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Network specific change in white matter integrity in mesial temporal lobe epilepsy

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ABSTRACT

Objectives: To identify the specific change of white matter integrity that occurs in the brain network related to epileptic activity in patients with mesial temporal lobe epilepsy (MTLE).
Methods: We recruited 18 patients with MTLE and 18 healthy subjects. In MTLE patients, the remote functional-deficit zone was delineated using fluorodeoxyglucose positron emission tomography as an extratemporal region showing glucose hypometabolism. Using diffusion magnetic resonance imaging tractography, we defined a seizure propagation tract (PT) as a white matter pathway that connects the focus with a remote functional deficit zone. We also used the corticospinal tract (CST) and inferior longitudinal fasciculus (ILF) as control tracts in the hemisphere ipsilateral to the focus. Fractional anisotropy (FA), mean diffusivity (MD), and volume of the tracts were compared among PT, CST, and ILF.
Results: Tractographic analysis identified the uncinate fasciculus, arcuate fasciculus, and fornix as PTs. A decrease in FA was found in MTLE patients compared with healthy subjects in all tracts, but PTs showed a more significant decrease in FA than did the two control tracts. Although the change in MD was also found in MTLE patients compared with healthy controls, a tract-specific change was not observed. Although white-matter damage was observed in all candidate tracts examined, the integrity of white matter was most significantly decreased in PTs in MTLE.
Conclusion: The change in white matter integrity occurs specifically in the pathways that connect the focus and remote functional deficit zones in patients with MTLE, i.e., the pathways that are assume to be associated with seizure propagation.

Introduction

In patients with mesial temporal lobe epilepsy (MTLE), glucose hypometabolism often extends beyond the temporal lobe. Among them, glucose hypometabolism in the prefrontal cortex is associated with cognitive changes (Jokeit et al., 1997; Takaya et al., 2006), suggesting that functional deficit zones exist in the remote cortical regions (Rosenow and Luders, 2001).

Glucose hypometabolism in the remote cortical regions from the epileptic focus reflects the preferential networks involved by ictal

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discharges and is also associated with seizure frequency (Chassoux et al., 2004; Takaya et al., 2006). In addition, after the epileptogenic lesion in the mesial temporal lobe is removed, the remote areas that supposedly receive projections from the affected area show improved glucose metabolism (Dupont et al., 2001; Spanaki et al., 2000; Takaya et al., 2009). These lines of evidence suggest that the functional deficit zones in remote cortical regions are most likely the result of the frequent propagation of epileptic activity from the epileptic focus through a white matter pathway.

Previous studies using voxel-wise whole brain analysis of white matter integrity such as tract-based spatial statistics (TBSS) have shown that the change in white matter integrity occurs throughout the brain in patients with MTLE (Focke et al., 2008; Schoene-Bake et al., 2009; Yogarajah et al., 2010). One possible reason is that inherent pre-existing abnormalities due to genetic factors or developmental abnormalities might exist in the whole brain in patients with MTLE (Velisek and Moshe, 2003; Love, 2005). However, whether there is any pathway that is specifically impaired compared with other white matter pathways in patients with MTLE remains unclear. Given that the epileptic activity arising from the focus is assumed to generate the functional deficit zone in remote cortical regions through white matter pathways as mentioned above, we would hypothesize that epileptic activity specifically impairs these pathways.

In this study, we first delineated the white matter pathways that connect the focus and the remote functional deficit zones in MTLE patients by combining FDG-PET and diffusion MRI tractography. We traced these specific white matter pathways into the cortices that showed glucose hypometabolism in FDG-PET by adopting probabilistic diffusion tractography that can trace beyond region of high uncertainty into the grey matter or across the crossing fibers (Behrens et al., 2007). Then we evaluated the change in white matter integrity of these pathways using tractography-based regions of interest (ROI) method. The advantage of this method is that it allows the cross-subject comparison of white matter integrity along the given tracts without requiring cross-subject registration (Smith et al., 2013). We expected to see that the pathway that connects the focus and the remote functional deficit zones is affected much more than other white matter pathways. Our findings may provide insight into the wide range of functional network impairment in patients with localization-related epilepsy.

Methods

Subjects

We recruited 18 right-handed patients with medically intractable MTLE (10 with left MTLE and 8 with right; mean age, 30.7 years; ranging, 19–45 years; 8 men, 10 women). All patients underwent presurgical evaluation between 2007 and 2010 at the Kyoto University Hospital. These patients were diagnosed as MTLE on the basis of seizure semiology, electroencephalography (EEG), video EEG monitoring, and neuroimaging data. We detected hippocampal atrophy or sclerosis in all 18 MTLE patients by means of 3-T MRI. Patients with additional MRI anomalies outside the mesial temporal lobe were excluded from this study. Eight patients underwent surgery. Ten patients are on a waiting list for surgery. The details of the patients' demographic data are shown in Table 1. We also analyzed 18 age-matched right-handed healthy control subjects (mean age, 31.3 years; ranging, 18–47 years; 10 men, 8 women).

Standard protocol approvals, registrations, and patient consents

This study was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (approval# E-430), and written informed consent was obtained from all patients and healthy volunteers.

FDG-PET data analysis

The FDG-PET scans were performed using a PET scanner (Advance, General Electric Medical System, Milwaukee, WI, USA). [18F]-FDG at 370 MBq (10 mCi) was injected intravenously into subjects who had been fasting for at least 4 h. Then, 40 min after the administration of the radiotracer, 35 slices of brain-emission images were acquired over a 20-min period. The subjects were studied in an awake, resting state, with their eyes closed and

Table 1
Patient Profile.

Pt. No.	Focus	Age	Onset age	FS	MRI	Seizure semiology	Ictal EEG	Spike	Ope
1	L	32	22	–	HS, HA	Nausea → CPS with dystonic posture of right hand	L	L 80%	–
2	L	23	19	–	HS	Epigastric rising sensation, ecstacy aura → CPS	L	L	–
3	L	45	1	+	HA	Epigastric rising sensation → CPS with automatism	Not captured	L 98%	–
4	L	26	12	–	HS, HA	Nausea, psychic aura → CPS	L	L	–
5	L	30	22	+	HS, HA	Epigastric rising sensation, deja vu and anxious feeling → CPS with automatism	L	L	+
6	L	35	17	+	HS	CPS with oral automatism	L	L	–
7	L	23	22	+	HS	Epigastric rising sensation → CPS	L	–	–
8	L	35	20	+	HA	Abdominal pain → CPS with oral automatism	No VEEG	L 95%	–
9	L	43	15	+	HA	CPS with automatism, and dystonic posture of right hand	L	L	+
10	L	43	19	–	HA,HS	CPS with automatism, and dystonic posture of right hand	No VEEG	L	–
11	R	38	9	+	HS, HA	Nausea → CPS with dystonic posture of left hand	R	R	+
12	R	45	5	+	HS, HA	Epigastric rising sensation, psychic aura → CPS	R	R	+
13	R	18	12	+	HS, HA	Epigastric rising sensation → CPS with automatism and dystonic posture of left hand	R	R	+
14	R	23	15	+	HS	CPS with automatism	No VEEG	R	–
15	R	25	24	+	HS, HA	nausea → CPS	R	R	–
16	R	24	12	–	HS, HA	CPS with automatism	R	R	+
17	R	26	4	–	HS, HA	Epigastric rising sensation → CPS with automatism	R	R 90%	+
18	R	19	11	+	HA	nauseous and uncomfortable feeling → CPS	R	R	+

FC = febrile convulsion, HS = hippocampal sclerosis, HA = hippocampal atrophy, CPS = complex partial seizure, VEEG = video electroencephalography monitoring.