



● IMAGING IN NEURAL REGENERATION

## Unusual neural tract between injured fornix and pedunclopontine nucleus in a patient with traumatic brain injury

It has been known that four cholinergic nuclei are located in the septal region and basal forebrain (Ch 1: medial septal nucleus, Ch 2: vertical nucleus of the diagonal band, Ch 3: horizontal limb of the diagonal band and Ch 4: nucleus basalis of Meynert) and two are located in the brainstem (Ch 5: pedunclopontine nucleus and Ch 6: laterodorsal tegmental nucleus) (Selden et al., 1998; Lucas-Meunier et al., 2003; Mesulam, 2004; Nieuwenhuys et al., 2007). The fornix transfers information on episodic memory between the medial diencephalon and the medial temporal lobe (Afifi and Bergman, 2005; Wolk and Budson, 2010). The fornix is known to obtain cholinergic innervation from Ch 1 and Ch 2, and to project to the hippocampal formation (Selden et al., 1998; Lucas-Meunier et al., 2003; Mesulam, 2004; Nieuwenhuys et al., 2007; Dere et al., 2008; Naidich and Duvernoy, 2009; Isaacson and Pribram, 2013).

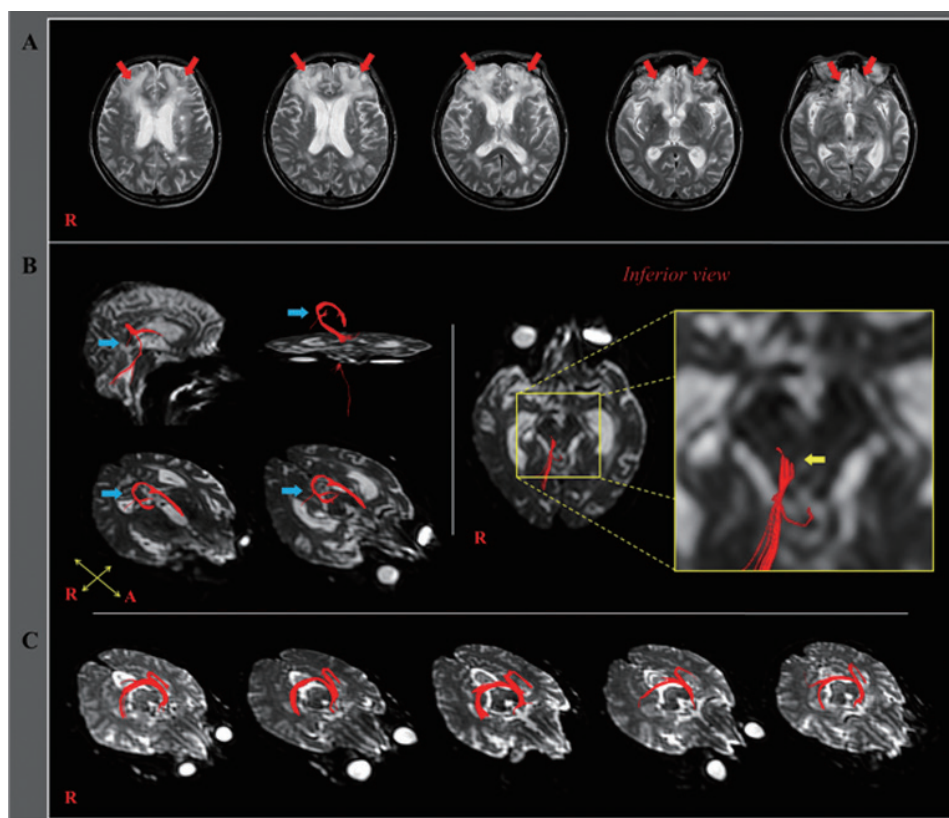
In this study, using DTT, we attempted to demonstrate an unusual neural tract between the injured fornix and Ch 5 *via* the thalamus in a patient with TBI.

A 64-year-old, right-handed male patient who had suffered a traffic accident underwent conservative management for subarachnoid hemorrhage, subdural hematoma, and skull fracture at the department of neurosurgery of a university hospital. Findings on brain MRI performed 6 months after onset showed multiple leukomalactic lesions in both frontal lobes and basal

forebrain (Figure 1A). Evaluation of cognitive function performed at 6 months after onset showed severe cognitive impairment (decreased alertness, Mini-Mental State Exam (Tombaugh and McIntyre, 1992) score: uncheckable) and severe quadriparesis (Manual Muscle Test (Wintz, 1959): right upper and lower extremities – 0–2, left upper and lower extremities – 3–4. Five normal age-matched normal subjects (2 males; mean age: 59.6 years, range: 55–65 years) without history of neurologic or psychiatric disease were included as controls. Our institutional review board approved the study protocol.

Using a sensitivity-encoding head coil, DTIs were acquired on a 1.5-T at 6 months after onset. We acquired 60 contiguous slices parallel to the anterior and posterior commissure lines for each of the 32 non-collinear diffusion sensitizing gradients. DTI parameters were as follows: total scanning time = 7 minutes 32 seconds; repetition time = 10,726 ms; acquisition matrix =  $96 \times 96$ ; echo time = 76 ms; number of excitations = 1; reconstruction matrix =  $192 \times 192$  matrix; thickness = 2.5 mm;  $b = 1,000$  s/mm<sup>2</sup>; and field of view =  $240 \times 240$  mm<sup>2</sup>. Fiber assignment continuous tracking (FACT) algorithm was used for fiber tracking (Mori et al., 1999). For analysis of the fornix, the first region of interest (ROI) was placed on the middle of the body and the second ROI was placed on the junction between the body and crus on the coronal slice of the color map (green color) (Hong and Jang, 2010). Termination criteria were fractional anisotropy > 0.2 and angle change < 45°.

Findings on 6-month DTT showed discontinuations in the anterior portion of the fornix body and both crus. The end of the fornix body was connected to the right pedunclopontine nucleus (Ch 5) *via* a neural tract that passed through the right thalamus (Figure 1B). However, we did not find this neural tract between the fornix and Ch 5 in five normal age-matched normal subjects (2 males; mean age: 59.6 years, range: 55–65 years)(Figure 1C).



**Figure 1** T2-weighted MRI and DTT images in a 64-year-old male patient with traumatic brain injury.

(A) T2-weighted MR images taken at 6 months after onset showed leukomalactic lesions in both frontal lobes and basal forebrain (red arrows). (B) Findings on 6-month diffusion tensor tractography showed discontinuations in the anterior portion of the fornix body and both crus. The end of the fornix body was connected to the right pedunclopontine nucleus *via* a neural tract (blue arrows) that passed through the right pedunclopontine nucleus (yellow arrow). (C) The absence of neural connection between the fornix and the pedunclopontine nucleus was observed in five normal control subjects. R: Right; A: anterior.



In the current study, we observed an unusual neural tract between the injured fornix and Ch 5 via the thalamus in a patient with TBI. This neural tract was not observed in any of five age-matched normal subjects. Findings on 6-month DTT for the fornix showed severe injury (discontinuation) of the anterior portion of the fornix body. Consequently, it appears that the neural pathway from Ch 1 and Ch 2 was completely injured. The fornix is known to obtain cholinergic innervation from Ch 1 and Ch 2 (Selden et al., 1998; Lucas-Meunier et al., 2003; Mesulam, 2004; Dere et al., 2008; Naidich and Duvernoy, 2009; Isaacson and Pribram, 2013). On the other hand, some studies have reported that the thalamus is a target area of Ch 5 (Mesulam et al., 1983; Woolf and Butcher, 1986; Mesulam, 1990; Paxinos, 1990; Butcher and Woolf, 2004; Naidich and Duvernoy, 2009). Therefore, the unusual neural tract between the injured fornix and Ch 5 appears to be a compensatory phenomenon to allow the injured fornix to obtain cholinergic innervation from Ch 5 instead of Ch 1 and 2, following destruction of the cholinergic pathway from Ch 1 and Ch 2 to the fornix. Because the cholinergic nuclei are interconnected with each other, this unusual neural connection observed on DTT might be the result of process of recovery for injured cholinergic innervations or facilitation of a weak already existing neural connection (Mesulam, 1990).

Since introduction of DTI, unusual neural tracts between an injured fornix and brainstem cholinergic nuclei have recently been reported in stroke patients (a patient with subarachnoid and intraventricular hemorrhage: the neural tract between the injured fornix and Ch 5, and a patient with cerebral infarct: the neural tract between the injured fornix and Ch 6 (Yeo and Jang, 2013; Jang and Seo, 2016). As a result, as far as we are aware, this is the first study to demonstrate the unusual neural tract which connected between injured fornix and brainstem cholinergic nuclei in patients with TBI. However, our results are limited to this case report. Further studies involving larger numbers of patients are warranted. In addition, the lack of DTI at onset and long-term follow up DTI should be considered in future studies. Moreover, studies on the clinical significance of this unusual neural tract should be encouraged.

In conclusion, we report on a patient who showed an unusual neural tract between the injured fornix and Ch 5 following traumatic brain injury. We believe that our findings may suggest a possible recovery phenomenon between cholinergic nuclei and the Papez circuit following brain injury.

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