Observational Study

Medicine®

OPEN

Mechanism of cognitive impairment in chronic patients with putaminal hemorrhage

A diffusion tensor tractography

Jeong-Hee Yang, PhD[a], Han Do Lee, BS[b], So Young Kwak, MD[b], Ki Hyun Byun, MD[c], Sung Ho Park, PhD[d], Dongseok Yang, MD, PhD[c,*]

Abstract

It is not clear whether the fornix and cingulum are involved in cognition after putaminal hemorrhage (PH). We investigated structural changes and differences of the neural tracts, and the relationship between the integrity of the neural tracts and cognition not only at the affected but also at the unaffected side.

Sixteen patients with left chronic putaminal hemorrhage and 20 healthy volunteers were enrolled. Using diffusion tensor tractography (DTT), we compared fiber number (FN), fractional anisotropy (FA), and apparent diffusion coefficient (ADC) of the neural tracts between patient and control groups. The relationship between the neural tract parameters and neuropsychological results was also analyzed.

The left fornix FN was significantly lower than the right fornix FN in the patient group. Except for the cingulum FA, the neural tracts parameters for both the affected and unaffected hemispheres differed significantly between the groups. The fornix FA and ADC at the affected side were significantly correlated with intelligence quotient (IQ), mini-mental status examination (MMSE), and short-term memory. Interestingly, the fornix ADC at the unaffected side was significantly correlated with MMSE. However, none of the cingulum parameters was correlated with neuropsychological results.

The fornix integrity is critical for cognitive impairment after putaminal hemorrhage.

Abbreviations: ADC = apparent diffusion coefficient, DTI = diffusion tensor imaging, DTT = diffusion tensor tractography, FA = fractional anisotrophy, FN = fiber number, ICH = intracranial hemorrhage, IQ = intelligence quotient, MAS = memory assessment scale, MMSE = mini-mental status examination, PH = putaminal hemorrhage, ROI = region of interest, TBI = traumatic brain injury.

Keywords: cognitive impairment, diffusion tensor tractography, fornix, putaminal hemorrhage

1. Introduction

Although the prevalence of cognitive impairment including dementia after intracranial hemorrhage (ICH) has not been well studied, it is assumed to occur in 5% to 44% of patients.[1] Recently, some prospective cohort studies reported incidence rates of cognitive impairment and dementia after ICH.[2–5] One study indicated 37% of patients showed cognitive decline during 4-year follow-up and another study noted major vascular cognitive disorders in 2.5% of patients within 4 months after ICH.[2,5] In new-onset dementia, incidence of dementia was 14.2% of patients within 1 year and an estimated yearly incidence rate was 5.8% of patients per year during 4-year follow-up.[3,4] The mechanism of cognitive impairment after ICH is unknown. Understanding the mechanism is necessary for development of rehabilitative and therapeutic strategies.

The putamen is one of the most commonly affected structures in spontaneous primary ICH.[6,7] Therefore, investigating the relationship between cognitive neural tracts surrounding the putamen and neuropsychological subscores in patients with putaminal hemorrhage (PH) may provide clues relevant to the mechanism underlying cognitive impairment after ICH. Cognitive impairment after PH has not been intensively studied; studies that have been done focused on the disability level, motor, and language function in patients.[7–9] Anatomically, the putamen is enclosed in the fornix and cingulum, which are the part of the limbic system. The limbic system is vital in cognition and emotion.[10,11] Diffusion tensor tractography (DTT) is a novel neuroimaging technique and derived diffusion tensor imaging (DTI) is used to reconstruct the neural tracts of the limbic system in a three-dimensional (3D) view with quantitative analysis.[10]

Recently, the structural changes in the fornix and/or cingulum using DTI and DTT have been suggested to explain cognitive impairment after stroke, traumatic brain injury (TBI), and Alzheimer dementia.[12–17] Cognition and motor functions are

Editor: Heye Zhang.

Previous presentation: The abstract was presented at the poster session of 22nd Annual Meeting of the Organization for Human Brain Mapping, 2016, Geneva, Switzerland.

Supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education (grant no. 2013R1A1A4A01013178).

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

[a] Division of Brain Fusion Research, Biomedical Research Center, Ulsan University Hospital, [b] Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Taegu, [c] Department of Physical Medicine and Rehabilitation, University of Ulsan College of Medicine, [d] Department of Neurosurgery, Ulsan University Hospital, Ulsan, Republic of Korea.

[*] Correspondence: Dongseok Yang, Department of Physical Medicine and Rehabilitation, University of Ulsan College of Medicine, Ulsan University Hospital, 877 Bangeojin sunhwando-ro, Dong-gu, Ulsan, 44033, Republic of Korea (e-mail: fnew1@hanmail.net).

Medicine (2018) 97:29(e11035)

Received: 13 October 2017 / Accepted: 17 May 2018

http://dx.doi.org/10.1097/MD.0000000000011035

reportedly correlated with the integrity of white matter at the ipsilesional and contralesional hemispheres.[18–20] These observations suggest that studies need to pay special attention to the structural integrity of white matter at the unaffected as well as the affected side in ICH patients. Three DTT analyses have addressed the structural integrity of the fornix or cingulum after ICH.[16,17,21] Although these studies are valuable in that they revealed the structural integrity of the fornix or cingulum in a 3D view and the relationship between the tract parameters and cognition, they had several limitations. DTT was performed mainly at the acute stage of ICH (1–14 weeks), and 2 studies did not simultaneously evaluate the fornix and cingulum to assess the association between the neural tract and cognition.[16,21] In addition, the mini-mental status examination (MMSE) was mainly used to evaluate cognition in the enrolled patients. In this DTT-based study, we chose patients with chronic left PH with an onset of 2.35 ± 1.65 years previously to minimize the volume effect of acute hemorrhage.

In the study, we investigated whether structural changes of the fornix and cingulum occur at the affected and unaffected sides, and whether the structural integrity of the fornix or cingulum correlates with neuropsychological results with the following approaches. Firstly, we evaluated the structural differences between the affected and unaffected sides in PH patients. Secondly, we compared the structural changes of the 2 neural tracts in patients with those in the control group at the unaffected and affected sides. Thirdly, we assessed the association between the parameters of the neural tracts and the neuropsychological results at both sides in the patient group.

2. Methods

2.1. Subjects

Sixteen chronic patients with left PH (11 men, 5 women; mean age, 54.12 ± 11.27 years; age range, 35–69 years) and no previous history of neurological and psychiatric disease were enrolled. Inclusion criteria were first-ever stroke, hematoma located primarily in the putamen of the basal ganglia, and DTT scan performed at least 6 months after PH (2.35 ± 1.65 years). Twenty age and sex-matched control subjects (12 men, 8 women; mean age, 51.95 ± 8.23 years; age range, 31–66 years) were recruited as a control group for comparison with the patient group. There were no significant demographic differences between the groups (Table 1). All subjects understood the aim of the study and participated in research with written informed consent. The study protocol was approved by the Institutional Review Board of the Yeungnam University Hospital (Daegu, Korea).

2.2. Neuropsychological assessment

Cognitive function of the patients was evaluated by measuring the intelligence quotient (IQ) using the Wechsler intelligence scale, and MMSE, and the memory assessment scale (MAS).[22–24] The MAS is a comprehensive standardized memory assessment battery that consists of 4 memory subsets (global memory, short-term memory, verbal memory, and visual memory).

Table 1

Demographic data.

	Age (years)	Male/Female	Duration to DTI from onset (years)
Patient group (n = 16)	54.12 (11.27)	11/5	2.35 (1.69)
Control group (n = 20)	51.95 (8.23)	12/8	
P-value	0.508	0.587	

Values indicate mean (±standard deviation).
DTI = diffusion tensor imaging.

2.3. Diffusion tensor tractography

DTI data were obtained using a 6-channel head coil on a 1.5T Philips Gyroscan Intera (Philips Ltd., Best, The Netherlands) with single-shot echo-planar imaging. For each of the 32 non-collinear, diffusion-sensitizing gradients, 70 contiguous slices were acquired parallel to the anterior commissure–posterior commissure line. Imaging parameters were: acquisition matrix = 96×96, reconstructed to matrix = 192×192, field of view = $240 \times 240\,mm^2$, TR = 10,726 ms, TE = 76 ms, parallel imaging reduction factor (SENSE factor) = 2, echo-planar imaging factor = 49, $b = 1000\,s/mm^2$, number of excitation = 1, and slice thickness = 2.5 mm. Fiber tracking was performed using the fiber assignment continuous tracking algorithm implemented within the DTI task card software (Philips Extended MR Work Space 2.6.). For the reconstruction of the fornix, the seed region of interest (ROI) was placed on the junction between the body and column of the fornix on a coronal image of the color map. The target ROIs were placed on each side of the crus of the fornix on a coronal image of the color map.[10] Fiber tracking was performed using a fractional anisotropy (FA) threshold of >0.2 and a direction threshold <45°. In addition, for the reconstruction of the cingulum, the seed ROI was placed on the middle portion of the cingulum. The target ROI was placed on the posterior portion of the cingulum.[16] Fiber tracking was performed using an FA threshold of >0.15 and a direction threshold <27°. We reconstructed all tracts of the fornix and cingulum in the control group and all cingulum tracts in the patient group three dimensionally. However, the fornix injury occurred in 9 patients at the affected side, and in 2 patients at the unaffected side, respectively (Fig. 1).

2.4. Statistical analysis

To identify any possible differences in the DTT parameters of fiber number (FN), FA, and apparent diffusion coefficient (ADC) of the fornix or cingulum between the affected (left) and unaffected (right) sides in the patient group, independent *t* test was done. The same analysis was repeated in the control group. Next, to evaluate whether ICH had caused structural changes of the neural tracts at the unaffected as well as at the affected side, parameters of the neural tracts at both sides of the patient group were compared with those of the control group using an independent *t* test. Significance levels for group differences were set up at $P < .05$. Lastly, to evaluate the association between the parameters of the neural tract (FN, FA, and ADC) at both sides and neuropsychological subscores (IQ, MMSE, short-term, verbal, visual, and global memory), the Pearson correlation coefficient was carry out. For the correction of multiple comparisons, we also used Bonferroni correction for 3 correlations (FN, FA, ADC) and significance levels were set up at $P < .0167$.[25] All statistical analyses were assessed using SPSS version 17.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Structural differences of neural tracts between unaffected and affected sides in control and patient groups

We first studied symmetry by measuring the parameters of the neural tracts between the left and right sides in the control group.

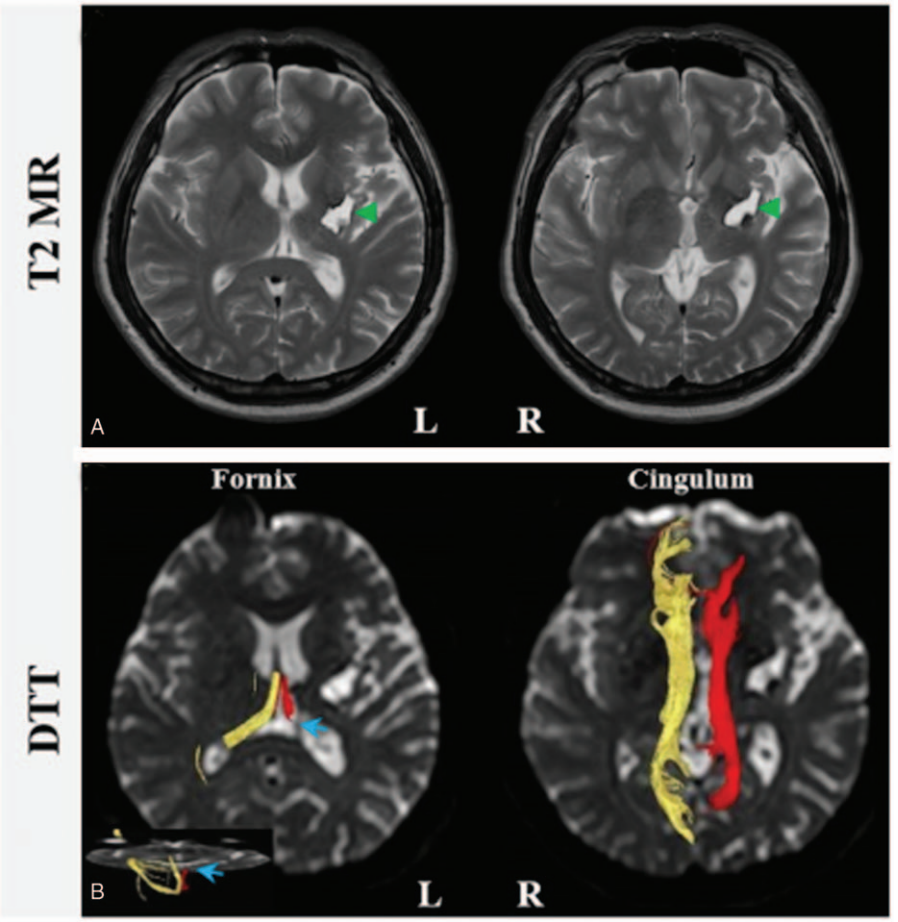

Figure 1. Representative T2-weight magnetic resonance images and diffusion tensor tractography (DTT) of a 42-year-old man with a putaminal hemorrhage at 55 months after onset in the left hemisphere. The magnetic resonance images reveal a chronic lesion (green arrowheads) in the left putamen (A). DTT images show that the left fornix is discontinued compared with the right fornix (blue arrows). The right fornix and the cingulum at the both sides were well reconstructed (B). L=left hemisphere, R=left hemisphere.

None of the parameters showed any significant differences. The values (right vs left) of the fornix and cingulum in control group were: fornix FN, 848.85±175.25 versus 780±139.71, $P=.18$; fornix FA, 0.39±0.02 versus 0.40±0.03, $P=.32$; fornix ADC, 1.41±0.20 versus 1.42±0.19, $P=.76$; cingulum FN, 2112.55±331.29 versus 2066.35±261.91, $P=.63$; cingulum FA, 0.41±0.02 versus 0.41±0.02, $P=.53$; and cingulum ADC, 0.80±0.02 versus 0.78±0.03, $P=.26$.

Next, we investigated the structural differences in the neural tracts between the affected (left) and unaffected (right) sides in the patient group. Only the left fornix FN was significantly lower than that of the right fornix FN (left: 584.88±346.92 vs right: 250±144.67; $P\leq.001$). However, other FA or ADC of the fornix and the FN, FA, or ADC of the cingulum did not show significant differences between the affected and unaffected sides (Fig. 2).

3.2. Structural changes in neural tracts at unaffected and the affected sides in patient group

To understand whether PH causes structural changes in the neural tracts at the unaffected and affected sides, we compared the parameters of the fornix and cingulum between the patient and control groups (Fig. 3).

At the affected side, all fornix parameters were significantly different in the patient group compared with the control group. More interestingly, significant differences were also observed at the unaffected side (FN/FA/ADC: $P\leq.005/P\leq.001/P\leq.001$, respectively). The cingulum FN and ADC of the patient group showed significant differences at the affected and unaffected sides compared with the control group. However, the cingulum FA of the patient group did not show significant differences compared with the control group at either side ($P=.60$ and .50 at the affected and unaffected side, respectively).

3.3. Relationship between neural tract parameters and cognitive function

To determine whether alternations in the structural integrity of the fornix or cingulum may cause cognitive impairment in chronic patients with PH, we investigated the relationship between neural tract parameters and neurophysiological subscores at the both sides. Assessments of the cognitive function in the patient group revealed average values of neuropsychological test as follows: IQ, 93.9±13.5; verbal memory, 74.0±16.0; visual memory, 90.5±16.0; short-term memory, 84.3±16.5; global memory, 77.5±16.0; MMSE, 24.6±6.2. The relationships between the fornix or cingulum parameters at both

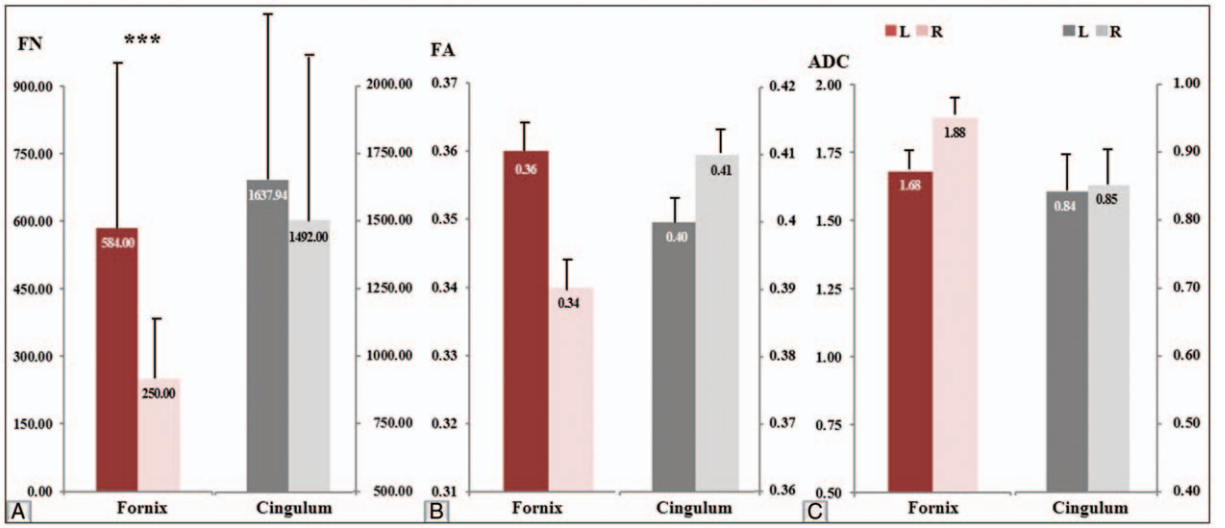

Figure 2. Structural differences of the fornix and cingulum between the left and right sides in patient group. ADC = apparent diffusion coefficient ($\times 10^{-3}$ mm^2/s), FA = fractional anisotropy, FN = fiber number, L = left (affected) side, R = right (unaffected) side. Data are expressed as mean ± SD; significant differences, $^{***}P \leq .001$

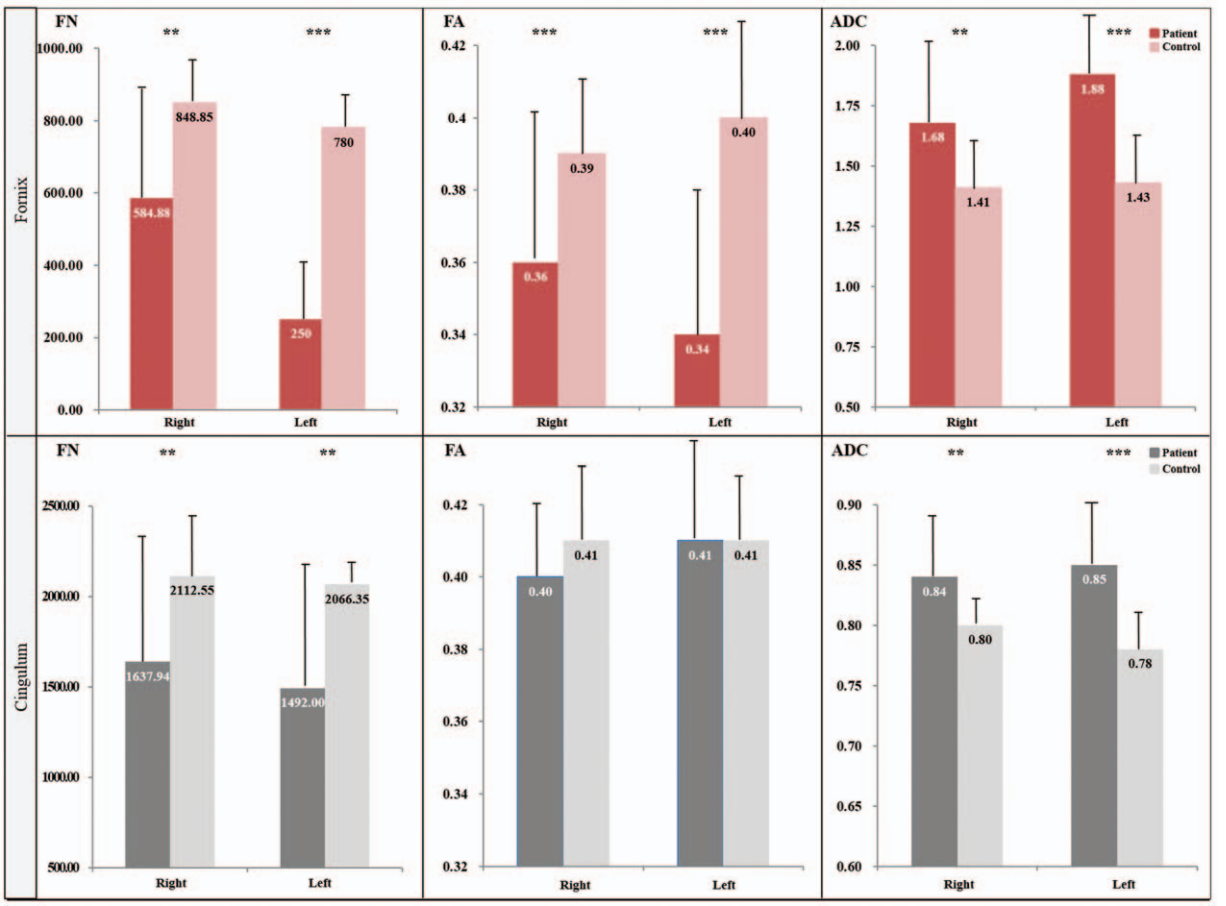

Figure 3. Structural changes of the fornix and cingulum at the affected (left) and unaffected (right) sides in control and patient groups. ADC = apparent diffusion coefficient ($\times 10^{-3}$ mm^2/s), FA = fractional anisotropy, FN = fiber number. Data are expressed as mean ± SD; significant differences, $^{**}P \leq .01$, $^{***}P \leq .001$.

Table 2

Relationship between parameters of the fornix and cingulum and neuropsychological subscores at the affected (left) and unaffected (right) sides.

	FN		FA		ADC	
	Fornix	Cingulum	Fornix	Cingulum	Fornix	Cingulum
Affected side						
IQ	0.178 (0.508)	−0.323 (0.223)	0.638 (0.008)**	0.065 (0.810)	−0.602 (0.014)**	−0.265 (0.321)
Short-term memory	0.458 (0.074)	−0.106 (0.696)	0.514 (0.042)	−0.291 (0.273)	−0.651 (0.006)**	−0.268 (0.315)
Verbal memory	0.445 (0.084)	0.021 (0.938)	0.535 (0.033)	−0.217 (0.420)	−0.508 (0.045)	−0.138 (0.610)
Visual memory	0.027 (0.931)	−0.066 (0.807)	0.295 (0.267)	−0.341 (0.196)	−0.168 (0.535)	−0.327 (0.216)
Global memory	0.268 (0.315)	0.004 (0.989)	0.438 (0.090)	−0.380 (0.147)	−0.392 (0.133)	−0.221 (0.410)
MMSE	0.420 (0.105)	0.016 (0.952)	0.678 (0.004)**	0.225 (0.403)	−0.724 (0.002)**	−0.392 (0.134)
Unaffected side						
IQ	0.211 (0.433)	−0.117 (0.666)	0.454 (0.077)	0.372 (0.156)	−0.496 (0.051)	0.031 (0.908)
Short-term memory	0.239 (0.373)	0.183 (0.498)	0.279 (0.295)	0.056 (0.838)	−0.311 (0.242)	0.305 (0.250)
Verbal memory	0.155 (0.566)	0.355 (0.178)	0.146 (0.590)	0.197 (0.464)	−0.143 (0.597)	0.187 (0.487)
Visual memory	0.225 (0.403)	0.354 (0.179)	0.239 (0.373)	0.133 (0.624)	−0.125 (0.646)	0.276 (0.301)
Global memory	0.204 (0.449)	0.415 (0.110)	0.202 (0.454)	0.106 (0.696)	−0.137 (0.612)	0.327 (0.216)
MMSE	0.387 (0.139)	−0.034 (0.900)	0.552 (0.027)	0.453 (0.078)	−0.651 (0.006)**	−0.25 (0.337)

Values indicate *r* (*P*-value).

Significant differences are shown using asterisk (**). The level of significance for group differences was set at $P < .0167$ based on Bonferroni's correction for 3 correlations (FN, FA, and ADC).

ADC = apparent diffusion coefficient ($\times 10^{-3}$ mm^2/s), FA = fractional anisotropy, FN = fiber number, IQ = intelligence quotient, MMSE = mini-mental status examination.

hemispheres and neuropsychological subscores are summarized in Table 2.

At the affected side, the fornix FA was positively correlated with IQ and MMSE (IQ, $r = 0.638$, $P \leq .008$; MMSE, $r = 0.678$, $P \leq .004$ (Fig. 4A and B). In contrast, the fornix ADC was negatively correlated with IQ ($r = -0.602$, $P \leq .0014$), short-term memory ($r = -0.651$, $P \leq .006$), and MMSE ($r = -0.724$, $P \leq .002$) (Fig. 4C–E). No correlations were found between the fornix FA and memory scores. Interestingly, the fornix ADC was negatively correlated with MMSE at the unaffected side ($r = -0.651$, $P \leq .006$) (Fig. 4F). For the cingulum, no correlations were observed between all parameters and neuropsychological subscores at both sides.

Collectively, the results suggest that the fornix parameters at the affected side can be a good indicator of cognitive impairment in chronic patients with PH. Additionally, the significant damage of white matter at the unaffected side may influence cognitive impairment.

4. Discussion

Our study demonstrates the relationship between structural integrity of the neural tract and cognition in chronic patients with left PH. After PH, the fornix plays a critical role in cognitive impairment; structural changes of the fornix were observed at the affected as well as the unaffected side.

Similar to the subject of our chronic patient with brain injury, prior studies have revealed a relationship between the cingulum and cognition in TBI.[12,14,26] Notably, the cingulum was appeared as one of the major neural tracts involved in cognitive impairment and the cingulum FA was related to visuoperceptual ability, cognitive speed, language, verbal memory, and delayed recall.[14,26] Furthermore, the cingulum FA was significantly positively related to IQ and MAS, and the cingulum voxel number was related to MAS, implicating the cingulum parameters as useful indicators of cognitive impairment.[12] These results correspond with anatomical findings showing that the common sites of TBI are located at the frontal lobe and the corpus callosum close to the cingulum pathway.[27,28] However, application of these results to our study as a way of better understanding the mechanism of cognitive impairment is limited due to several issues. For TBI, shearing force plays a major role in the progression of the pathology. Moreover, while TBI is not always accompanied by hemorrhage, a hematoma caused by ICH that increases intracranial pressure may alter the cellular architecture in the brain.[29,30] Prior studies on the relationship between the injury of the fornix and/or cingulum and cognition in patients with ICH have focused on the acute stage.[16,17,21] Yeo et al[17] found that the complete disruption of the fornix body occurred in 10% of patients (6 of 58 patients) with acute ICH. In that study, no significant correlation was observed between the structural disruption of the fornix and MMSE scores. In a study of patients with ruptured anterior communicating artery aneurysm, cingulum injury occurred in 6 of 11 patients and fornix injury in 7 of 11 patients, but no relationship was evident between MMSE and parameters of the 2 neural tracts.[21] In another study, patients with bilateral cingulum injury after acute PH showed a significantly lower MMSE compared with the patients with a preserved cingulum or unilateral cingulum injury.[16] Those studies have drawn much attention as they showed, for the first time, the structures of the fornix and/or cingulum in a 3D view in acute patients with different types of ICH. Nevertheless, it remains unclear which neural tracts are specifically responsible for cognitive impairment depending on the site of ICH. One of the limitations of those studies is that only one neural tract—either the cingulum or fornix—was investigated to study its involvement in cognition. In addition, these studies used MMSE, this is a coarse and incomplete cognitive assessment. Although, anatomically, the cingulum is located farther from the putamen compared with the fornix, it is likely that cingulum injury may occur during acute large PH.

Reconstructing the neural tract of the fornix using DTT is difficult due to the large volume effect because of the close proximity of the fornix to the putamen, compared with that of the cingulum. Minimizing the volume effect is essential to clarify the mechanism of cognitive impairment after ICH. To resolve this hurdles, firstly, we recruited patients with at least 6 months after the onset of PH. We evaluated detailed their cognitive function

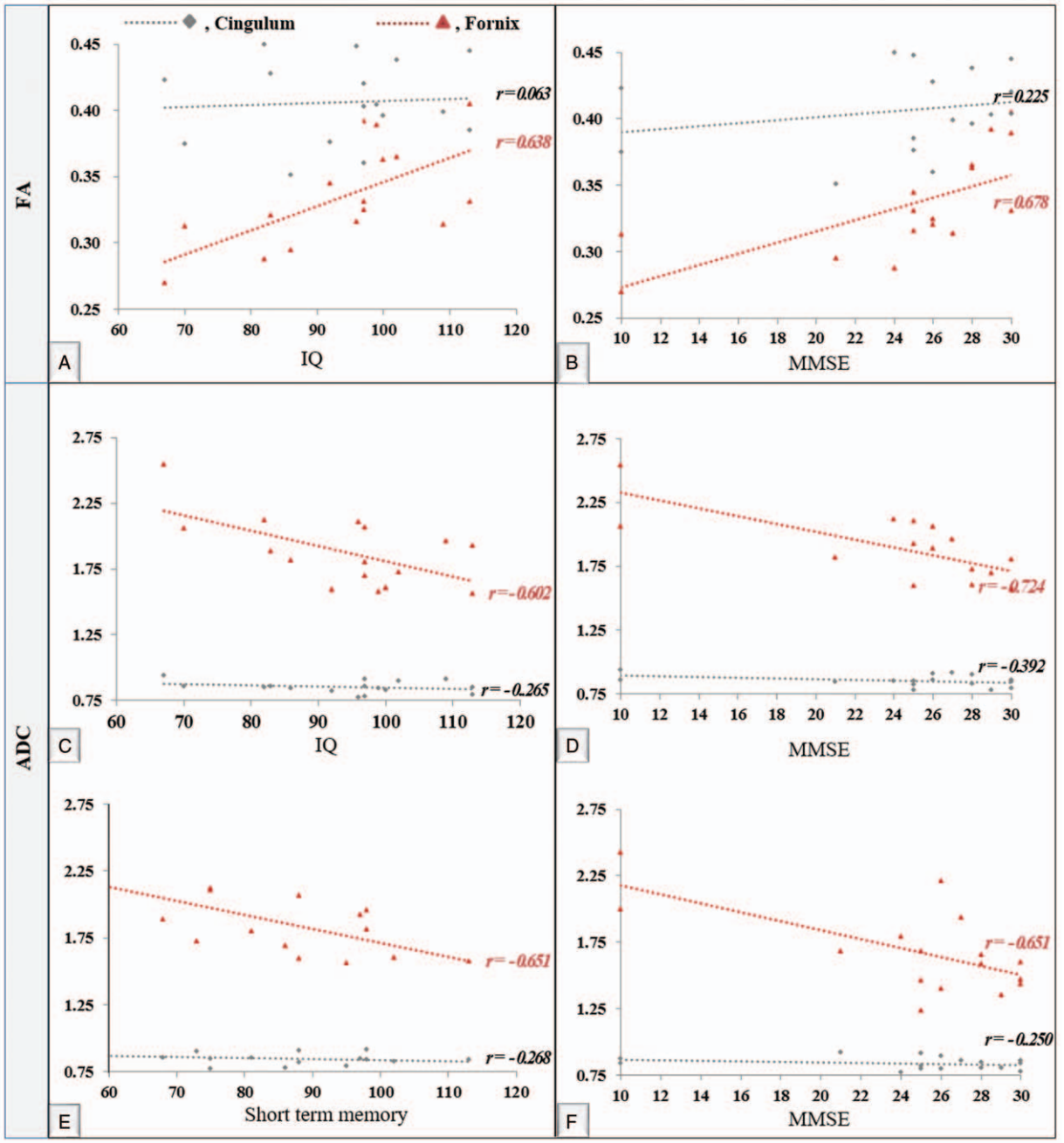

Figure 4. Relationship between parameters of the fornix and cingulum and neuropsychological subscores at the both sides in patient group. At the affected side, the fornix FA was positively correlated with IQ and MMSE (A and B), whereas the ADC was negatively correlated with short-term memory as well as IQ and MMSE (C, D, and E). At the unaffected side, the fornix ADC was negatively correlated with MMSE (F). ADC = apparent diffusion coefficient ($\times 10^{-3}$ mm^2/s), FA = fractional anisotropy, FN = fiber number, IQ = intelligence quotient, MMSE = mini-mental status examination.

using neuropsychological assessment as well as MMSE. Secondly, the enrolled patients were homogenous as only left hemisphere was damaged, which is important because the nature of memory impairment differs significantly depending on the location of the lesion.[31] These precautions allowed us to demonstrate significantly lower (16.5 points) verbal memory scores compared with visual memory scores. Thirdly, we simultaneously analyzed the relationship between neuropsychological subscores and the integrity of the fornix and cingulum. Using the condition of subjects and strictly quantitative methods, we demonstrated that only the fornix FA and ADC at the affected side were correlated with the neuropsychological results, which strongly suggests that fornix integrity is a good indicator of cognitive function after PH. The present results agree with prior studies that revealed the important role of the fornix in cognition. Zhuang et al[15] studied 206 patients with mild cognitive impairment and found a lower left fornix FA and higher radial diffusivity of the bilateral fornix in the amnestic group than in those with non-amnestic mild cognitive impairment. Another study compared changes of the neural tracts over time in control, mild cognitive impairment, and

Alzheimer disease groups.[32] In that study, the fornix was affected mostly during the mild cognitive impairment, and a mean diffusivity of the fornix was a better indicator of neural changes than FA of the fornix. In addition, a significant and notable correlation was observed between the mean diffusivity of the left fornix and the memory function in the patients with Parkinson disease.[33] Although there was no correlation with memory function, attention and language functions related to the cingulum parameters were shown.

Interestingly, our study found that the fornix ADC at the unaffected side was negatively correlated with MMSE. This result reflects the possibility that cognition in chronic patients with ICH is influenced by integrity of white matter at the affected and unaffected sides over time. Until now, only 2 studies have reported that a correlation between cognitive impairment and neural tract at both hemispheres in patients with cerebral infarct.[19,20] Dacosta-Aguayo et al[19] found that in poor cognitive stroke recovery group significantly different values of FA, axial and radial diffusivity of several white matter tracts at the unaffected hemisphere were observed compared with healthy control group. Furthermore, there were stronger disruptions of white matter at the unaffected hemisphere of the patient group. Another study suggested that a higher FA of the white matter at the unaffected side was related to a higher cognition, and a higher mean diffusivity of the white matter was linked to worse cognition.[20] The structural changes at the unaffected side were also observed in chronic patients with stroke in whom the posterior limb of internal capsule FA at the unaffected side was significantly correlated to the grip strength and hand dexterity during motor recovery.[18] In addition, complex network analysis in patients with left basal ganglia stroke has revealed reduced communicability not only at the affected hemisphere but also in homologous locations at the unaffected hemisphere.[34]

Our study is the first to show that in patients with ICH the integrity of the cognitive neural tract at the unaffected side is correlated with cognitive function. With regard to the structural changes of the neural tracts after ICH as described in Fig. 3, it is interesting to note that, except for the cingulum FA, all parameters of the fornix and cingulum showed significant differences at the unaffected as well as at the affected side between the patient and control groups, respectively. We postulate that these findings resulted from the resolution of hematoma or reorganization of the injured neural tracts after PH over time. It is assumed that normal FA means healing of injured neural fibers, whereas low FN with high ADC is a sequela of the ICH. The parameter of the FN reflects the volume or the number of neural fibers contained in the neural tract, in which the FA values indicate the integrity of the microstructure of axons and myelin, and the ADC values indicate a magnitude of water diffusion. Thus, the tightened fibers of axons in the white matter force water to diffuse in a more uniform direction parallel to axons, which are referred to as a high FA and low ADC.[28,35] In our study, the observations of low FA, high ADC, and low FN in chronic patients suggest that membrane degradation and cellular lysis of the neural fiber would provide more space for water to diffuse after ICH. Consequently, it is possible that the first ICH may have a long-term effect at the unaffected side of the fornix and cingulum through an accelerated degenerative process of the white matter at the affected hemisphere. The cingulum FA at the affected and unaffected hemispheres in the patient group was not significantly different compared with that of the control group regardless of the low FN and high ADC as shown in the fornix.

However, there are some limitations in the study. Firstly, we did not conduct a prospective longitudinal study, so it is hard to explain a causal relationship between the decreased integrity of the neural tracts and cognitive impairment in the patients with PH. Secondly, ROI analysis is not free from some degree of intra- and inter-subject variation because DTT analysis with algorithm of tract based spatial statistics was not performed. Lastly, we did not take account other neural tracts of limbic system such as mammillothalamic and thalamocingulate tracts.

5. Conclusions

The mechanism of the cognitive impairment after PH was investigated using DTT. Our findings suggest that the fornix is associated with the cognitive impairment after PH. In addition, PH may lead to structural changes at the unaffected side as well as at the affected side over time. These findings may contribute to the pathophysiologic mechanism of cognitive impairment and therapeutics after ICH.

Author contributions

Conceptualization: Jeong-Hee Yang, Dongseok Yang.
Data curation: Han Do Lee, So Young Kwak, Sung Ho Park, Dongseok Yang.
Formal analysis: Han Do Lee, So Young Kwak, Ki Hyun Byun, Sung Ho Park, Dongseok Yang.
Funding acquisition: Dongseok Yang.
Investigation: Jeong-Hee Yang, So Young Kwak, Ki Hyun Byun, Dongseok Yang.
Methodology: Han Do Lee, So Young Kwak, Sung Ho Park, Dongseok Yang.
Project administration: Jeong-Hee Yang, Han Do Lee, Dongseok Yang.
Resources: Han Do Lee.
Software: Jeong-Hee Yang, Han Do Lee, So Young Kwak, Sung Ho Park.
Supervision: Jeong-Hee Yang.
Validation: So Young Kwak.
Writing – original draft: Jeong-Hee Yang, Dongseok Yang.
Writing – review and editing: Jeong-Hee Yang, So Young Kwak, Dongseok Yang.

References

[1] Moulin S, Cordonnier C. Prognosis and outcome of intracerebral haemorrhage. Front Neurol Neurosci 2015;37:182–92.
[2] Benedictus MR, Hochart A, Rossi C, et al. Prognostic factors for cognitive decline after intracerebral hemorrhage. Stroke 2015;46: 2773–8.
[3] Biffi A, Bailey D, Anderson CD, et al. Risk factors associated with early vs delayed dementia after intracerebral hemorrhage. JAMA Neurol 2016;73:969–76.
[4] Moulin S, Labreuche J, Bombois S, et al. Dementia risk after spontaneous intracerebral haemorrhage: a prospective cohort study. Lancet Neurol 2016;15:820–9.
[5] Planton M, Saint-Aubert L, Raposo N, et al. High prevalence of cognitive impairment after intracerebral hemorrhage. PLoS One 2017;12: e0178886.
[6] Ghetti G. Putaminal hemorrhages. Front Neurol Neurosci 2012;30: 141–4.
[7] Inagawa T, Ohbayashi N, Takechi A, et al. Primary intracerebral hemorrhage in Izumo City, Japan: incidence rates and outcome in relation to the site of hemorrhage. Neurosurgery 2003;53:1283–97. discussion 1297-1288.
[8] Komiya K, Sakai Y, Horikoshi T, et al. Recovery process and prognosis of aphasic patients with left putaminal hemorrhage: relationship between

hematoma type and language modalities. J Stroke Cerebrovasc Dis 2013;22:132–42.
[9] Nagaratnam N, Saravanja D, Chiu K, et al. Putaminal hemorrhage and outcome. Neurorehabil Neural Repair 2001;15:51–6.
[10] Mori S, Aggarwal M. In vivo magnetic resonance imaging of the human limbic white matter. Front Aging Neurosci 2014;6:321.
[11] Thomas AG, Koumellis P, Dineen RA. The fornix in health and disease: an imaging review. Radiographics 2011;31:1107–21.
[12] Baek SO, Kim OL, Kim SH, et al. Relation between cingulum injury and cognition in chronic patients with traumatic brain injury; diffusion tensor tractography study. NeuroRehabilitation 2013;33:465–71.
[13] Fletcher E, Raman M, Huebner P, et al. Loss of fornix white matter volume as a predictor of cognitive impairment in cognitively normal elderly individuals. JAMA Neurol 2013;70:1389–95.
[14] Kurki T, Himanen L, Vuorinen E, et al. Diffusion tensor tractography-based analysis of the cingulum: clinical utility and findings in traumatic brain injury with chronic sequels. Neuroradiology 2014;56:833–41.
[15] Zhuang L, Wen W, Trollor JN, et al. Abnormalities of the fornix in mild cognitive impairment are related to episodic memory loss. J Alzheimers Dis 2012;29:629–39.
[16] Kwon HG, Choi BY, Kim SH, et al. Injury of the cingulum in patients with putaminal hemorrhage: a diffusion tensor tractography study. Front Hum Neurosci 2014;8:366.
[17] Yeo SS, Choi BY, Chang CH, et al. Injury of fornix in patients with intracerebral hemorrhage. Int J Neurosci 2012;122:195–9.
[18] Borich MR, Mang C, Boyd LA. Both projection and commissural pathways are disrupted in individuals with chronic stroke: investigating microstructural white matter correlates of motor recovery. BMC Neurosci 2012;13:107.
[19] Dacosta-Aguayo R, Grana M, Fernandez-Andujar M, et al. Structural integrity of the contralesional hemisphere predicts cognitive impairment in ischemic stroke at three months. PLoS One 2014;9:e86119.
[20] Schaapsmeerders P, Tuladhar AM, Arntz RM, et al. Remote lower white matter integrity increases the risk of long-term cognitive impairment after ischemic stroke in young adults. Stroke 2016;47:2517–25.
[21] Hong JH, Choi BY, Chang CH, et al. Injuries of the cingulum and fornix after rupture of an anterior communicating artery aneurysm: a diffusion tensor tractography study. Neurosurgery 2012;70:819–23.
[22] Han C, Jo SA, Jo I, et al. An adaptation of the Korean mini-mental state examination (K-MMSE) in elderly Koreans: demographic influence and population-based norms (the AGE study). Arch Gerontol Geriatr 2008;47:302–10.
[23] Wechsler D. Manual for the Wechsler Adult Intelligence Scale, Revised. 1st ed.Psychological Corporation, New York:1981.
[24] Williams J. Memory Assessment Scales: Professional Manual. Odessa, FL: Psychological Assessment Resources; 1991.
[25] Curtin F, Schulz P. Multiple correlations and Bonferroni's correction. Biol Psychiatry 1998;44:775–7.
[26] Sugiyama K, Kondo T, Oouchida Y, et al. Clinical utility of diffusion tensor imaging for evaluating patients with diffuse axonal injury and cognitive disorders in the chronic stage. J Neurotrauma 2009;26:1879–90.
[27] Malykhin N, Concha L, Seres P, et al. Diffusion tensor imaging tractography and reliability analysis for limbic and paralimbic white matter tracts. Psychiatry Res 2008;164:132–42.
[28] Zappala G, Thiebaut de Schotten M, Eslinger PJ. Traumatic brain injury and the frontal lobes: what can we gain with diffusion tensor imaging? Cortex 2012;48:156–65.
[29] Keep RF, Hua Y, Xi G. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets. Lancet Neurol 2012;11:720–31.
[30] Le TH, Gean AD. Imaging of head trauma. Semin Roentgenol 2006;41:177–89.
[31] Gillespie DC, Bowen A, Foster JK. Memory impairment following right hemisphere stroke: a comparative meta-analytic and narrative review. Clin Neuropsychol 2006;20:59–75.
[32] Nowrangi MA, Lyketsos CG, Leoutsakos JM, et al. Longitudinal, region-specific course of diffusion tensor imaging measures in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement 2013;9:519–28.
[33] Zheng Z, Shemmassian S, Wijekoon C, et al. DTI correlates of distinct cognitive impairments in Parkinson's disease. Hum Brain Mapp 2014;35:1325–33.
[34] Crofts JJ, Higham DJ, Bosnell R, et al. Network analysis detects changes in the contralesional hemisphere following stroke. NeuroImage 2011;54:161–9.
[35] Jones DK. Studying connections in the living human brain with diffusion MRI. Cortex 2008;44:936–52.