Abstract

Purpose: In general, confabulation is defined as confusion of reality with past events without apparent prompting, in association with disruption of the capacity for retrieval and encoding of memory. We report on a patient who showed spontaneous confabulation associated with injury of the Papez circuit following middle cerebral artery (MCA) infarction.

Methods: A 67-year-old female patient suffered cerebral infarct resulting from spontaneous MCA territory. After onset of the MCA infarct, she showed severe memory impairment and provoked confabulation. The Papez circuit was reconstructed for evaluation of part of it using diffusion tensor tractography (DTT). Fractional anisotropy (FA), mean diffusivity (MD), and tract volume were measured.

Results: The right thalamocingulate tract showed a significant decrement of FA value and tract volume, and an increment of MD value by more than two standard deviations of that of normal control subjects. The tract volume in the left fornix and mammillothalamic tract decreased by more than two standard deviations of that of normal control subjects.

Conclusion: Injuries of the Papez circuit were demonstrated in a patient who showed severe memory impairment and provoked confabulation following MCA infarct. We believe that analysis of the Papez circuit tract using DTT is useful in elucidating the cause of provoked confabulation in patients with MCA infarct.

Key Words: Diffusion tensor imaging, Papez circuit, Confabulation, Memory, Middle cerebral artery infarction
I. Introduction

The Papez circuit play an important roles as relay pathway for the memory encoding that is composed of the thalamocingulate tract, cingulum, fornix and mammillothalamic tract (Papez, 1937; Granziera et al, 2011; Concha et al, 2005; Kwon et al, 2010; Jang & Yeo, 2013). The prominent neuropsychological disturbances after injury of Papez circuit is known as global amnesia and cognitive impairment (DeLuca, 1993; Barba et al, 1997; DeLuca & Cicerone, 1991; Kapur & Coughlan, 1980; Schnider et al, 2005). On the other hand, as part of the Papez circuit, specific lesion in the orbitofrontal cortex, anterior cingulate cortex, thalamus and medial temporal lobe can cause the symptoms of confabulation (DeLuca, 1993; Schnider et al, 2005; Dalla Barba, 1993; Gilboa & Verfaellie, 2010; Nahum et al, 2012). The confabulation originates from the combination of amnesia and executive dysfunction; patient with spontaneous confabulation shows confusion of ongoing reality with past events, and provoked confabulation showed faulty memory with normal response by questions (Dalla Barba, 1993; Gilboa & Verfaellie, 2010; Nahum et al, 2012; Kopelman, 1987; Schneider et al, 1996). Understanding of the confabulation in stroke patients could provide useful information for clinicians and researchers in cognitive rehabilitation therapy for stroke rehabilitation.

The recent development of diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), enables visualization and localization of the neural tracts in the Papez circuit in three dimensions (Papez, 1937; Granziera et al, 2011; Concha et al, 2005; Kwon et al, 2010; Jang & Yeo, 2013). Several DTI studies have reported on injury of the components of Papez in patients with impairment of memory (Papez, 1937; Granziera et al, 2011; Concha et al, 2005; Kwon et al, 2010; Jang & Yeo, 2013). However, no study on injury of the Papez circuit in patients with confabulation using DTT has been reported so far.

In this study, using DTT, we investigated injury of the Papez circuit in a patient who showed confabulation following middle cerebral artery (MCA) infarction.

II. Methods

1. Case Presentation

One patient and six age-matched control subjects (three male; mean age: 61.3 years, range: 58-64) with no history of neurologic disease participated in this study. All subjects provided signed, informed consent, and Yeungnam University Hospital institutional review board approved the study protocol.

A 67-year-old, female patient underwent conservative treatment for a cerebral infarct resulting from spontaneous MCA territory at the neurology department of a university hospital (Fig.1-A). At three weeks after onset she was transferred to the rehabilitation department of the same university hospital in order to undergo rehabilitation. An MRI scan of the brain performed three weeks after onset revealed infarct lesions in the right MCA territory over the orbitofrontal cortex, basal ganglia, corona radiata, anterior cingulate cortex and premotor cortex (Fig.1-A). Since the onset of the MCA infarction, she suffered mild left side weakness with mild memory impairment and confabulation in her daily life at the hospital. She produced most of confabulation in informal conversation, both in answering specific questions and spontaneously. She believed that the hospital is her house and medical staffs are acquaintance with her from the past. In addition, she showed provoked confabulation by the specific question during the cognitive therapy.
2. Clinical evaluation

Cognitive function was evaluated using the Memory Assessment Scale (MAS), Wechsler Adult Intelligence Scale (WAIS) and Mini-Mental State Exam (MMSE) at four weeks after onset. The reliability and validity of MAS, WAIS and MMSE are well-established (Folstein et al, 1975; Williams, 1991). The patient showed mild memory impairment and normal cognitive function: in short-term memory (103: 58%ile), verbal memory (99: <47%ile), visual memory (73: <4%ile), global memory (83: <13%ile), and cognitive function (WAIS: 88, MMSE: 26).

For the provoked confabulation test, we used the Korean translation of five fables previously used for eliciting confabulations in a structured setting (Lorente-Rovira et al, 2010). The rater read each story to the patient while also viewing the written text, and immediately after, the patient was asked to recall the story. The subjects' responses were scored according to the following methods: a correctly recalled idea was scored as 1, a partially recalled idea as ½, and an idea not present in the story was coded as a confabulation. In the result of the confabulation test, the patient produced 5 items not present in the original story (mean confabulation items=2.73 according to Lorente-Rovira’s study (2010)) (Lorente-Rovira et al, 2010).

3. Diffusion tensor image tractography

DTI data were acquired at 3 weeks after onset using a 6-channel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Ltd, Best, The Netherlands) with single-shot echo-planar imaging. For each of the 32 non-collinear diffusion sensitizing gradients, 67 contiguous slices were acquired parallel to the anterior commissure-posterior commissure line. Imaging parameters were as follows: acquisition matrix = 96×96, reconstructed to matrix = 128×128 matrix, field of view= 221×221mm², TR= 10,726ms, TE = 76ms, parallel imaging reduction factor (SENSE factor) = 2, EPI factor = 49 and b=1000s/mm², NEX=1,and a slice thickness of 2.3mm (acquired isotropic voxel size 2.3×2.3×2.3mm³).

4. Probabilistic fiber tracking

Diffusion-weighted imaging data were analyzed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Head motion effect and image distortion due to eddy current were corrected by affine multi-scale two-dimensional registration. Fiber tracking was performed using a probabilistic tractography method based on a multifiber model, and applied in the current study utilizing tractography routines implemented in FMRIB Diffusion (5000 streamline samples, 0.5mm step lengths, curvature thresholds = 0.2). Each neural tract of the Papez circuit was determined by selection of fibers passing through seed and target regions of interest (ROI) as follows: Thalamocortical tract: seed ROI-the cingulate gyrus, 1st target ROI-anterior limb of the internal capsule, 2nd target ROI-anterior thalamic nuclei; Fornix: seed ROI-mammillary body, target ROI-crus of the fornix; Mammillothalamic tract: seed ROI - anterior thalamic nucleus, first target ROI-middle portion of the mammillothalamic tract, second target ROI-mammillary body; Cingulum: seed ROI-anterior pole of the superior cingulum, target ROI-posterior pole of the superior cingulum (Papez, 1937; Granziera et al, 2011; Concha et al, 2005; Kwon et al, 2010; Jang & Yeo, 2013). Values of fractional anisotropy (FA), mean diffusivity (MD), and tract volume of each neural tract of the Papez circuit were also measured.
### III. Results

The DTT parameters of each neural tract in the Papez circuit for the patient and normal control subjects are summarized in Table 1. The right thalamocingulate tract showed significant decrement of FA value and tract volume, and increment of MD value by more than two standard deviations of that of normal control subjects. The tract volume in the left fornix and mammillothalamic tract were decreased by more than two standard deviations of that of normal control subjects. On the DTT configuration of the Papez circuit in the patient, discontinuations were observed in right thalamocingulate tract and left crus of fornix. The right thalamocingulate tract between the anterior thalamic nuclei and cingulate gyrus was discontinued across the level of genu and body of the corpus callosum (Fig. 1-B).

### IV. Discussion

In the current study, partial injury of the Papez circuit was investigated in a patient with MCA infarction who showed confabulation with mild memory impairment. The thalamocingulate tract showed significant decrement of FA value and tract volume, and increment of MD value in ipsi-lesional hemispheres. In addition, the fornix and mammillothalamic tract showed significant decrement of the fiber volume in the contra-lesional hemisphere. The FA value represents the white matter organization: in detail, the degree of directionality and integrity of white matter microstructures such as axon, myelin, and microtubule, and MD value indicates the magnitude of water diffusion (Seo & Jang, 2013). The tract volume is determined by the number of voxels contained within a neural tract (Assaf & Pasternak, 2008). Therefore, the decrement of FA value and tract volume and increment of MD value in the thalamocingulate tract appear to indicate injury of these neural tracts, and the decrement of the tract volume in the fornix and mammillothalamic tract may reflect the degree of the injury.

Table 1. Diffusion tensor tractography parameters of the Papez circuit in the patient and normal subjects

<table>
<thead>
<tr>
<th></th>
<th>Thalamocingulate tract</th>
<th>Cingulum</th>
<th>Fornix</th>
<th>MTT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FA</td>
<td>0.33*</td>
<td>0.33</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>0.81**</td>
<td>0.91</td>
<td>1.34</td>
</tr>
<tr>
<td>Rt</td>
<td>FA</td>
<td>0.43</td>
<td>0.38</td>
<td>0.29</td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>0.80</td>
<td>0.79</td>
<td>1.53</td>
</tr>
<tr>
<td></td>
<td>TV</td>
<td>652.00</td>
<td>734.00</td>
<td>148.00*</td>
</tr>
<tr>
<td>Lt</td>
<td>FA</td>
<td>0.42 (0.03)</td>
<td>0.37 (0.03)</td>
<td>0.32 (0.03)</td>
</tr>
<tr>
<td></td>
<td>MD</td>
<td>0.77 (0.01)</td>
<td>0.83 (0.06)</td>
<td>1.57 (0.24)</td>
</tr>
<tr>
<td></td>
<td>TV</td>
<td>444.17 (152.20)</td>
<td>725.33 (348.84)</td>
<td>549.67 (189.89)</td>
</tr>
</tbody>
</table>

Data are presented as mean (±standard deviation) FA: fractional anisotropy; MD: mean diffusivity; TV: tract volume; MTT: mammillothalamic tract

*more than two standard deviations lower than that of normal control value

**more than two standard deviations higher than that of normal control value
tract also appears to indicate injury of the neural tract. In the results of DTT configuration, discontinuations of the thalamocingulate tract in ipsi-lesional hemisphere and the crus of fornix in contra-lesional hemisphere also suggest injury of the neural tracts. We believe that these partial neural injuries of the Papez circuit in this patient...
might be concerned with confabulation.

The thalamocingulate tract, component of Papez circuit, was known as originated from the anterior thalamic nuclei and terminated at the anterior cingulate cortex through the genu and anterior limb of the internal capsule. Several previous studies suggested that the cingulate cortex is critical region for production of confabulation. In 2008, Turner et al. suggested that the single lesion of the anterior cingulate cortex can be concerned with transitory confabulation in the acute phase, and chronic confabulation had relevance to additional ventral damage in the prefrontal cortex (Turner et al, 2008). In 2012, Kozlovskiy et al. reported that the size of the anterior cingulate cortex in the healthy elderly people has negative correlation with number of confabulations in semantic-coding tests (Kozlovskiy et al, 2012). Recently, Ghosh et al (2014) reported that the confabulation patients by rupture of anterior communicating artery (ACoA) aneurysm showed common lesion in the subgenual cingulate cortex with orbitofrontal cortex (Ghosh et al, 2014).

On the other hand, as a part of fornix and mammillothalamic tract, anterior nuclei of the thalamus transfers afferent signals to the cingulate cortex through the thalamocingulate tract (Hayashi et al, 2003; Nys et al, 2004). Therefore, thalamic region is also critical region for production of confabulation. In 2003, Hayashi et al. reported on a patient who developed amnesia and confabulation after the left thalamic infarction (Hayashi et al, 2003). They suggested that the lesion of the thalamus can caused the disturbance of connectivity with the left frontal lobe, and as a result, these dysfunctions caused the confabulation and abnormal verbal response in a patient. In 2004, Nys et al. reported on a patient with spontaneous confabulation following bilateral thalamic infarction involving the territory of the paramedian arteries (Nys et al, 2004). We think that these results of previous studies are compatible with the results of the current study, which showed confabulation in a patient following injury of the thalamocingulate tract, fornix, and mammillothalamic tract. However, to the best of our knowledge, this is the first study demonstrating occurrence of confabulation in a patient with injury of the Papez circuit by MCA territory infarction, using DTI. However, limitations of this study should be considered. DTI analysis is operator dependent and, due to fiber complexity and crossing fiber effect, it may underestimate the fiber tracts (Yamada et al, 2009).

V. Conclusion

In conclusion, specific and partial injury of the Papez circuit was demonstrated in a patient with confabulation following MCA territory infarction. It appears that the specific and partial injury related with the cingulate cortex and thalamic regions can be associated with confabulation in patients with MCA territory infarction. Conduct of further studies involving large numbers of patients and more detailed evaluation of confabulation according to injury of the Papez circuit should be encouraged.

References

Kwon HG, Hong JH, Jang SH. Mammillothalamic tract in


