reserve axons and synapses for particular functions after failure of the ordinarily dominant system and 2) collateral sprouting from intact neurons to a denervated region) (Bach y Rita, 1981a, b).

Since the introduction of DTI, we have reported two studies on the neural connectivity of the anterior and posterior bodies of the fornix in normal subjects (Jang and Kwon, 2013, 2014). The characteristics of connectivity of the fornix can be summarized as follows: 1) the anterior and posterior bodies of the fornix showed high connectivity with the anterior commissure and splenium of the corpus callosum,

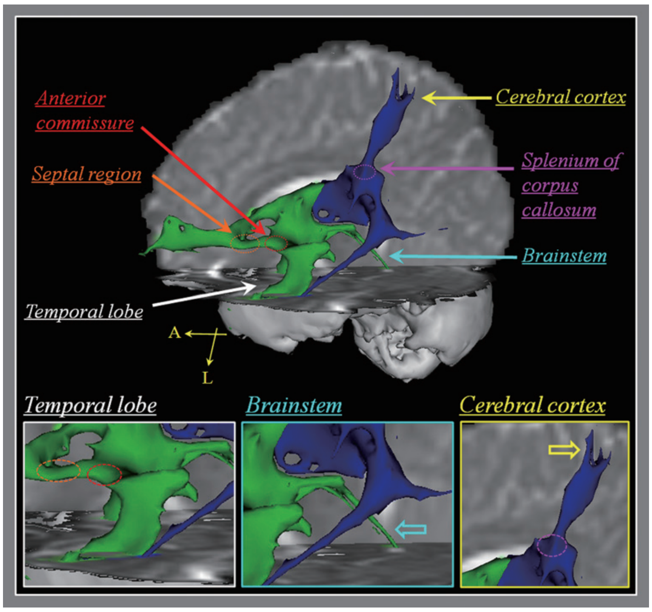

Figure 1 Results of diffusion tensor tractography for the connectivity of the anterior (green color) and posterior (blue color) bodies of the fornix in a 24-year-old normal male subject.
The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library is used to reconstruct the connectivity of the anterior (green color) and posterior (blue color) bodies of the fornix. For regions of interest (ROIs), we draw the ROIs at the portion of the anterior and posterior bodies of the fornix (green color) on the color map, respectively. Temporal lobe (bottom left image): the anterior body of the fornix shows connectivity with the medial temporal lobe *via* the anterior commissure (red-dotted circle). Brainstem (bottom centre image): the anterior body of the fornix shows connectivity with the brainstem (skyblue arrow). Cerebral cortex (bottom right image): the posterior body of the fornix shows connectivity with the cerebral cortex (yellow arrow) *via* the splenium of the corpus callosum (purple-dotted circle).

Table 1 Neural connectivity of the anterior and posterior body of the fornix in the human brain

*Anterior fornical body	⇔	Anterior commissure	⇔	Basal forebrain
			⇔	Medial temporal lobe
	⇔	Thalamus	⇔	Brainstem
*Posterior fornical body	⇔	Splenium of corpus callosum	⇔	Cerebral cortex
	⇔	Thalamus	⇔	Brainstem

respectively, 2) the anterior fornical body showed high connectivity with areas known to contain cholinergic neurons (basal forebrain and brainstem), and the medial temporal lobe, in particular the hippocampus and entorhinal cortex which are important structures for memory function, and 3) the posterior fornical body showed high connectivity with the cerebral cortex (precentral gyrus, postcentral gyrus, and posterior parietal cortex) through the splenium of the corpus callosum and also the brainstem through the thalamus (Jang and Kwon, 2013, 2014) (**Table 1, Figure 1**).

The fornix is known to obtain cholinergic innervation from the medial septal nucleus (Ch 1) and the vertical nucleus of the diagonal band (Ch 2) in the basal forebrain; in contrast, the cerebral cortex obtains cholinergic innervation mainly from the nucleus basalis of Meynert (Ch 4) (Meibach and Siegel, 1977; Mesulam et al., 1983; Lucas-Meunier et al., 2003; Naidich and Duvernoy, 2009). However, the results of the study on the neural connectivity of the posterior fornical body showed that the posterior cerebral cortex, located posterior from the precentral gyrus, obtained cholinergic innervations from the posterior fornical body (Jang and Kwon, 2013). According to this finding, it appears that the posterior cerebral cortex obtained cholinergic innervations from Ch 1 and Ch 2 as well as Ch 4. On the other hand, previous animal studies have reported that the thalamus is a target area of brainstem cholinergic nuclei (the pedunculopontine nucleus [Ch 5] and laterodorsal tegmental nucleus [Ch 6]) (Mesulam et al., 1983; Butcher and Woolf, 2004; Naidich and Duvernoy, 2009). Regarding the neural connectivity between the fornix and thalamus, the results of the study on the neural connectivity of the posterior fornical body showed that 12% of subjects had neural connectivity between the posterior fornical body and the brainstem through the thalamus. Therefore, according to the results of this study, the posterior fornical body appears to have neural connection with cholinergic nuclei in the brainstem through the thalamus in some of the subjects.

Two recent studies using DTI demonstrated that the neural connectivity of normal subjects can be used to study the neural reorganization of the fornix after brain injury (Jang and Kwon, 2013, 2014; Yeo and Jang, 2013a, b). In 2013, Yeo and Jang reported on a patient who showed neural reorganization of an injured fornix following traumatic axonal injury of both fornical crura (Yeo and Jang, 2013a). A neural tract originating from the right fornical crus passed through the splenium of the corpus callosum and then connected with the right temporal lobe. By contrast, in the left fornix, another neural tract originating from the left fornical column was connected with the left medial temporal lobe through the anterior commissure. They suggested that these new neural tracts of the fornix were the result of neural reorganization triggered by bilateral injury of the fornical crus because these neural tracts were not observed in normal control subjects. The same authors (2013) recently reported on a patient with subarachnoid hemorrhage due to rupture of an anterior communicating cerebral artery aneurysm (Yeo and Jang, 2013b). The proximal portion of both fornical crura showed discontinuations on six-week and seven-month DTIs; however, seven-month DTI showed that the end of the right fornical body was connected with the splenium of the corpus callosum and then branched to the right medial temporal lobe and right thalamus. This patient showed severe cognitive impairment at six weeks after onset, however, her cognition showed continuous improvement with time and was found to become within normal range at seven months after onset. Therefore, it was suggested that the neural connections between the injured fornical body, and the medial temporal lobe and thalamus, which is known to be connected to the brainstem cholinergic nuclei, were the result of neural reorganization of an injured fornix.

In conclusion, the anterior fornical body has high connectivity with the anterior commissure, and brain areas relevant to cholinergic nuclei (the septal forebrain region and brainstem) and memory function (the medial temporal lobe). By contrast, the posterior fornical body has connectivity with the cerebral cortex and brainstem through the splenium of the corpus callosum in the normal subjects. Recent clinical studies using DTI have demonstrated that this neural connectivity of the fornix can be used for the study of neural reorganization after injury of the fornix (Yeo and Jang, 2013a, b). In particular, the high connectivity to the medial temporal lobe through the anterior commissure and splenium of the corpus callosum might suggest the possibility that these connections could be reorganization routes whose unmasking occurred after injury of the fornix. We believe that knowledge of the neural connectivity of the fornix would be helpful in investigation of the neural network associated with memory and recovery mechanisms following injury of the fornix in patients with brain injury. Further clinical studies involving large numbers of patients and various brain pathologies should be encouraged.

Conflicts of interest: *None declared.*

References

Bach y Rita P (1981) Brain plasticity as a basis of the development of rehabilitation procedures for hemiplegia. Scand J Rehabil Med 13:73-83.

Bach y Rita P (1981) Central nervous system lesions: sprouting and unmasking in rehabilitation. Arch Phys Med Rehabil 62:413-417.

Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, Barker GJ, Sillery EL, Sheehan K, Ciccarelli O, Thompson AJ, Brady JM, Matthews PM (2003) Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 6:750-757.

Behrens TE, Berg HJ, Jbabdi S, Rushworth MF, Woolrich MW (2007) Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage 34:144-155.

Butcher LL, Woolf NJ (2004) Cholinergic neurons and networks revisited.; In: Paxinos G, editor. The rat nervous system. Amsterdam; Boston: Elsevier Academic Press.

Concha L, Gross DW, Beaulieu C (2005) Diffusion tensor tractography of the limbic system. AJNR Am J Neuroradiol 26:2267-2274.

Gaffan EA, Gaffan D, Hodges JR (1991) Amnesia following damage to the left fornix and to other sites. A comparative study. Brain 114:1297-1313.

Hodges JR, Carpenter K (1991) Anterograde amnesia with fornix damage following removal of IIIrd ventricle colloid cyst. J Neurol Neurosurg Psychiatry 54:633-638.

Hong JH, Choi BY, Chang CH, Kim SH, Jung YJ, Byun WM, Jang SH (2012) Injuries of the cingulum and fornix after rupture of an anterior communicating artery aneurysm: a diffusion tensor tractography study. Neurosurgery 70:819-823.

Jang SH, Kwon HG (2013) Neural connectivity of the posterior body of the fornix in the human brain: diffusion tensor imaging study. Neurosci Lett 549:116-119.

Jang SH, Kwon HG (2014) Neural connectivity of the anterior body of the fornix in the human brain: diffusion tensor imaging study. Neurosci Lett 559:72-75.

Jones HR, Burns T, Aminoff MJ, Pomeroy SL, Netter FH, Machado CAG (2013) The Netter collection of medical illustrations. Volume 7, Part 1. Brain, 2nd edition. Edition.

Lucas-Meunier E, Fossier P, Baux G, Amar M (2003) Cholinergic modulation of the cortical neuronal network. Pflugers Arch 446:17-29.

Meibach RC, Siegel A (1977) Efferent connections of the hippocampal formation in the rat. Brain Res 124:197-224.

Mesulam MM, Mufson EJ, Wainer BH, Levey AI (1983) Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6). Neuroscience 10:1185-1201.

Naidich TP, Duvernoy HM (2009) Duvernoy's atlas of the human brain stem and cerebellum: high-field MRI: surface anatomy, internal structure, vascularization and 3D sectional anatomy. Wien; New York: Springer.

Nolte J, Angevine JB (2013) The human brain in photographs and diagrams, Fourth edition. Edition. Philadelphia, PA: Elsevier/Saunders.

Sugiyama K, Kondo T, Higano S, Endo M, Watanabe H, Shindo K, Izumi S (2007) Diffusion tensor imaging fiber tractography for evaluating diffuse axonal injury. Brain Inj 21:413-419.

Thomas AG, Koumellis P, Dineen RA (2011) The fornix in health and disease: an imaging review. Radiographics 31:1107-1121.

Tucker DM, Roeltgen DP, Tully R, Hartmann J, Boxell C (1988) Memory dysfunction following unilateral transection of the fornix: a hippocampal disconnection syndrome. Cortex 24:465-472.

Wolk DA, Budson AE (2010) Memory systems. Continuum (Minneap Minn) 16:15-28.

Yeo SS, Jang SH (2013a) Neural reorganization following bilateral injury of the fornix crus in a patient with traumatic brain injury. J Rehabil Med 45:595-598.

Yeo SS, Jang SH (2013b) Recovery of an injured fornix in a stroke patient. J Rehabil Med 45:1078-1080.

Yeo SS, Seo JP, Kwon YH, Jang SH (2013) Precommissural fornix in the human brain: a diffusion tensor tractography study. Yonsei Med J 54:315-320.