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Disruption of the Posterior Medial Network during the Acute Stage of Transient Global Amnesia: A Preliminary Study

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Abstract

Acute perturbation of the corticohippocampal circuitry is a primary pathophysiological mechanism underlying transient global amnesia (TGA). With regard to memory, 2 distinct corticohippocampal circuitries potentially exist: the anterior temporal network and the posterior medial network. We used electroencephalography (EEG) spectral analysis to determine which network is disrupted during the acute stage of TGA. Patients with TGA who visited Seoul National University Bundang Hospital within 24 hours after symptom onset were retrospectively identified. Twenty patients underwent EEG twice, once in the acute stage (<24 hours after symptom onset) and once in the resolved stage (>2 months after symptom onset). A fast Fourier transform was applied to compute the spectral power of the 6 frequency bands: delta, theta, alpha, beta 1, beta 2, and gamma. We assumed that the frontocentral and temporal regions belonged to the anterior temporal network, whereas the parieto-occipital regions belonged to the posterior medial network. A paired Student's *t* test was used to evaluate the difference in the regional spectral powers in each frequency band between the acute and resolved TGA stages. Compared with the resolved stage, relative theta power in the left parieto-occipital region was increased and relative alpha power in the right parieto-occipital region was reduced during the acute stage of TGA, with a statistical significance of $P < .05$ (uncorrected). The cortical regions that belonged to the posterior medial network showed alterations of neuronal activity, which reflects disruption of the posterior medial network during the acute stage of TGA.

Keywords

transient global amnesia, electroencephalography, quantitative analysis, hippocampus

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Introduction

TGA is an interesting syndrome of sudden-onset amnesia that is not associated with other neurological deficits and resolves spontaneously within 24 hours.[1] Although the exact mechanism is still not completely understood, focal injury in the hippocampal CA1 field, detected as a tiny hyperintense diffusion-weighted imaging (DWI) lesion,[2] and subsequent perturbation of the corticohippocampal circuitry are thought to be key to the pathogenesis of TGA.[1]

With regard to memory, 2 distinct corticohippocampal circuitries potentially exist: the anterior temporal network and the posterior medial network.[3] The posterior medial network is thought to be more involved in episodic memory than the anterior temporal network.[4] Given that TGA patients show marked impairment of episodic memory during the acute stage,[5] the posterior medial network might be disrupted primarily during the acute stage of TGA. However, the particular network involved during the acute stage of TGA has not been studied using neuroimaging or electrophysiological techniques.

In this study, we investigated which network is disrupted during the acute stage of TGA by spectral analysis of EEG. We included TGA patients with hippocampal DWI lesions, and

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analyzed the differences in EEG spectral powers between the acute (<24 hours after symptom onset) and resolved (>2 months after symptom onset) TGA stages by paired comparison. We identified the cortical regions that exhibited a difference in spectral power between two stages, and determined the network associated with these cortical regions. In addition, we evaluated whether the different networks are disrupted according to the DWI lesion site (hippocampal head, body and tail) during the acute TGA stage.

Methods

Participants

A retrospective analysis of TGA patients was performed based on a prospective registry database. We identified 21 patients who visited Seoul National University Bundang Hospital within 24 hours after onset, between January 2007 and June 2013, and fulfilled the TGA criteria proposed by Hodges and Warlow.[6] The diagnostic criteria were as follows: (*a*) the presence of anterograde amnesia (eg, asking repetitive questions or exhibiting temporal disorientation) that was witnessed by an observer, (*b*) no clouding of consciousness or loss of personal identity, (*c*) cognitive impairments limited to amnesia (eg, lack of symptoms such as inability to recognize faces or common objects, difficulty thinking of common words while speaking or uncharacteristic mood change), (*d*) no focal neurologic signs or epileptic features, (*e*) no recent history of head trauma or seizures, and (*f*) resolution of symptoms within 24 hours. The patients had 1 to 5 mm punctate hyperintense lesions in the lateral portion of the hippocampus on DWI (Figure 1).[7] Single-shot spin-echo echo-planar imaging was used for DWI using the following parameters: matrix, 128 × 128 interpolated to 256 × 256; field of view, 220 mm; repetition time, 9400 ms for 1.5 T (Intera; Philips Medical Systems, Best, Netherlands) and 5000 ms for 3 T (Intera Achieva; Philips, Best, Netherlands); echo time, 66 ms for 1.5 T and 59 ms for 3 T; SENSE factor, 2; number of acquisitions, 4; *b* value, 2000 s/mm^2; and section thickness, 3 mm.[8] DWI was performed again at day 3 post-onset with the same imaging parameters. Fifteen patients had hippocampal lesions on the initial DWI, whereas 6 patients had hippocampal lesions only on the follow-up DWI. They underwent EEG twice, once in the acute stage (<24 hours after symptom onset) and once in the resolved stage (>2 months after symptom onset). After excluding 1 patient with EEG data that were unsuitable for analysis because of artifacts, the remaining 20 patients comprised the study population. In a previous EEG spectral analysis, the mean difference of beta 1 power in the left parietal region between TGA patients and normal controls was 19.8 with a standard deviation of 23.6.[9] Using 20 pairs of subjects, we calculated a statistical power of 94.3% to detect this difference based on a paired Student's *t* test with $\alpha = .05$. The patients' demographics and clinical profiles were obtained through medical record review.

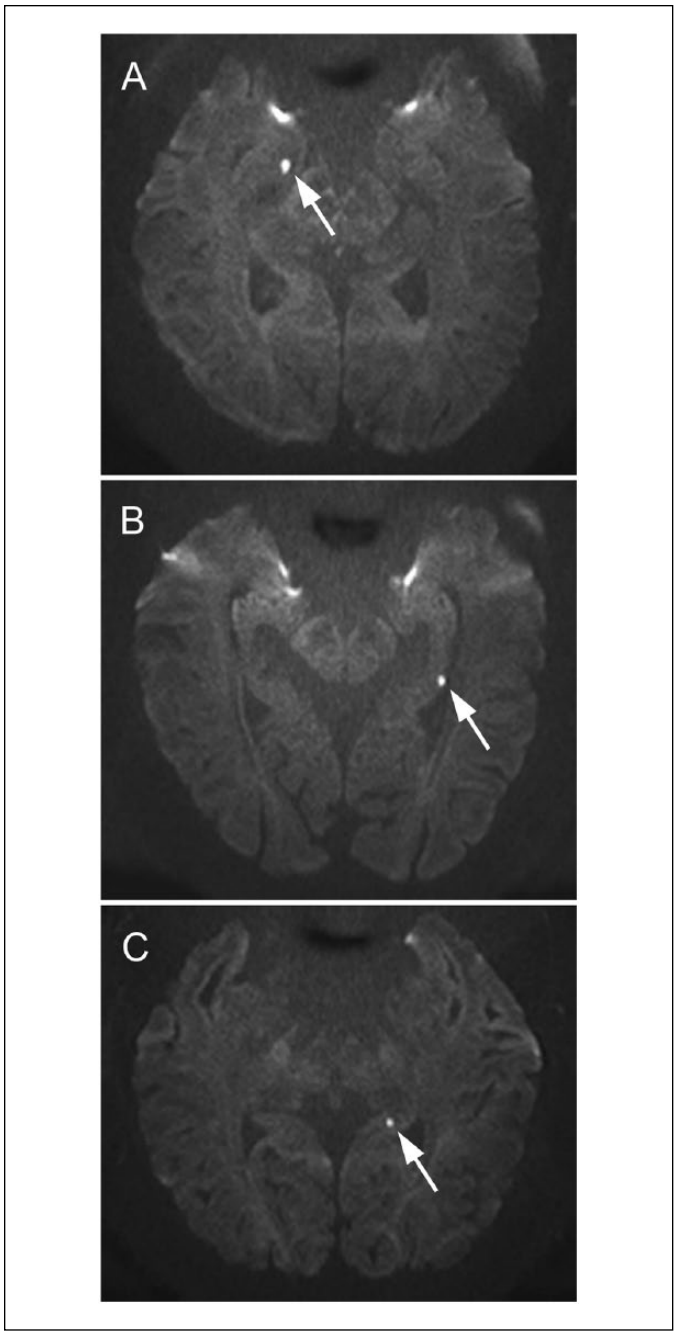

Figure 1. Examples of hippocampal lesions on diffusion-weighted imaging in transient global amnesia. Punctuate hyperintense lesions in the hippocampal head (A), body (B), and tail (C) are indicated with white arrows on axial diffusion-weighted images. Modified from Park et al.[7]

Electroencephalographic Recordings

All spontaneous EEG data were acquired for 15 minutes on a computer-based system (Natus Neurology, Inc, Warwick, RI) from 21 electrode locations (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T1, T2, T3, T4, T5, T6, P3, P4, Pz, O1, O2), according to the international 10-20 system with a linked ear

Table 1. Baseline Characteristics of the Study Population (n = 20).

Age in years, mean (SD)	62.05 (8.80)
Males, n (%)	6 (30.0)
Duration of TGA in hours, mean (SD)	4.87 (4.22)
Precipitating factor, n (%)	
Physical stress	4 (20.0)
Emotional stress	5 (25.0)
Vomiting	1 (5.0)
Associated symptoms, n (%)	
Headache	2 (10.0)
Nausea	3 (15.0)
Hypertension, n (%)	6 (30.0)
Diabetes, n (%)	0 (0.0)
Hyperlipidemia, n (%)	9 (45.0)
Hours from symptom onset to the initial DWI, mean (SD)	8.35 (5.74)
Laterality of DWI lesion, n (%)	
Left	5 (25.0)
Right	8 (40.0)
Bilateral	7 (35.0)
Location of DWI lesion,[a] n (%)	
Head	6 (30.0)
Body	9 (45.0)
Tail	6 (30.0)
Days from symptom onset to the EEG recording in the resolved stage, mean (SD)	245.2 (269.6)

Abbreviations: DWI, diffusion-weighted imaging; EEG, electroencephalography; SD, standard deviation; TGA, transient global amnesia.
[a]One patient had simultaneous lesions of the hippocampal head and tail.

reference. They were recorded at a sampling rate of 200 Hz. The band-pass filter was 1 to 70 Hz, and a notch filter removed 60-Hz noise. EEG data for analysis were selected, by visual inspection, to obtain 20 series of 2-second epochs (400 samples) that were free of artifacts. The data were then set to an average reference. The direct current offset component was subtracted in each epoch, and epochs exceeding ±75 μV amplitude at any electrode were rejected from the analysis. A fast Fourier transform computed the spectral power of 6 frequencies: delta (1.0-3.8 Hz), theta (4.0-7.8 Hz), alpha (8.0-11.8 Hz), beta 1 (12.0-17.8 Hz), beta 2 (18-26 Hz), and gamma (27-55 Hz). Each 2-second epoch was zero-padded to 2.5 times the length, to set the frequency resolution to 0.2 Hz. Band powers were normalized by dividing them by the whole band power (1-55 Hz) across all electrodes. The electrodes were grouped into the following 6 scalp regions: left frontocentral (F3, F7, C3), right frontocentral (F4, F8, C4), left temporal (T1, T3, T5), right temporal (T2, T4, T6), left parieto-occipital (P3, O1), and right parieto-occipital (P4, O2). We considered the frontocentral and temporal regions to belong to the anterior temporal network and the parieto-occipital regions to belong to the posterior medial network.[4] The Fp1, Fp2 (because of eyebrow movement contamination) and midline (Fz, Cz, and Pz) electrodes were excluded from the statistical analysis.

Statistical Analysis

A paired Student's *t* test was used to evaluate the difference in the regional relative spectral powers in each frequency band, and in each scalp region, between the acute and resolved TGA stages. The mean differences were obtained by subtracting the resolved stage. from the acute stage. We also calculated the effect size using Cohen's *d* values.[10] In addition, we divided the population into the 3 groups, based on the DWI lesion site along the anterior–posterior axis (hippocampal head, body, and tail)[7] and compared the mean differences of the relative spectral powers using the Kruskal–Wallis test. One patient, who exhibited simultaneous lesions of the hippocampal head and tail, was excluded from this analysis based on the location of the DWI lesion.

Statistical analyses were performed using PASW statistical software version 18.0 (IBM Corp, Somers, NY) for most analyses, and MATLAB 2009a (Mathworks, Inc, Natick, MA) for the EEG analysis. A power calculation was performed using PS version 3.0.43, 2011 (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize). The study protocol was approved by the local institutional review board, with an informed consent waiver because of the study's retrospective nature and minimal risk to participants.

Results

Baseline characteristics of the study population were summarized (Table 1). Mean differences in the relative spectral powers between the stages of acute and resolved TGA were demonstrated by the frequency band and scalp region (Figure 2). Relative theta power in the left parieto-occipital region and relative alpha power in the right parieto-occipital region were significantly different between stages. Compared with the resolved stage, the relative theta power in the left parieto-occipital region was increased (uncorrected $P = .026$, Cohen's $d = 0.41$) and relative alpha power in the right parieto-occipital region was reduced (uncorrected $P = .025$, Cohen's $d = -0.48$) during the acute stage of TGA (Figure 3). The effect sizes were medium, with Cohen's *d* ranging from 0.41 to 0.48.[10] With respect to the site of the DWI, lesion along the anterior–posterior axis, the mean differences in the relative spectral powers were not significantly different between the 3 groups (head, body, and tail).

Discussion

Our results indicate that the cortical regions that belonged to the posterior medial network showed alteration of neuronal activity during the acute stage of TGA: theta power was increased and alpha power was reduced in the parieto-occipital region. It is known that theta activity in the neocortex is regulated by corticohippocampal feedback loops.[11] When the hippocampus is damaged, theta activity increases because of the dysfunction of inhibitory interneurons in the hippocampal CA1 field.[12] Therefore, the increased theta power in our study

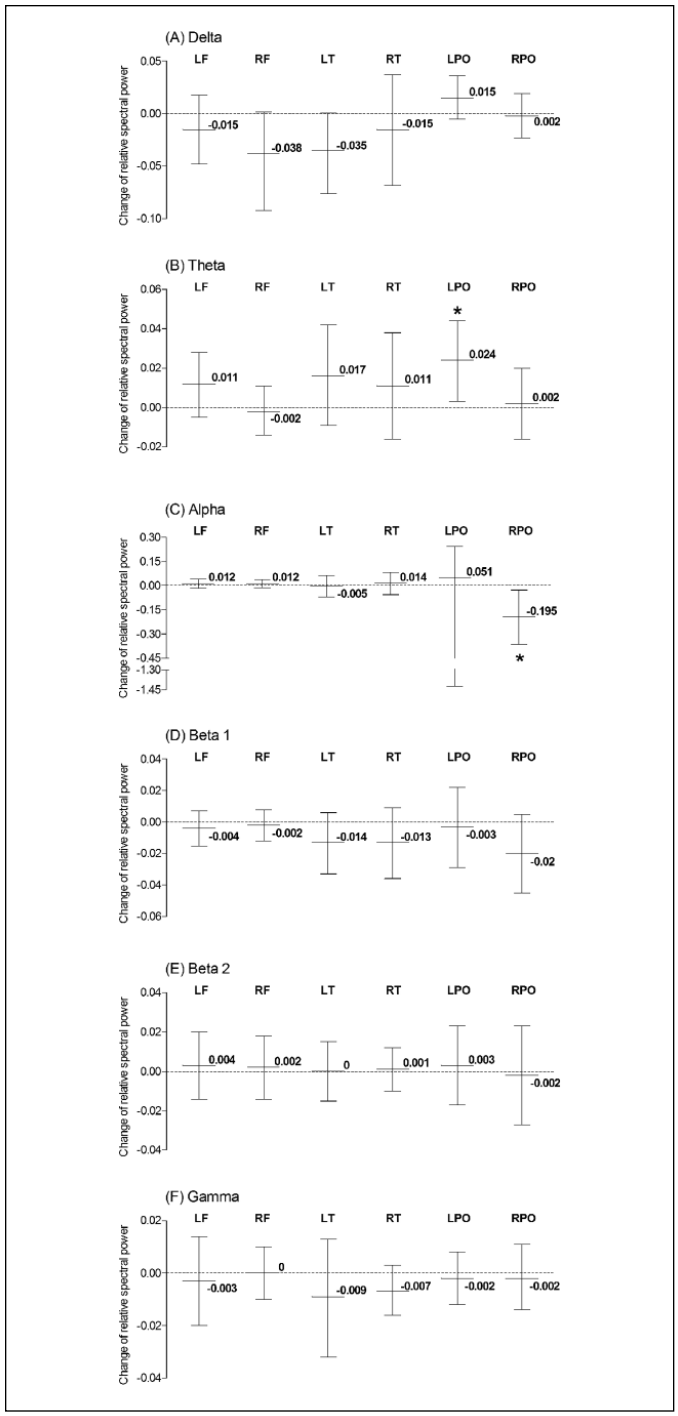

Figure 2. The mean differences in the regional relative spectral powers between the stages of acute and resolved TGA. The mean differences were obtained by subtracting the relative spectral powers of the resolved stage from the relative spectral powers of the acute stage of TGA. The mean differences were demonstrated by the frequency band and scalp region. The horizontal line and the number in the center of each vertical line denote the mean difference, and the whiskers indicate the 95% confidence interval. Abbreviations: LF, left frontocentral; LPO, left parieto-occipital; LT, left temporal; RF, right frontocentral; RPO, right parieto-occipital; RT, right temporal; TGA, transient global amnesia.
*$P < .05$ by a paired Student's t test.

reflects perturbation of the corticohippocampal circuitry during the acute stage of TGA. Regarding alpha, hippocampal dysfunction induces prevalent depolarizing of the brainstem cholinergic system on the thalamus and subsequently reduces cortical alpha power.[13]

It was recently reported that hippocampal atrophy alone could not induce episodic memory impairment in neurodegenerative disease.[14] When the posterior medial network connecting the hippocampus and posterior cortical areas is damaged, episodic memory is impaired.[14] We hypothesize that the alteration of cortical neuronal activity in the parieto-occipital area during the acute stage of TGA explains the amnesia that our patients exhibited. The critical relay function of hippocampal CA1 neurons within the hippocampal–parietal network has also been demonstrated in acute TGA patients using a navigation task.[15]

Previously, we reported that more anterior hippocampal DWI lesions were associated with hypoperfusion of the anterior temporal and frontal areas, whereas more posterior lesions were associated with hypoperfusion of the posterior temporal, parietal and occipital areas in patients with TGA, which reflects two parallel pathways between the hippocampus and neocortex.[7] However, the mean differences in the relative spectral powers were not significantly different, according to the location of the DWI lesion in this study. The inconsistent results could be explained by different characteristics of each technique: hemodynamic response tends to be more widespread in space and lasts longer in time compared with neuronal activity.[16]

Although EEG spectral analysis has been previously conducted in patients with TGA,[9] the described methods differed from those in this study. First, the EEG data in that study were recorded in a less acute stage of TGA, as it included patients who were within 1 week after symptom onset. Second, the TGA patients in that study did not undergo DWI. A more homogeneous group of patients with evidence of hippocampal CA1 injury on DWI was included in our study.

There are several limitations to this study. First, detailed neuropsychological assessments were unavailable during the acute and resolved stages of TGA, and were therefore not included in the analysis. The pathophysiologic mechanisms responsible for the phenomenon of TGA might be more clearly elucidated by evaluating whether episodic memory impairment is correlated with the alteration of regional spectral powers. Second, we could not compare the regional spectral powers between TGA patients and normal controls, because we did not have normal EEG data available. Third, the significance levels were not corrected for multiple comparisons. Although it might be acceptable not to perform adjustments for multiple comparisons in an explorative study,[17] the results should be interpreted with caution. Fourth, this study is retrospective; therefore, we could not control variables that might affect the EEG spectral powers. Fifth, we could not collect information about comorbidity with migraine. We also could not determine whether the nature of the headache, in two patients who complained of headache during

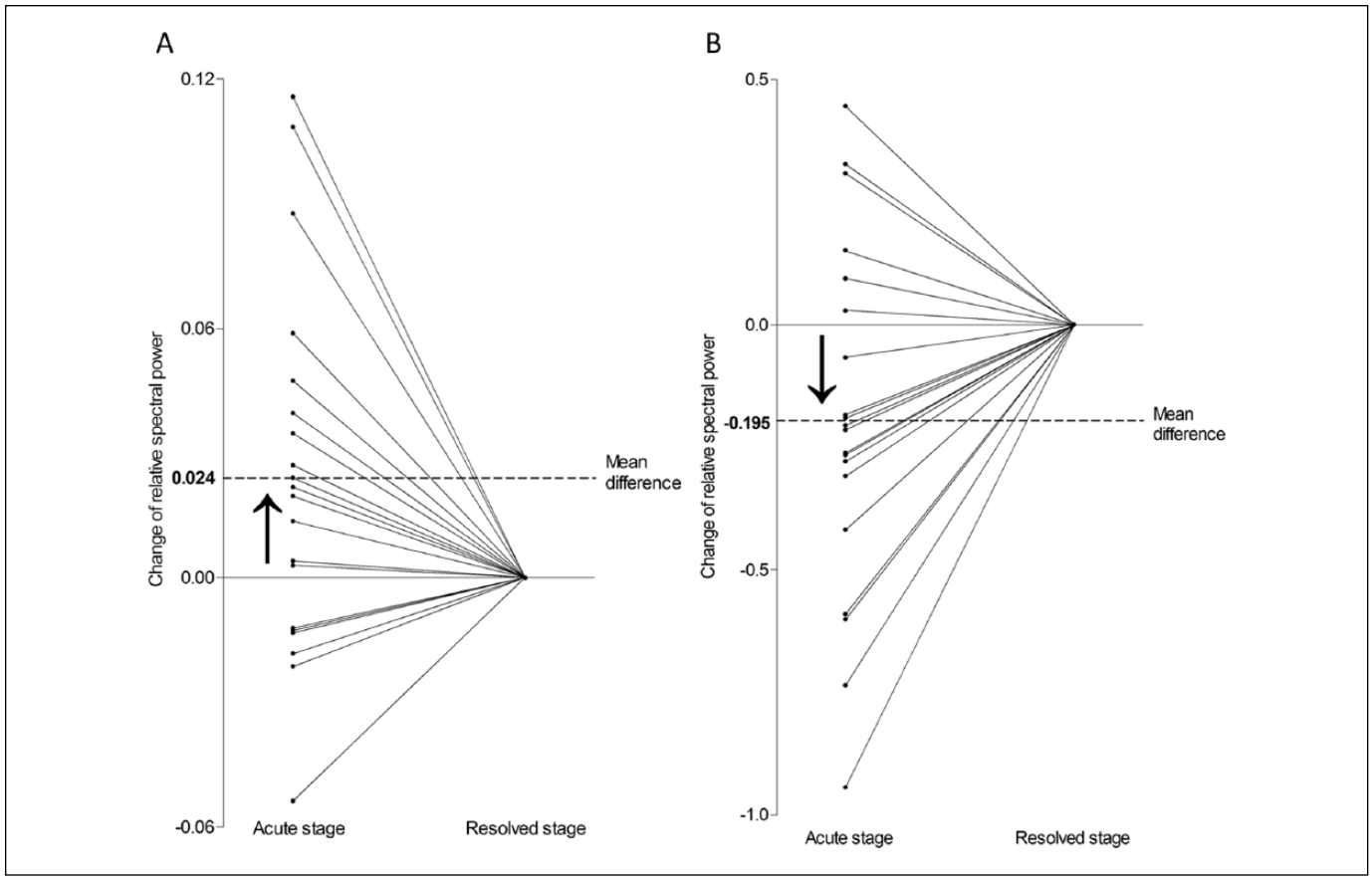

Figure 3. Change in relative spectral power between the acute and resolved transient global amnesia (TGA) stages. The relative spectral power of each participant was plotted to demonstrate the change between the stages. The change was evaluated by a paired Student's *t* test and was significant only in the left parieto-occipital area in the theta band (A) and the right parieto-occipital area in the alpha band (B).

the acute TGA stage, was migrainous. Migraine is known to be one of the triggering factors of TGA[18,19] which might be related to cortical spreading depression.[20] It needs to be investigated whether the migraine is associated with alterations in EEG spectral powers in TGA patients. Finally, we targeted relative spectral power rather than absolute spectral power. Relative spectral power analysis may underestimate the real changes in the spectral power of each frequency band.[21] However, relative spectral power analysis is frequently used in dementia studies[22] because this method attenuates the interindividual variability[21] and correlates well with dementia severity.[23]

In this study, we demonstrated that the posterior medial network is disrupted during the acute stage of TGA, which might be associated with the amnesia of TGA patients. Further research on the mechanism of selective involvement of the posterior medial network in TGA will aid our understanding of the pathophysiology of other neurological disorders that primarily affect the hippocampus.

Declaration of Conflicting Interests

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