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Relationship between bilateral temporal hypometabolism and EEG findings for mesial temporal lobe epilepsy: Analysis of ^{18}F-FDG PET using SPM

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Summary

Purpose: To investigate the clinical significance of bilateral temporal hypometabolism (BTH) for patients with mesial temporal lobe epilepsy (MTLE) by using statistical parametric mapping (SPM).
Methods: Interictal ^{18}F-FDG PET scans were performed for 29 patients with surgically treated MTLE. Clinical data, interictal epileptiform discharges (IEDs), ictal scalp EEG and intracarotid amobarbital test (IAT) were analyzed. To assess an ^{18}F-FDG PET image, an SPM analysis as well as visual interpretation were applied.
Results: In 9 of 29 patients, the ^{18}F-FDG PET scan revealed BTH by the SPM analysis, while only 3 patients showed BTH by the visual assessment. When the patients were classified into the unilateral temporal hypometabolism (UTH) and BTH groups based on the SPM results, bitemporal IEDs occurred significantly more frequently in the BTH group than in the UTH group (66.7% versus 22.2%). Bilateral independent seizure onset seen on the scalp EEG and bitemporal epilepsy were present only in the BTH group. Lateralized ictal onset was present less frequently in the BTH group than in the UTH group (44.4% versus 83.3%). There was no statistically significant difference in age at onset, duration of epilepsy, generalized seizure, history of febrile convulsion and CNS infection, lateralization throughout the whole tracing, lateralization on the IAT test,

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and surgical outcome between the UTH and BTH groups.
Conclusion: Bilaterality of the EEG findings correlated with BTH on ^{18}F-FDG PET by the SPM method. Our results suggest that analysis of ^{18}F-FDG PET by using SPM may have a role in predicting those patients with bitemporal excitability or bitemporal independent epileptogenicity, and these patients should be monitored carefully.

Introduction

Regional hypometabolism found upon testing with 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) highly correlates with the lateralization of the epileptogenic zone in temporal lobe epilepsy.[1–4] Patients with unilateral temporal hypometabolism (UTH) on ^{18}F-FDG PET have been reported to be associated with a favorable surgical outcome[5,6]; however, in contrast to UTH, bilateral temporal hypometabolism (BTH) has received a little attention. Previous studies using semiquantitative analysis have suggested that BTH was associated with bilateral temporal epilepsy, diffuse or extratemporal seizure onsets, bilateral magnetic resonance imaging (MRI) changes and worse cognitive function.[7–9] Statistical parametric mapping (SPM) can provide an objective way for interpretation through an automated voxel-based analysis,[10] and this has been successfully adopted in the interpretation of mesial temporal lobe epilepsy (MTLE).[10–13]

In this study, we compared the interictal epileptiform discharges (IEDs), ictal onset and Wada test of patients with UTH with those of patients with BTH, which were assessed by SPM analysis.

Methods

Subjects

Interictal ^{18}F-FDG PET images from 29 consecutive patients (11 men, 18 women; aged 14–41 years; mean age 26 years) with MTLE who had undergone surgical resection were analyzed. Presurgical evaluations included brain MRI, neuropsychologic test, video EEG monitoring, and ^{18}F-FDG PET scan. All patients showed unilateral mesial temporal sclerosis (MTS) ipsilateral to the side of surgery without any other focal abnormalities on the MRI by visual inspection; MTS was proven pathologically in all patients. When the ictal recordings from the scalp/sphenoidal EEG were inconclusive or suggested bitemporal independent onset, invasive EEG study confirmed unilateral ictal onset in the mesial temporal region of the surgery side, although two patients showed bitemporal independent onsets with predominant unilateral involvement on the invasive EEG findings. The control group for SPM analysis was comprised of eight healthy volunteers (six men, two women; aged 27–32 years; mean age 29.5 years). All volunteers had no history of neurological disease, psychiatric disease or medical disease, and they gave their informed consent.

EEG analysis

EEG recordings using the international 10-20 system, including sphenoidal electrodes, and long-term video EEG monitoring were performed in all patients. The EEG findings were analyzed by two neurologists (K.H., J.H.C.), with any differences of opinion being resolved by consensus.

Interictal EEG recordings of 20-min epochs were randomly collected twice for every 24 h of monitoring. The lateralization ratio of IEDs was calculated as expressing the number of IEDs counted on the either side as a percentage of the total number of IEDs recorded independently on the bilateral temporal regions. Unitemporal IED (UIED) required a minimum of 90% of lateralization to the side of surgery, otherwise the patients were placed in the bitemporal IED (BIED) group. We defined lateralization of the ictal EEG as an amplitude ratio higher than 2:1 in favor of one side in bipolar and referential montages. The ictal onset of each seizure was defined as the first unequivocal ictal EEG pattern lasting for at least 3 s (pattern at onset, PAO) and the dominant ictal EEG pattern was taken after the first 10 s of seizure onset (later significant pattern, LSP). We defined the lateralized ictal onset as the lateralization of PAO, or when PAO was not lateralized, as the lateralization of the LSP lasting for longer than 10 s. An ictal pattern was considered correctly lateralized if it corresponded to the side of surgery and incorrectly lateralized if it pointed to the opposite side. The switch of lateralization was defined as lateralization of the dominant ictal discharge from the side of the ictal onset to the contralateral hemisphere and if it lasted for more than 10 s. A patient was considered to have a lateralized ictal onset when at least 50% of the recorded ictal EEG onsets were lateralized to the side of surgery. Non-lateralized ictal onset was assigned if less than 50% of ictal EEG onsets were lateralized (diffuse

ictal onset) or if an independent bilateral ictal onset was present. Lateralization throughout the whole tracing for each patient was defined as the lateralization of the ictal EEG to the side of surgery throughout the whole tracing for more than 50% of the seizures.

When the patient had diffuse ictal onset or independent bilateral ictal onset on the scalp EEG, the invasive EEG using depth or foramen ovale electrodes was performed.

^{18}F-FDG PET image procedure

The PET images were acquired using GE ADVANCE PET scanner (GE, Milwaukee, WI, USA) in 3D mode. The transaxial resolution of the system was 5.2 mm FWHM (full-width-half maximum) at the center of FOV (field of view). Approximately 5 mCi of ^{18}F-FDG was injected intravenously after 6 h of fasting, and the patients were required to lay still with their eyes closed in a quiet, dimly lit room during the injection and 40 min thereafter. The emission scan started at 40 min after the injection for 15 min, and an 8-min transmission scan was subsequently acquired for the purpose of attenuation correction. EEG was not performed during FDG uptake. Ictal studies cannot be entirely excluded, but were unlikely because the patients were carefully monitored and did not report any aura or seizure during the procedures.

Visual interpretation of ^{18}F-FDG PET

Two-experienced nuclear medicine physicians (M.Y., J.D.L.) independently interpreted the images of ^{18}F-FDG PET, and they were given no clinical information about the patients. The presence of BTH was considered only if two of the readers agreed with each other.

Analysis of ^{18}F-FDG PET by SPM

The analysis of data was performed on a SUN UltraSpare 10 workstation (Sun Microsystems, Silicon Valley, CA, USA) using SPM99 (Institute of Neurology, University College of London, UK).[14] All reconstructed PET images were spatially normalized into the MNI template (Montreal Neurological Institute, McGill University, Canada) using the affine transformation of SPM99.[15] The normalized images were smoothed by convolution with an isotropic Gaussian kernel with 8-mm FWHM to increase the signal-to-noise ratio. The images of each patient were statistically compared with those of healthy volunteers at every voxel by using a t-test to detect a significant decrease in the regional metabolism. We used a voxel height threshold at $p = 0.01$ (uncorrected) and at $p = 0.001$ (uncorrected). Considering the general size of epileptic sources in temporal lobe, we selected the minimal cluster size as 90 voxels of spatially normalized images with a voxel unit of 2 mm $\times$ 2 mm $\times$ 2 mm. The patients were divided into two groups (UTH or BTH) based on the results of the SPM analysis.

Intracarotid amobarbital test (IAT)

Amobarbital (125 mg) was injected in 3—5 s into the internal carotid artery. Ten items (two words, one figure, one colored shape, four object drawings, two abstract designs) were presented during the time of hemiparesis after each injection, and EEG monitoring was continued throughout the test. Follow-up testing for the patient's memory of the test items was performed 15 min after the injection, after the EEG had returned to normal and the patient had regained their normal neurological function. A retention score was calculated for each injection, and it was defined as the percentage of test items recalled. IAT failure was defined as those retention scores of less than 50% on both sides, or a retention score on the side contralateral to surgery that was 20% lower than the ipsilateral side.[16]

Surgical outcome

Patients were categorized into one of three groupings, with criteria: class I, seizure free, except auras; class II, worthwhile improvement with a $\geq$75% reduction of seizure occurrence; and class III $<$75% of seizures.[17] Surgical outcome data were obtained from the medical records.

Statistics

Comparisons between UTH and BTH groups on the continuous variables were conducted by using Student's t-test. For categoric variables, Fisher's two-tailed exact test was used to elucidate the significance between two groups. For all tests, the statistical significance was accepted at $p < 0.05$.

Results

The clinical data are summarized in Table 1.

PET: SPM analysis versus visual assessment

The SPM analysis using uncorrected p-value $<$0.01 revealed UTH ipsilateral to the side of surgery for 18 (62.1%) patients, BTH with a more prominent invol-

Table 1 Clinical data of patients

Patient number	Sex/age	Duration	GTC on Hx	Hx of FC	Hx of CNS infection	Op and MTS on MRI	PET SPM[a]	PET visual
1	M/33	32	+	+	–	R	R T	R T
2	F/17	14	–	–	–	L	L T	L T
3	F/22	9	–	–	+	L	**B(L) T**	L T
4	F/26	14	–	+	–	R	R T	R T
5	M/20	5	–	–	+	R	**B(R) T**	R T
6	M/33	21	+	+	–	R	R T	R T
7	F/23	12	–	–	+	L	L T	L T
8	F/14	5	–	+	–	L	L T	L T
9	F/27	13	–	–	+	R	**B(R) T**	**B(R) T**
10	M/41	25	+	–	–	R	**B(R) T**	**B(R) T**
11	F/30	25	–	+	–	L	**B(L) T**	L T
12	F/16	7	–	–	+	L	L T	L T
13	F/25	21	+	–	+	L	L T	L T
14	F/28	18	–	+	–	R	R T	R T
15	F/30	22	–	+	–	L	L T	L T
16	M/25	8	+	+	–	R	R T	R T
17	F/30	19	–	+	–	L	**B(L) T**	**B(L) T**
18	M/30	10	+	+	–	R	R T	R T
19	M/23	14	–	–	–	R	–	R T
20	M/21	2	–	+	–	R	R T	R T
21	F/19	4	–	+	–	L	L T	L T
22	M/37	22	–	+	–	R	R T	R T
23	F/20	18	–	+	–	L	–	L T
24	F/24	19	–	+	–	R	R T	R T
25	M/22	19	–	+	–	L	L T	L T
26	M/39	12	–	–	–	L	**B(L) T**	L T
27	F/34	20	–	+	–	R	R T	R T
28	F/34	16	–	+	–	R	**B(R) T**	R T
29	F/21	7	–	+	–	L	**B(L) T**	L T

Patient number	Lateralization of IED	Bilateral independent ictal onset	Diffuse ictal onset	Ictal switch of lateralization	Lateralized throughout the whole tracing	Invasive EEG	IAT	Surgical outcome
1	R	–	+	–	–	FO	P	Class II
2	L	–	–	–	+		P	Class II
3	**B**	–	–	–	–		F	Class III
4	R	–	–	–	+	FO	P	Class II
5	R	–	–	–	+		P	Class I
6	R	–	–	–	–		P	Class I
7	L	–	–	+	–		F	Class I
8	L	–	–	–	+		P	Class III
9	R	–	–	+	+		P	Class I
10	R	–	–	–	+		F	Class II
11	**B**	+	–	–	–	depth	P	Class II
12	L	–	–	–	+		F	Class I
13	L	–	–	+	–		P	Class II
14	R	–	–	–	+		P	Class I
15	L	–	–	–	–		P	Class I
16	R	–	–	–	–		P	Class II
17	**B**	+	–	–	–	FO	F	Class I
18	R	–	–	–	+		P	Class I
19	R	–	–	–	+		P	Class I
20	R	–	–	–	–		P	Class I
21	L	–	–	–	+		P	Class II
22	**B**	–	+	–	–	FO	P	Class I
23	**B**	–	–	–	+		F	Class I

Table 1 (*Continued*)

Patient number	Lateralization of IED	Bilateral independent ictal onset	Diffuse ictal onset	Ictal switch of lateralization	Lateralized throughout the whole tracing	Invasive EEG	IAT	Surgical outcome
24	R	–	–	–	–		P	Class I
25	**B**	–	–	–	+		P	Class I
26	**B**	+	–	+	–	depth	P	Class II
27	**B**	–	+	–	–	FO	P	Class II
28	**B**	–	+	–	–	FO	P	Class I
29	**B**	+	–	–	–	FO/depth	F	Class II

F, female; M, male; Hx, history; FC, febrile convulsion; Op, operation; MTS, mesial temporal sclerosis; R, right; L, left; **B(R) T**, bilateral temporal hypometabolism, more prominent in the right side; **B(L) T**, bilateral temporal hypometabolism, more prominent in the left side; PET Visual, analysis of temporal lobe hypometablism by visual assessment; **B**, bitemporal independent; FO, foramen ovale electrodes; IAT, intracarotid amobarbital test; P and F, pass and failure on IAT, respectively.

[a] Analysis of temporal lobe hypometablism by the SPM analysis of PET using a threshold of uncorrected $p < 0.01$.

vement on the side of surgery for 9 (31.0%) patients, and no significant hypometabolism for 2 (6.9%) patients (Fig. 1). The SPM analysis using uncorrected *p*-value <0.001 showed BTH for only a patient (Patient 28), UTH for 26 (89.7%) patients and no significant hypometabolism for 2 (6.9%) patients (Patient 19 and Patient 23). Therefore, the patients were classified into UTH and BTH groups based on the SPM analysis using uncorrected *p*-value <0.01 for comparison with clinical variables. Upon visual assessment, 26 (89.7%) patients were interpreted to have UTH ipsilateral to the side of surgery and 3 (10.3%) patients had BTH with the predominant involvement on the side of surgery; these patients also had BTH on the SPM analysis using uncorrected *p*-value <0.01. Among the 26 patients who were assigned as UTH by visual assessment, 6 patients were found to have BTH and 2 had no significant hypometabolism on either side by the SPM analysis using uncorrected *p*-value <0.01 (Table 2).

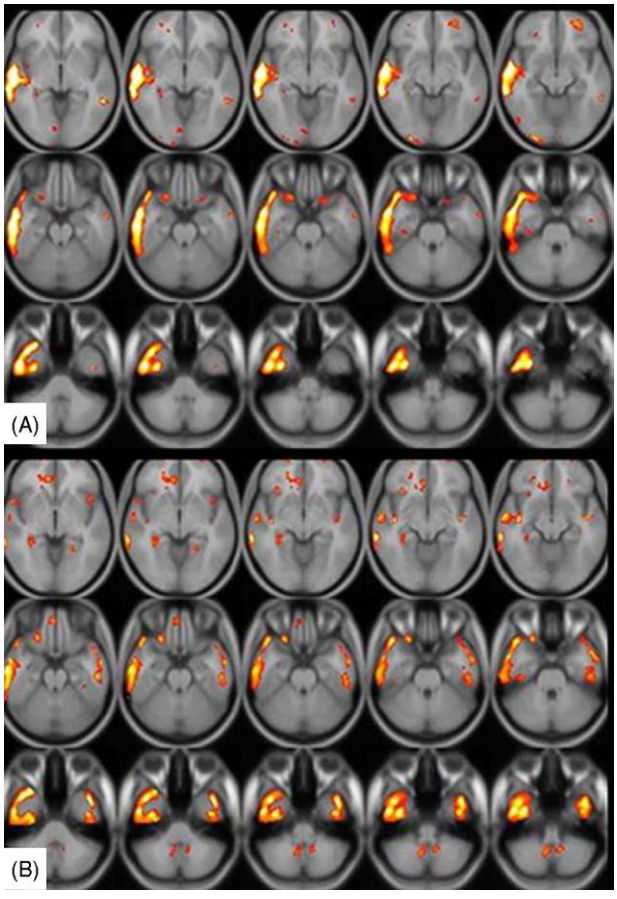

Figure 1 (A) Unilateral temporal hypometabolism (UTH). Statistical parametric mapping (SPM) analysis of ^{18}F-FDG PET shows the decreased metabolism in right temporal lobe (Patient 24 in Table 1). (B) Bilateral temporal hypometabolism (BTH). Statistical parametric mapping analysis of ^{18}F-FDG PET shows the decreased metabolism in bilateral temporal lobes, which is more prominent in the right side (Patient 28 in Table 1).

PET and EEG findings

Six (66.7%) of nine patients with BTH showed BIED, whereas four (22.2%) of 18 patients with UTH showed BIED ($p = 0.026$). Four patients showed bilateral independent seizure onset on the scalp EEG and they all had BTH ($p = 0.007$). These

Table 2 Comparison of results of visual assessment and SPM analysis of ^{18}F-FDG PET[a]

SPM	Visual assessment		
	Unilateral	Bilateral	
Unilateral	18	0	18
Bilateral	6	3	9
Negative	2	0	2
	26	3	29

There was a significant difference in detection of BTH between SPM analysis and visual assessment (31.0% vs. 10.3%, $p = 0.029$).

[a] The SPM analysis of PET using a threshold of uncorrected $p < 0.01$.

patients underwent invasive EEG study. Two patients (Patient 11 and Patient 26) were found to have unilateral seizure onset on the invasive EEG study. The other two (Patient 17 and Patient 29) showed bilateral independent seizure onsets, but they could have undergone surgery because they had more frequent ictal onsets from the side of MTS upon the findings of invasive EEG, and they also had more prominent hypometabolism on the ipsilateral side. The IAT in these patients revealed a non-lateralizing memory function with high scores for both sides. Diffuse ictal onset occurred in three (16.6%) patients with UTH and one (11.1%) patient with BTH. Eventually, 4 (44.4%) patients with BTH showed the lateralized ictal onset, whereas 15 (83.3%) patients with UTH showed the lateralized ictal onset, although the difference was not statistically significant ($p = 0.072$). For patients with the lateralized ictal onset, lateralization throughout the whole tracing was present in 10 (66.7%) of 15 patients with UTH and in 3 (60.0%) of 5 patients with BTH. The switch of lateralization occurred in one (11.1%) patient with UTH and in four (22.2%) patients with BTH.

PET and IAT

Those patients with BTH showed IAT failure more frequently than patients with UTH did, but this difference did not reach statistical significance (44.4% versus 11.1%, $p = 0.073$). The mean retention scores after the contralateral injection were not different between UTH and BTH groups. There was a trend that the mean retention score after the ipsilateral injection was lower in the BTH group (74.5% versus 63.3%, $p = 0.097$).

PET and clinical data

There was no statistically significant difference for age at onset, duration of epilepsy, generalized seizure, history of febrile convulsion and CNS infection between the UTH and BTH groups (Table 3).

Table 3 Comparison of clinical characteristics between patients with UTH and BTH

Parameter	UTH ($n = 18$)	BTH ($n = 9$)	p-value
Age at onset	10.39	14.78	0.559
Disease duration	15.00	14.56	0.714
Febrile convulsion, n (%)	14 (77.8)	4 (44.4)	0.083
CNS infection, n (%)	3 (16.7)	3 (33.3)	0.326
GTC on history, n (%)	7 (38.9)	5 (55.6)	0.411

CNS: central nervous system; GTC: generalized tonic clonic seizure.

Table 4 Comparison of surgical outcome between patients with UTH and BTH

Parameter	UTH ($n = 18$)	BTH ($n = 9$)
Class I	10 (55.6%)	4 (44.4%)
Class II	7 (38.9%)	4 (44.4%)
Class III	1 (5.6%)	1 (11.1%)

$p = 0.803$.

PET and surgical outcome

Mean follow up period after surgery was 2.6 years (2.5 ± 0.6 years for UTH and 2.8 ± 0.8 years for BTH) with minimum of 1.4-year follow-up. There was no statistically significant difference for surgical outcome between the UTH and BTH groups (Table 4).

Discussion

We investigated the incidence and the clinical significance of BTH in MTLE with unilateral MTS for those patients who underwent surgery. In this study, for 9 (31%) of 29 patients, the ^{18}F-FDG PET scan revealed BTH by the SPM analysis. On visual assessment, only three (10%) patients showed BTH. When the patients were classified into the UTH and BTH groups by the SPM results, bitemporal IEDs and the non-lateralized ictal onsets occurred significantly more frequently for the BTH group, as compared with the UTH group, and the bilateral independent seizure onset on the scalp EEG and bitemporal epilepsy were present only for the BTH group. These findings suggest that BTH by SPM analysis may correlate with bitemporal excitability. However, because the SPM analysis did not reveal hypometabolism in the two patients judged to have UTH by visual assessment, the SPM method may not have any higher sensitivity than visual interpretation for the lateralization of MTLE. This result may suggest a complementary role of the SPM analysis with the visual assessment. For assessing a ^{18}F-FDG PET image, visual interpretation has been commonly used in clinical practice; however, the results can be highly dependent on the observer's expertise. Interpretation may be focused on an asymmetry and the more severely involved area. Any symmetric involvement may be interpreted to the side of surgery as being either normal or bilateral, but asymmetric involvement is more likely to be reported as unilateral hypometabolism on visual assessment. In this aspect, a semiquantitative ana-

lysis can improve the sensitivity of the PET interpretation by providing more precise information on the involvement of individual temporal areas.[7–9] The region of interest technique is cumbersome and time consuming; moreover, regional values are normalized to the "uninvolved" area, such as the cerebellum or contralateral hemisphere, which may also demonstrate the hypometabolism due to diaschisis. From this point of view, the SPM method may provide more useful information for the evaluation of BTH. In this study, to increase the sensitivity of detection of BTH, we used a lower threshold (uncorrected p-value <0.01) in SPM analysis than that (uncorrected p-value <0.001) of the previous study[10] which reported similar rate of BTH. The use of uncorrected p-value <0.001 increased the sensitivity of detection of UTH but did not change the sensitivity in cases of no significant hypometabolism. It was considered that a small number of controls could decrease the sensitivity of SPM analysis in detecting BTH.

Previous studies that used semiquantitative analysis reported that BTH was found in 10–12% of the intractable epilepsy patients, including extratemporal lobe epilepsy.[8,9] Recently, Kim et al.[10] reported that temporal hypometabolism was bilateral on SPM-analyzed ^{18}F-FDG PET for 30% of intractable TLE patients who underwent surgery, and this was comparable to our results. However, Kim et al.'s study did not look for the electroclinical correlates of the BTH. Koutroumanidis et al.[9] reported that the bilateral independent ictal discharges found upon depth EEG occurred for 8 (53%) of 15 TLE patients with BTH and without bilateral MTS upon MRI scanning (eight and three patients could not undergo surgery due to bilateral TLE and adverse IAT, respectively), and BTH was associated with a longer disease duration and poor memory performance during the IAT, as compared with patients with UTH. This association of BTH with bilateral TLE is in line with our results, although the relatively low incidence of bilateral TLE in our patients may have resulted from our inclusion criteria for patients who had undergone surgery. Comparing with UIEDs, BIEDs have been reported to be more frequently associated with a lateralized onset, a bilateral independent seizure onset and a poorer seizure outcome, and these items are considered to suggest bitemporal epileptogenicity.[18–22] IEDs in the contralateral mesial temporal region were reported to be associated with the neuronal dysfunction or the damage detected by magnetic resonance spectroscopy.[23] BTH was found in MTLE patients who had electroclinical features suggesting an early contralateral temporal spread.[24] In MTLE, BTH may reflect the early and widespread propagation of the ictal discharge due to a decrease of the inhibitory mechanisms in the contralateral temporal lobe, or it may be due to bitemporal independent epileptogenicity. However, the postoperative surgical outcome was similar between UTH and BTH groups in our study. We investigated only surgically treated patients with unilateral MTS on MRI. Because MTS itself is a powerful prognostic factor in temporal lobe resection, other factors may lose their predictive value when the subgroup with MTS is examined.[25] Because a small number of patients were included to this study and only two patients showed class III outcome, different surgical outcome between UTH and BTH might be discovered in a much larger patient population.

In IAT, failure was found more frequently for patients with BTH than with UTH, but this difference did not reach statistical significance. The mean retention score after a contralateral injection had a tendency to be lower in the BTH group, and although we expected to find a higher failure rate and a decreased memory function of the side contralateral side to the surgery for patients with BTH than with UTH, there was only a tendency, and it did not reach a significant level. This may be related to the relatively small number of cases as well as the lack of any direct correlation between memory function and hypometabolism. Henry et al.[26] reported that hippocampal neuronal loss explaining the memory impairment could not account for the regional interictal hypometabolism of TLE.

In conclusion, the bilaterality of EEG findings correlated with BTH on ^{18}F-FDG-PET by the SPM method. SPM analysis may provide an advantage over visual analysis on the evaluation of BTH, and it may have a specific value in predicting MTLE patients with bitemporal excitability or bitemporal independent epileptogenicity, and these patients should be carefully monitored.

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