doi:10.1093/brain/awn311 Brain 2009: 132; 369–376 | 369

BRAIN
A JOURNAL OF NEUROLOGY

Mammillothalamic functional connectivity and memory function in Wernicke's encephalopathy

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There is still debate over the neural mechanisms underlying pathogenic and even recovery processes of Wernicke's encephalopathy. Therefore, we attempted to validate the usefulness of resting-state functional connectivity analysis in assessing memory function and its neural correlation with the mammillothalamic tract in patients recovering from Wernicke's encephalopathy. Seven chronic alcoholics recovering from Wernicke's encephalopathy, 14 alcoholic comparisons without Wernicke's encephalopathy, and 14 healthy comparisons underwent functional connectivity MRI scans, as well as verbal and non-verbal memory tests after at least a 1 month abstinence from alcohol. Resting-state functional connectivity strength between the anterior thalamus and the mammillary bodies was investigated by calculating temporal correlations in magnetic resonance signal levels between the two regions during a 5-min passive viewing task. The mean values of the functional connectivity strength between the left anterior thalamus and the ipsilateral mammillary body differed significantly between Wernicke's encephalopathy patients and healthy comparisons ($P = 0.014$). This connectivity strength in alcoholic comparisons fell between those of the former two groups, with a significant difference from that of healthy comparisons ($P = 0.038$). In addition, the strength of this left-sided functional connectivity significantly correlated with delayed verbal recall scores ($r = 0.771$, $P = 0.042$) and verbal recognition score ($r = 0.825$, $P = 0.022$) in patients with Wernicke's encephalopathy. Our findings indicate that memory function in patients recovering from Wernicke's encephalopathy parallels the level of the mammillothalamic functional connectivity; this supports the usefulness of resting-state functional connectivity analysis as a practical alternative to pathological examination of the mammillothalamic tract in living patients with Wernicke's encephalopathy.

Keywords: Wernicke's encephalopathy; memory; mammillothalamic tract; resting-state functional connectivity

Introduction

Wernicke's encephalopathy, an acute neuropsychiatric disorder caused by deficiency of vitamin B1, also known as thiamine, can progress to a chronic amnesic state called Korsakoff's syndrome (Kopelman, 1995; Sechi and Serra, 2007). Given this pathophysiological continuum, these two conditions are often coupled and known as the Wernicke-Korsakoff syndrome, which is seen mostly in patients with chronic alcohol dependence and is a relatively persistent condition (Mair *et al*., 1979). However, recent

Received July 23, 2008. Revised October 2, 2008. Accepted October 30, 2008. Advance Access publication November 26, 2008

studies have suggested that Korsakoff's syndrome is not inevitable in alcoholics with Wernicke's encephalopathy (Caine *et al*., 1997; Chu *et al*., 2002; Thomson and Marshall, 2006).

There has been extensive debate on critical lesions for memory deficits in Wernicke's encephalopathy (Harding *et al*., 2000; Aupee *et al*., 2001; Chu *et al*., 2002). This uncertainty may be ascribed in part to the impossibility of a confirmatory pathological examination in the brain of living patients. Another equally important explanation may come from the disregard for the inter- and intra-connecting properties of brain structures, which have generally been examined as discrete units (Markowitsch, 1984; Vann and Aggleton, 2004). Even a small disruption of neural connectivity might exert a significant impact on memory function rather than a comparable injury *per se* within either one of the interconnected gross structures (Tatemichi *et al*., 1992; Kim *et al*., 1994; Aggleton *et al*., 1995; Aupee *et al*., 2001; Yoneoka *et al*., 2004). Conversely, subtle recovery of the connectivity may practically contribute to a significant improvement in cognitive function. One method to practically link such connectivity with memory function in living patients may be the resting-state functional connectivity study using MRI. Recently, this approach has received increasing attention for its unique advantages in both theoretical and practical aspects, particularly in studies with cognitively compromised patients (Liu *et al*., 2008).

Therefore, to examine the potential usefulness of this method, we measured memory function and resting-state functional connectivity strength between the two most relevant regions in Wernicke's encephalopathy: the anterior thalamus (Harding *et al*., 2000) and mammillary bodies (Vann and Aggleton, 2004). Our hypothesis is that resting-state functional connectivity of the mammillothalamic tract would be reduced in patients recovering from Wernicke's encephalopathy compared with healthy normal controls. We also predicted that functional connectivity strength would be associated with memory function in patients recovering from Wernicke's encephalopathy.

Methods

Subjects

Seven chronic alcoholic patients who were admitted to a university hospital with a diagnosis of Wernicke's encephalopathy were included in our study. Fourteen alcoholic comparisons without Wernicke's encephalopathy and 14 healthy comparisons with social drinking were also included. The diagnosis of Wernicke's encephalopathy was made on the basis of the operational criteria proposed by Caine *et al*. (1997); the item of dietary deficiency was applicable to all Wernicke's encephalopathy patients and any of other three items applied in each subject are described in Table 1. The definition of the social drinking was based on the Clinician's Guide provided by the National Institute on Alcohol Abuse and Alcoholism (NIAAA, 2005), i.e. consuming not more than four standard drinks in a day or not more than 14 drinks per week. All subjects were right-handed. Exclusion criteria were a history of stroke, severe head trauma or other neurologic and psychiatric disorders. Any individuals who were suspected to have acute alcoholic hepatitis or hepatic encephalopathy were not included in this study, either. In fact, two candidates initially supposed to have Wernicke's encephalopathy were ineligible to participate in the study as they were later found to have hepatic encephalopathy. One alcoholic patient without Wernicke's encephalopathy and one with Wernicke's encephalopathy had Type 2 diabetes. Another patient without Wernicke's encephalopathy had the serum levels of liver enzymes (AST/ALT) more than two times the upper limit of normal value (<40 IU/l) and was found to have fatty liver, suggesting chronic alcoholic liver disease. Only 3 out of 14 alcoholic comparisons without Wernicke's encephalopathy and two out of seven Wernicke's encephalopathy patients were found to have normal gamma-GT level (<30 IU/l), suggesting that the rest of the patients might have had chronic liver disease due to their chronic alcohol abuse. However, none of these hepatic conditions including the abnormal liver function test in isolation is considered sufficient to meet the Caine's criteria (Caine *et al*., 1997) for the Liver Disease domain, such as jaundice, haematemesis, melaena, ascites and asterixis.

All patients except for two alcoholic comparisons were in-patients in a closed ward. MRI scan and memory tests were conducted during the hospitalization period; abstinence from alcohol in the two out-patients was verified based on self-reports and reports from their caregivers. We regarded these as reliable since they had regular follow-up visits to our out-patient clinic. The characteristics of the subjects are summarized in Table 1. Image scans and memory functions were examined after at least a 1-month duration of both alcohol abstinence and thiamine replacement therapy according to the guidelines of Thomson *et al*. (2002). Wernicke's encephalopathy patients received daily intravenous infusions of 1000 mg of thiamine during the acute phase, followed by daily oral administration of 300 mg of thiamine, while patients without Wernicke's encephalopathy received 120 mg of thiamine perorally from the outset. We conducted MRI scan and memory tests in Wernicke's encephalopathy patients after remission of the acute phase, which was judged when clinical signs were no longer improved apparently as before under the ongoing thiamine administration. Therefore, at the time of examination, both Wernicke's encephalopathy patients and alcoholic comparisons were receiving peroral thiamine. Memory function was evaluated by the Korean Auditory Verbal Learning Test (Cheong *et al*., 1999) for verbal memory and Rey Complex Figure Test (Kim *et al*., 2005) for non-verbal memory. Informed consent was obtained from all subjects and this study was approved by the Institutional Review Board of Severance Mental Health Hospital.

Functional MRI acquisition/ preprocessing

Subjects underwent a 5-min passive-viewing block scan and were instructed to fixate on a white crosshair in the center on a screen with a black background and refrain from any cognitive, lingual or motor tasks as much as possible.

Functional images were acquired on a 1.5 T GE scanner and the data were collected using a gradient echo EPI sequence (TR = 2 s, TE = 14.3 s, flip angle = 90°, field of view = 240 mm, 64 × 64 × 30 matrix with 3.75 × 3.75 × 5 mm spatial resolution, 30 axial slices and slice thickness = 5 mm). A high-resolution anatomical dataset was obtained for each subject using a fast spoiled gradient-echo sequence (TR = 8.5 s, TE = 1.8 s, flip angle = 12°, field of view = 240 mm, 256 × 256 × 256 matrix with 0.94 × 0.94 × 1.5 mm spatial resolution, 116 axial slices and slice thickness = 1.5 mm). The fMRI data were preprocessed using the Analysis of Functional Neuroimage (AFNI) software (Cox, 1996). The first five time points in all of the time series datasets were discarded. Slice timing correction, motion correction and mean-based intensity

Table 1 Demographic and clinical characteristics of subjects

	Alcoholics with Wernicke's Encephalopathy (7 males)								Alcoholics without Wernicke's encephalopathy (14 males) Mean (SD)	Healthy social drinkers[e] (14 males) Mean (SD)	*P*-value
	Subject A	Subject B	Subject C	Subject D	Subject E	Subject F	Subject G	Mean (SD)			
Age (years)	50	52	68	45	63	41	69	55.4 (11.2)	53.9 (9.3)	53.9 (6.9)	0.942
Education (years)	14	16	18	9	8	16	6	12.4 (4.7)	12.5 (3.2)	14.2 (2.6)	0.354
Wernicke's symptoms[a]	+++	++	+++	+++	+++	++	+	–	–	–	
Duration of abstinence (days)	93	70	83	37	30	38	30	54.4 (26.8)	90.5 (75.4)	–	0.154
Duration of heavy drinking (years)								7.9 (4.4)	7.1 (5.7)	–	0.767
Lifetime alcohol consumption ($\times 10^3$ drinks[b])								85.7 (39.2)	59.6 (57.8)	–	0.310
Intelligence quotient[c]	105	104	124	90	101	112	94	104.3 (11.3)	113.5 (17.6)	122.2 (14.9)	0.059
Memory scores[d]											
Immediate verbal recall	10	9	9	4	10	11	8	8.7 (2.3)	11.8 (3.2)	10.9 (2.6)	0.097
Delayed verbal recall	9	4	8	2	9	12	3	6.7 (3.7)	12.5 (2.6)	11.6 (3.0)	0.002
Verbal recognition	9	4	10	4	10	14	6	8.1 (3.7)	12.7 (3.1)	11.8 (2.7)	0.017
Immediate non-verbal recall	8	4	8	4	6	11	3	6.3 (2.9)	10.0 (1.6)	10.8 (2.8)	0.002
Delayed non-verbal recall	7	2	7	4	5	10	3	5.4 (2.8)	10.2 (2.3)	10.2 (3.1)	0.001

[a] +++ = Confusion, ophthalmoplegia, ataxia were all present; ++ = confusion, ataxia were present; + = only confusion was present.
[b] One drink = about 12 g of alcohol.
[c] Evaluated by the Korean version of the Wechsler Adult Intelligence Scale.
[d] Evaluated by Korean Auditory Verbal Learning Test for verbal memory and Rey Complex Figure Test for non-verbal memory (9–11: normal; 7–8: borderline; $\leqslant$6: defective level).
[e] Social drinking was defined as not more than 4 standard drinks in a day or not more than 14 drinks per week according to the NIAAA guide (2005).

normalization were performed for all slices within a volume. Spatial normalization was performed to transform the Talairach space using the Montreal Neurological Institute (MNI) N27 template provided in the AFNI package (bilinear interpolation, spatial resolution: $2 \times 2 \times 2$ mm). Further processing included spatial smoothing [Gaussian filter with 6-mm full-width at half-maximum (FWHM)], and then the data were temporally band-pass filtered (0.01–0.08 Hz) to reduce low frequency fluctuation of the signal in the blood oxygen level dependent (BOLD) signal for functional connectivity analysis (Biswal *et al*., 1995; Greicius *et al*., 2003).

Defining regions of interest

The anterior thalamus and mammillary bodies were identified in the coronal and axial section on MRI. Instead of delineating the boundaries of the whole structure, we defined a seed (a 4-mm and a 2-mm radius sphere for the anterior thalamus and the mammillary bodies, respectively) within each region (Fig. 1A). The location of the seeds was modified manually until it was actually placed within the boundaries of the anterior thalamus and mammillary bodies, referring to the fields used in previous volumetric studies (Visser *et al*., 1999; Callen *et al*., 2001; Bernasconi *et al*., 2003).

Functional connectivity analysis

The seed reference time series was calculated by extracting and averaging time series data from the subject-specific defined regions of interest (ROIs) within the anterior thalamus. A correlation map of the anterior thalamus was obtained via correlation analysis between the seed reference time series (from the left and right anterior thalamus) and the time series from the rest of the whole brain in a voxel-wise manner for each subject. Then, the functional connectivity map was generated by converting the correlation coefficients to *z*-values representing functional connectivity strength with the anterior thalamus using Fisher's *r*-to-*z* transformation $z = 0.5 \times \log[(1+r)/(1-r)]$, where r is the correlation coefficient at each voxel, to improve the normality of correlation coefficients (Zhou *et al*., 2007). This transformation yielded an approximately Gaussian distribution of connectivity strength for the functional connectivity map of each subject. By fitting the distribution [restricted to full-width at half maximum (FWHM)] with a Gaussian and adjusting for mean and standard deviation, the data from the functional connectivity map were transformed to a standard normal distribution. The *z*-value for each voxel was then corrected by subtracting the mean of the Gaussian fit and dividing by the standard deviation of the Gaussian fit (Lowe *et al*., 1998; Hampson *et al*., 2002), and then the averaged functional connectivity strengths were extracted from the transformed functional connectivity map with the anterior thalamus using defined ROIs (both hemispheres of the anterior thalamus and mammillary bodies, respectively) for each subject.

Data analysis

The normality of the data was confirmed by using the Kolmogorov-Smirnov test. We compared resting-state functional connectivity strength in each side hemisphere and the mean scores of memory function tests between groups by a multiple analysis of variance (MANOVA). Equality of covariance matrices was confirmed by Box's test and that of error variances by Levene's test. The results of *post hoc* comparisons were presented by using least significant difference method. The difference in connectivity strength between the right and left hemispheres within a group was examined using paired *t*-test. Pearson correlation analysis was conducted to qualify the correlation between functional connectivity strength and memory scores. Statistical analyses were conducted by using SPSS 12.0 (Chicago, IL) with two-tailed $P < 0.05$.

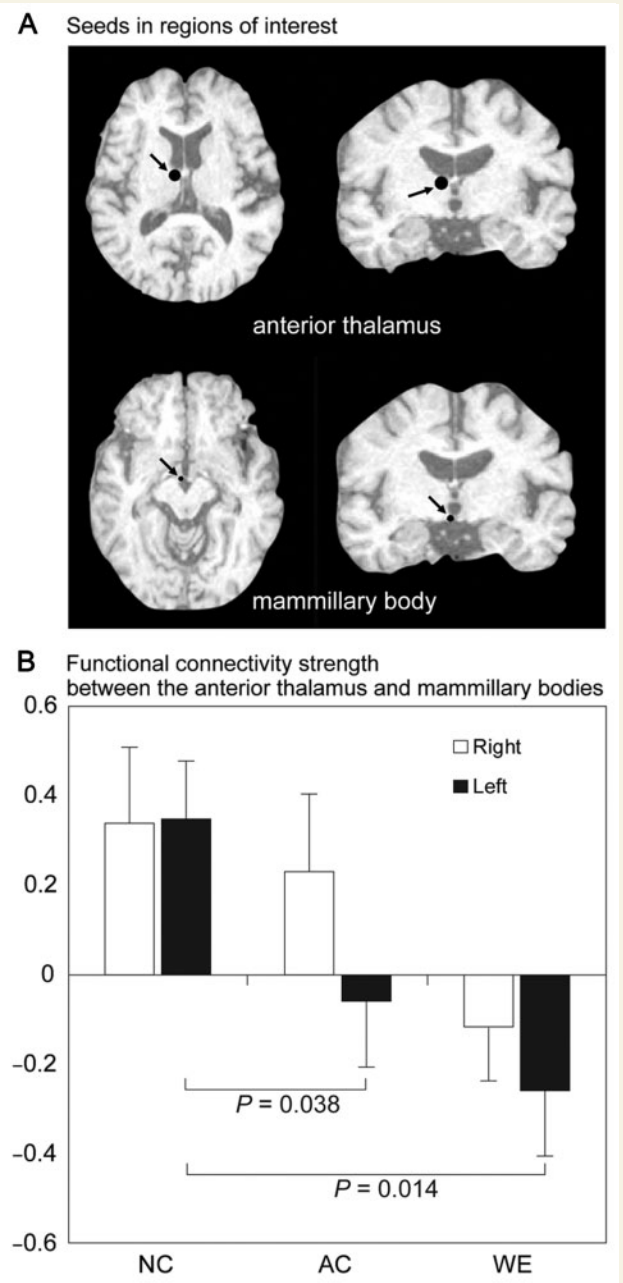

Fig. 1 Resting-state mammillothalamic functional connectivity. (**A**) The regions of interest are demonstrated. The round area indicated by an arrow is a defined seed for each region. (**B**) The mean mammillothalamic functional connectivity strength (Mean ± SE) was significantly more reduced in alcoholics with Wernicke's encephalopathy (WE) than in healthy comparisons (NC), with a statistically significant between-group difference in left-sided ones (MANOVA; right, $P = 0.266$; left, $P = 0.025$). The mean connectivity strength of alcoholic comparisons (ACs) without Wernicke's encephalopathy fell between those of healthy comparisons and Wernicke's encephalopathy patients.

Results

We obtained functional connectivity maps from the anterior thalamus in each of the three groups and they each seemed to show different coactivation patterns (see online Supplementary materials).

Connectivity strength between the anterior thalamus and mammillary bodies was more reduced in Wernicke's encephalopathy patients than in healthy comparisons (Fig. 1). The degree of the connectivity strength of alcoholic comparisons fell between those of the other two groups. However, statistically significant between-group differences were observed only in the left hemisphere [MANOVA; for the left, $F(2,32) = 4.13$, $P = 0.025$; for the right, $F(2,32) = 1.31$, $P = 0.266$]. Within-group differences in mammillothalamic connectivity strength between the right and left hemispheres was not significant in any of the groups (paired t-test; for Wernicke's encephalopathy patients, $t = 0.686$, $P = 0.518$; for healthy comparisons, $t = 1.445$, $P = 0.172$; for alcoholic comparisons, $t = 0.045$, $P = 0.965$).

In Wernicke's encephalopathy patients, left-sided mammillothalamic connectivity strength correlated with scores of verbal memory tests such as delayed verbal recall and recognition (Fig. 2). Significant correlations were also seen between left-sided connectivity strength and all memory scores except immediate verbal recall when combining the data of healthy comparisons with those of Wernicke's encephalopathy patients ($r = 0.517$–0.610, $P = 0.004$–0.020), but no such correlations were observed in data from all subjects including alcoholic comparisons (all $P > 0.112$). This could be accounted for by normal levels of memory performance but significantly reduced connectivity strengths in the alcoholic comparison group. The connectivity strength was not associated with age, education or intelligence in any of the groups, or with the duration of abstinence or the amount of lifetime alcohol consumption in the alcohol comparison and Wernicke's encephalopathy groups (data not shown).

Discussion

We measured the resting-state functional connectivity between the anterior thalamus and the mammillary bodies in patients recovering from Wernicke's encephalopathy compared with alcoholic comparisons without Wernicke's encephalopathy and healthy social drinkers. Our findings indicate that mammillothalamic functional connectivity is impaired in Wernicke's encephalopathy patients (Fig. 1B) and may index the degree of their improvement of verbal memory (Fig. 2). However, a significant difference in the connectivity and its correlation with verbal memory scores were only observed in the left hemisphere, partially consistent with the general dichotomy of left-verbal/right-nonverbal memory (Kelley *et al*., 1998). Some speculations could be made with respect to this finding.

First, this finding might suggest that the damage in left mammillothalamic connectivity is more crucial to the pathogenesis of Wernicke's encephalopathy than in the right. Alternatively, verbal memory dysfunction associated with damaged connectivity in the left may be a more easily detectable phenotype of Wernicke's encephalopathy to clinicians than non-verbal memory dysfunction. Thus, there could be a possibility that patients with more apparent functional damage in the left rather than the right hemisphere could be more readily detected and recruited in our study. However, in addition to verbal memory, non-verbal memory was also impaired in our Wernicke's encephalopathy patients. Furthermore, the connectivity did not differ between the right and left hemispheres among Wernicke's encephalopathy patients. Thus, our results on the whole are likely to support neither more susceptibility nor more pathoetiological role of the left-sided connectivity over the right-sided one. Taken together, we assumed that impairment of the connectivity in the right hemisphere might be as true as it is in the left although between-group differences of right-sided connectivity were not proven statistically in this study. Insufficient sample size, particularly in Wernicke's encephalopathy patients, may be responsible for the negative result in right-sided connectivity.

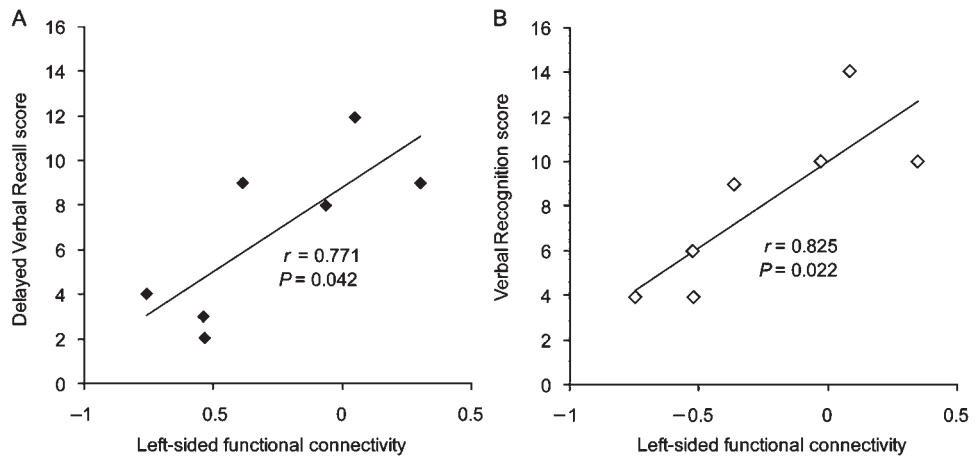

Fig. 2 Functional connectivity strength and memory deficits. The relationship between left-sided mammillothalamic connectivity strength and delayed verbal recall memory (**A**) and verbal recognition memory (**B**).

Meanwhile, most of the lesions that were found to cause amnesia clinically similar to Wernicke-Korsakoff syndrome in many previous case reports were in the left (anterior) thalamus (Goldenberg *et al*., 1983; Mori *et al*., 1986; Cole *et al*., 1992; Kim *et al*., 1994; Parkin *et al*., 1994; Rahme *et al*., 2007; Shim *et al*., 2008). These reports may collectively support the speculation that dysfunctions in left-sided connectivity might be critical in the development of Wernicke's encephalopathy rather than the right. However, there have also been studies, though more limited, of the right anterior thalamic lesion resulting in the same condition (Daum and Ackermann, 1994; Schnider *et al*., 1996). Furthermore, most of the studies with Wernicke's encephalopathy resulting from thiamine deficiency rather than infarct lesions have reported bilateral and symmetric lesions in key regions in Wernicke's encephalopathy (Gallucci *et al*., 1990; Chu *et al*., 2002; Weidauer *et al*., 2003; Zuccoli *et al*., 2007). In regard to this controversy, a report by Yoneoka *et al*. (2004) seems to be highly implicative. They reported an acute Korsakoff patient with localized bilateral infarction of the mammillothalamic tracts and identified that the left lesion was new and the right was old using T_2-weighted MRI. Notably, it was found that the patient had had no apparent symptoms of memory disorder while having had only the right-sided lesion (Yoneoka *et al*., 2004). This finding may suggest that bilateral mammillothalamic tract dysfunctions are necessary (or sufficient) to develop fully apparent symptoms of Korsakoff's syndrome but still leave the possibility that the left- rather than right-sided impairment in the functional connectivity might be essential to the ultimate development of clinical signs of the syndrome.

Beyond the 'statistical' between-group differences, the finding of the negative values of the mean connectivity strength in Wernicke's encephalopathy patients may also have a 'clinical' implication in that a negative value *per se* may indicate erroneous function in the network rather than merely a lesser degree of connectivity. Indeed, Fig. 2 shows that the closer the mammillothalamic connectivity strength of recovering Wernicke's encephalopathy patients approaches positive values from negative ones, the closer the memory scores reach normal range. Furthermore, our assumption that resting-state functional connectivity may reflect structural disruption in a neural tract is supported by a recent investigation (Greicius *et al*., 2008).

Recently, it has been suggested that in a significant portion of Wernicke's encephalopathy patients, memory dysfunctions or brain lesions could be substantially recovered through aggressive thiamine replacement therapy (Chu *et al*., 2002; Thomson and Marshall, 2006). However, the neurological process underlying such functional recovery is still unclear; it has not been fully understood whether recovery from Wernicke's encephalopathy is mediated simply by restoration of previously damaged brain regions (Chu *et al*., 2002) or if it depends on compensatory recruitment of other memory-neural networks such as a direct hippocampal and cingulate pathway (Harding *et al*., 2000), hippocampal-anterior thalamus axis (Aggleton and Brown, 1999) or amygdaloid (basolateral limbic) circuit (Yoneoca *et al*., 2004). The mammillothalamic tract is believed to be an intermediate pathway conveying information from the hippocampus ultimately to the frontal cortex via the anterior thalamus (Yoneoca *et al*., 2004). A recent functional MRI study in a case of Wernicke-Korsakoff syndrome demonstrated that, in contrast to normal controls, the patient did not show hippocampal activation during memory tasks even without damage to the medial temporal lobe (Caulo *et al*., 2005), suggesting failure of the hippocampal-anterior thalamic axis recruitment in this condition (Aggleton and Brown, 1999). On the other hand, our finding of normal memory but impaired mammillothalamic connectivity in alcoholic comparisons rather suggests the possibility that alcoholics without Wernicke's encephalopathy could have mobilized other memory networks to compensate for reduced functional connectivity of the mammillothalamic tract. This topic still remains a subject of interest for further studies.

Therefore, the primary implication of the current study might be that it provides potential evidence that the improvement of objective memory function in patients recovering from Wernicke's encephalopathy parallels the degree of recovery in mammillothalamic connectivity. However, this issue would be more adequately approached by measuring the connectivity and memory functions during and after the acute phase of Wernicke's encephalopathy or during the recovery phase. As described in the Methods section, we measured the connectivity and memory function only once when the acute phase was thought to have passed; which is an important limitation of this study. In fact, we had originally planned to measure it during and after the acute phase to identify the change in the functional connectivity as the acute condition improved. However, it was difficult to achieve the cooperation of Wernicke's encephalopathy patients in such an acute state of confusion. We changed our plan to examine the connectivity among patients who were clinically recovered or still impaired in memory function following the acute phase treatment of Wernicke's encephalopathy. Figure 2 may be indicating this point, showing that Wernicke's encephalopathy patients whose memory functions were still impaired also had impaired connectivity while those with normally recovered memory functions had higher connectivity strengths that were above or close to zero value. Therefore, although we failed to show the changes in the functional connectivity between the acute stage and follow-up in the same individuals, our results could be suggesting that functional abnormalities still exist, at least in some Wernicke's encephalopathy patients, despite the aggressive thiamine replacement therapy, while improvement of the connectivity can be seen in those with normalized memory scores. In turn, this can raise the concerns for factors influencing reversibility and the diagnostic or prognostic differentiation between Wernicke's encephalopathy and Korsakoff's syndrome. However, since no information on follow-up examination of our patients is now available, it is difficult to address these issues further in the current study.

Lastly, our results should be interpreted with a great deal of caution based on the small sample size. We cannot address the cause-and-effect issues owing to the cross-sectional comparison study design. Therefore, our data should be regarded as provisional in nature, describing the potential usefulness of the resting-state functional connectivity study in examining Wernicke's encephalopathy patients, although the statistical results were presented for the sake of clarity. The medication effect might also confound our results. The total dosage and route of thiamine administration differed between patients with and without

Wernicke's encephalopathy (see Methods section). Thus, there is a possibility that these differences could contribute to between-group differences in the connectivity or memory function. However, because total dosage was higher in Wernicke's encephalopathy patients and intravenous administration is regarded as more aggressive treatment, differences in dosage and route are not likely to have contributed to increasing the between-group differences in the connectivity or memory. On the other hand, it may be notable that the apparent effect of thiamine replacement therapy on the connectivity or memory function was observed in only some but not all Wernicke's encephalopathy patients as indicated in Fig. 2. To confirm the diagnostic and prognostic validity and the neuropsychological correlation of the mammillothalamic functional connectivity, a prospective study with a larger sample size is warranted.

Supplementary material

Supplementary material is available at *Brain* online.

Acknowledgement

The authors wish to thank Dr Kang Joon Yoon, Director, Department of Neurosurgery, St Peter's Hospital, Seoul, Korea, for providing a technical support. The authors also thank Mr Dong-Su Jang, Research Assistant, Department of Anatomy, Yonsei University College of Medicine, Seoul, Korea, for his help with the figures.

Funding

Yonsei University College of Medicine (6-2007-0131); Basic Research Program of the Korea Science & Engineering Foundation (R01-2008-000-12169-0).

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