■ **REVIEW** ■

# Functional Neuroimaging in Epilepsy: FDG PET and Ictal SPECT

Epileptogenic zones can be localized by F-18 fluorodeoxyglucose positron emission tomography (FDG PET) and ictal single-photon emission computed tomography (SPECT). In medial temporal lobe epilepsy, the diagnostic sensitivity of FDG PET or ictal SPECT is excellent, however, the sensitivity of MRI is so high that the incremental sensitivity by FDG PET or ictal SPECT has yet to be proven. When MRI findings are ambiguous or normal, or discordant with those of ictal EEG, FDG PET and ictal SPECT are helpful for localization without the need for invasive ictal EEG. In neocortical epilepsy, the sensitivities of FDG PET or ictal SPECT are fair. However, because almost a half of the patients are normal on MRI, FDG PET and ictal SPECT are helpful for localization or at least for lateralization in these non-lesional epilepsies in order to guide the subdural insertion of electrodes. Interpretation of FDG PET has been recently advanced by voxel-based analysis and automatic volume of interest analysis based on a population template. Both analytical methods confirmed the performance of previous visual interpretation results. Ictal SPECT was analyzed using subtraction methods (coregistered to MRI) and voxel-based analysis. Rapidity of injection of tracers, HMPAO versus ECD, and repeated ictal SPECT, which remain the technical issues of ictal SPECT, are detailed.

**Key Words :** *Epilepsy; Fluorodeoxyglucose F-18; Tomography, Emission, Computed; Tomography, Emission, Computed, Single-photon*

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## INTRODUCTION

It is well-established today that the success rate of operations for epilepsy reaches almost 85% (1-3). Preoperative evaluation of surgical candidates by F-18 fluorodeoxyglucose (F-18 FDG) positron emission tomography (PET) and ictal single-photon emission computed tomography (SPECT) has become a routine practice. This review describes the diagnostic performance of F-18 FDG PET and ictal perfusion SPECT in intractable epilepsies using the more recent image processing methods based on technological advancements as applied to brain F-18 FDG PET and ictal SPECT.

A review of the literature published in 1995, regarding the diagnostic performance of various imaging methods to find epileptogenic zones, showed the variable sensitivity of the several methods used in temporal lobe and extratemporal lobe epilepsies (4). The diagnostic accuracy of interictal SPECT from this data seems to be overestimated because another meta-analysis conducted in 1998 (5) revealed that the overall sensitivity of interictal SPECT was 44%. Until 1995, the sensitivity of FDG PET was not particularly high especially in the case of extratemporal epilepsy; however, recent progress has increased the sensitivity.

The diagnostic performance for medial temporal lobe epilepsy is different from that for extratemporal neocortical epilepsy (4-7). Lateral temporal lobe epilepsy falls into the group of extratemporal lobe epilepsy (2). According to a meta-analysis (5), the cumulative sensitivity of ictal SPECT was 97% in medial temporal lobe epilepsy. This meta-analysis also reported that the sensitivity of ictal SPECT in extratemporal lobe epilepsy is still elusive because of a lack of available data.

The sensitivity of ictal perfusion SPECT, FDG PET, and MRI in intractable epilepsy at our institution is shown in Table 1 (8). At the end of 1997, among more than 300 patients studied, 118 were operated and followed up for more than a year. This group included temporal lobe and extratemporal lobe epilepsy patients. As a whole, the sensitivity of ictal SPECT was determined to be around 75% and that of FDG PET was around 85%. In contrast, the sensitivity of MRI was determined to be 70%.

## DIAGNOSTIC PERFORMANCE OF FDG PET AND ICTAL SPECT IN MEDIAL TEMPORAL LOBE EPILEPSY

Medial temporal lobe epilepsy is well known for its pathologic diagnostic criteria of hippocampal sclerosis and/or atrophy. These hippocampal changes are easily found by the recent generation MRI machines (Fig. 1A). Both the quantitative and the qualitative MRI interpretation give similar
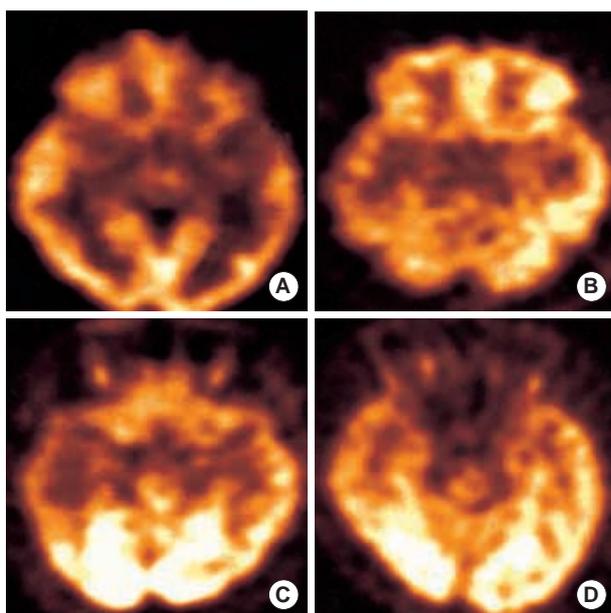
Fig. 1. FDG PET of medial temporal lobe epilepsy. (A) A typical matching case with hippocampal atrophy and hypometabolism in the left temporal lobe. (B) A case with ambiguous ictal EEG but with definite hypometabolism in the right temporal lobe. (C) An example of bilateral hippocampal atrophy on MRI but unilateral hypometabolism in the right temporal lobe. (D) A non-lesional cryptogenic case on MRI but with mild hypometabolism in the right temporal lobe. All of these 4 patients underwent operations and had surgical outcomes of Engel class 1.
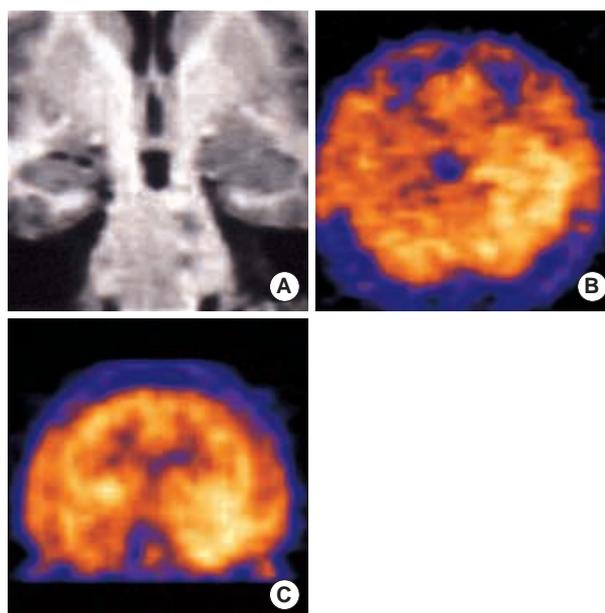


Fig. 2. Ictal SPECT in a case with cryptogenic medial temporal lobe epilepsy. MRI findings were normal. (A) Ictal hyperperfusion is found in the left temporal lobe on ictal perfusion SPECT. (B) Transaxial slice (C) Coronal view. Surgical outcome after left temporal lobectomy was excellent.

Table 1. Correct localization of MR, F-18 FDG PET, and ictal SPECT

|              | Pathology | Surgical Outcome |
|--------------|-----------|------------------|
| MRI          | 72%       | 77%              |
| F-18-FDG PET | 85%       | 86%              |
| Ictal SPECT  | 73%       | 78%              |

Modified from reference 8

diagnostic effectiveness for temporal lobe epilepsy with the recent generation MRI machines. Cases without any abnormal findings on MRI exist but rare (9).

Thus, FDG PET is helpful only for three types of cases in medial temporal lobe epilepsy. The first type is represented by those patients with ambiguous sclerosis (Fig. 1B). In a few patients with medial temporal lobe epilepsy, hippocampal sclerosis is not prominent even on three-dimensional MP-PAGE MR images. The second type is of bilateral sclerosis and/or atrophy (Fig. 1C). A few confusing cases have been filed among 600 fully-investigated epilepsy patients at our institution. The third type is represented by those patients with normal MRI findings (Fig. 1D). Ictal perfusion SPECT is also helpful in these three types of cases (Fig. 2). FDG PET and ictal SPECT were found to be similarly effective at localizing epileptogenic zones in non-lesional (MRI-negative) medial temporal lobe epilepsy (9).

## DIAGNOSTIC PERFORMANCE OF FDG PET AND ICTAL SPECT IN EXTRATEMPORAL LOBE EPILEPSY

In contrast to the temporal lobe epilepsy, the extratemporal lobe epilepsy poses several problems in terms of the local-

ization of epileptogenic zones. About one third to one half of intractable patients are usually suspected to have extratemporal lobe epilepsy (10-12). Extratemporal lobe epilepsy consists of lateral temporal, frontal, occipital and parietal lobe epilepsy, in decreasing order of prevalence (11).

Extratemporal lobe epilepsy poses two kinds of problems in localization of epileptogenic zones. The first is that if the MRI shows multiple candidate foci of epileptogenic zones, one cannot be sure which is the culprit lesion for the seizure induction. The second is that if the MRI does not show any structural lesion, that is to say, the lesion is cryptogenic, it is difficult to determine where to apply subdural grids and strips during subdural EEG studies. FDG PET and ictal SPECT are helpful in these cases. They may make it clear that a lesion is epileptogenic or localize a lesion in a totally cryptogenic case. In some patients, FDG PET and ictal SPECT can at least lateralize cryptogenic lesions, although cannot localize a lesion.

According to our previous study (13), positive predictive values of FDG PET and ictal SPECT in cryptogenic epilep-
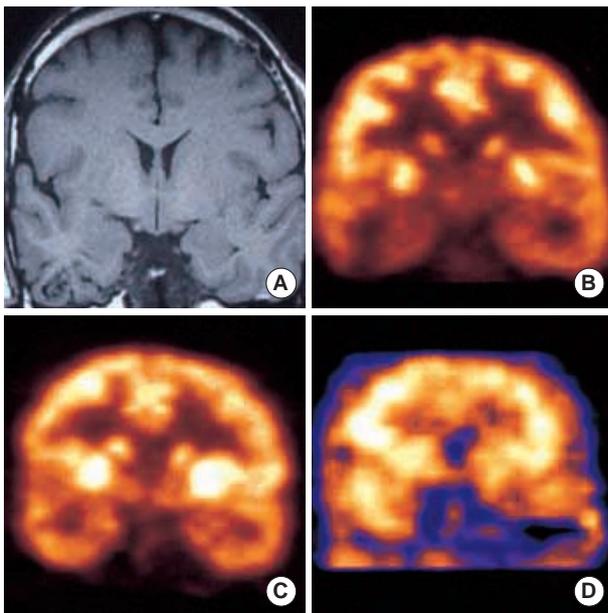
Fig. 3. FDG PET and ictal SPECT in lateral temporal lobe epilepsy. (A) An example of a lesional case with AV malformation on MRI. (B) On FDG PET, the metabolism is decreased in the right temporal lobe. (C) A cryptogenic case with normal hippocampus and neocortex on MRI. Metabolism is lower on FDG PET in the right temporal lobe. (D) Perfusion is increased on ictal SPECT in the same case.
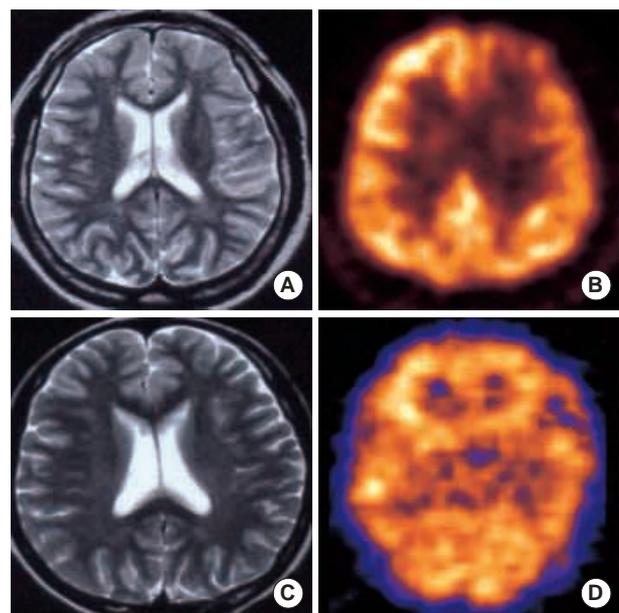


Fig. 4. FDG PET and ictal SPECT in frontal lobe epilepsy. MRI is normal (A), but localized decrease of metabolism is found in the left frontal lobe (B). In another case, the MRI is normal (C), but localized increased perfusion is found in the right frontal lobe (D). After neocortical resection of the frontal lobe in both patients, they were seizure free.
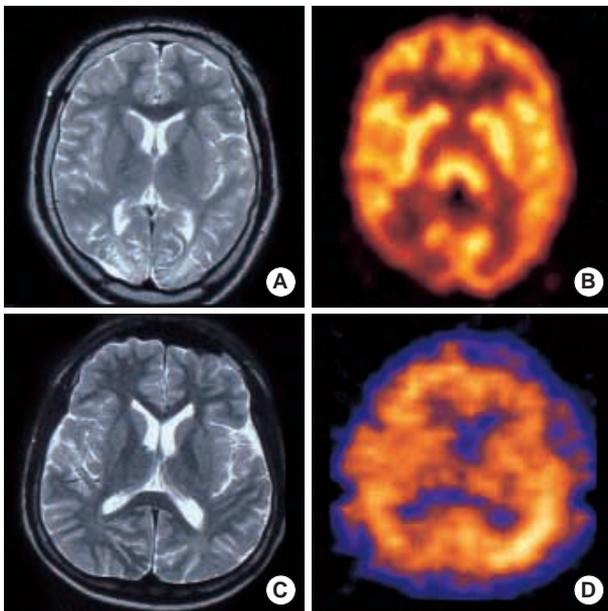


Fig. 5. FDG PET and ictal SPECT in occipital lobe epilepsy. MRI was normal (A), but metabolism is decreased in a case of right occipital lobe epilepsy (B). In another case, the MRI is normal (C), but perfusion is increased in the left occipital lobe on ictal SPECT (D). Both of the patients became seizure-free after neocortical resection.

sy are over 70%. Localization rates are different for different epileptogenic lobes. Among the complex partial seizure patients, lateral temporal lobe (Fig. 3) or frontal lobe seizures (Fig. 4) are relatively easy to diagnose. On the contrary, it is not easy to localize epileptogenic zones in occipital lobe epilepsy. Areas showing the most severe hypometabolism are limited to the occipital lobes in some patients (Fig. 5), however, this is not true in all patients. The areas of highest perfusion were not limited to occipital lobes, either. In some patients, the hypometabolism was localized to the ipsilateral temporal lobes. Moreover, epileptogenic zones could have been misdiagnosed for temporal lobes. As for the occipital lobe epilepsy, the localization rate was found to be 47% by MRI and 60% by PET (14). The localization rate of ictal SPECT was not excellent, however, the lateralization rate of ictal SPECT was 76%. This might have been caused by the rapid propagation of ictal discharges from the occipital lobe to adjacent lobes, especially to the temporal lobe. In confusing cases of occipital lobe epilepsy, the examination of visual symptoms and visual field is mandatory (14).

## UNCOUPLING OF METABOLISM AND PERFUSION IN EPILEPTOGENIC ZONES

The sensitivity of interictal SPECT was 44% on average according to a meta-analysis (5). However, in our cohort study (13), the sensitivity was lower (34%) in temporal and extra-
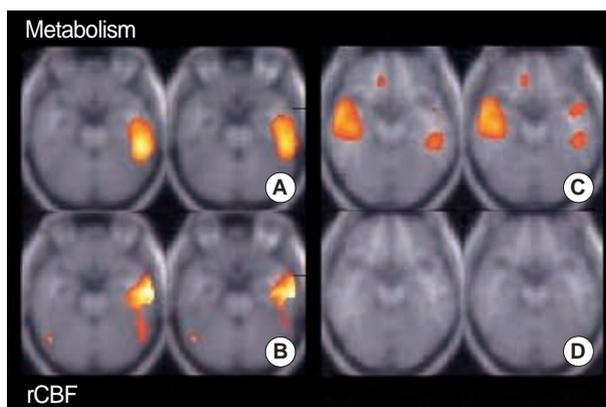
Fig. 6. SPM analysis result of FDG PET and water PET (39). Colored areas are the voxels that differ from the normal controls on both PETs. In a coupled case, the left temporal lobe is found to have hypometabolic voxels on FDG PET (A) and hypoperfused voxels on water PET (B). In an uncoupled case, the right temporal lobe is found to have hypometabolic voxels on FDG PET (C), however, there was no area of hypoperfusion on water PET (D).

temporal lobe epilepsy. When we consider the dogma of metabolism and perfusion coupling in brain, the significance of or the reason for this finding is important. The reason why interictal FDG PET is excellent but interictal SPECT is poor (Fig. 6) for the localization of epileptogenic zones could be explained as follows.

Among more than 300 patients, we identified 14 patients with increased perfusion in the epileptogenic zones as determined by surgical outcome or invasive studies (15). Four of these were the patients in whom interictal SPECT was performed on the second day after ictal study. In other four patients, seemingly hyperperfused, were studied on the 3rd to 5th day after ictal study (Fig. 7A, B). This means that the interictal SPECT was in fact not the interictal one. Subclinical seizure activity just before or during interictal studies could have resulted in this increased perfusion at the epileptogenic zones.

On the other hand, delayed postictal perfusion abnormalities even long after the previous ictus could have resulted in the increased perfusion (16). When we performed delayed postictal SPECT at 6 hr after ictal SPECT, we found remnant hyperperfusion in a half of the patients (Fig. 7C-E). In one patient, severe hypoperfusion was found on delayed postictal SPECT, which recovered on interictal SPECT. Based upon this investigation, we suggest that even with the EEG monitoring during interictal SPECT, one cannot be sure that the true interictal SPECT has been obtained.

## VOXEL-BASED ANALYSIS OF FDG PET

Statistical parametric mapping (SPM) is a voxel-based approach for determining the significantly different area from
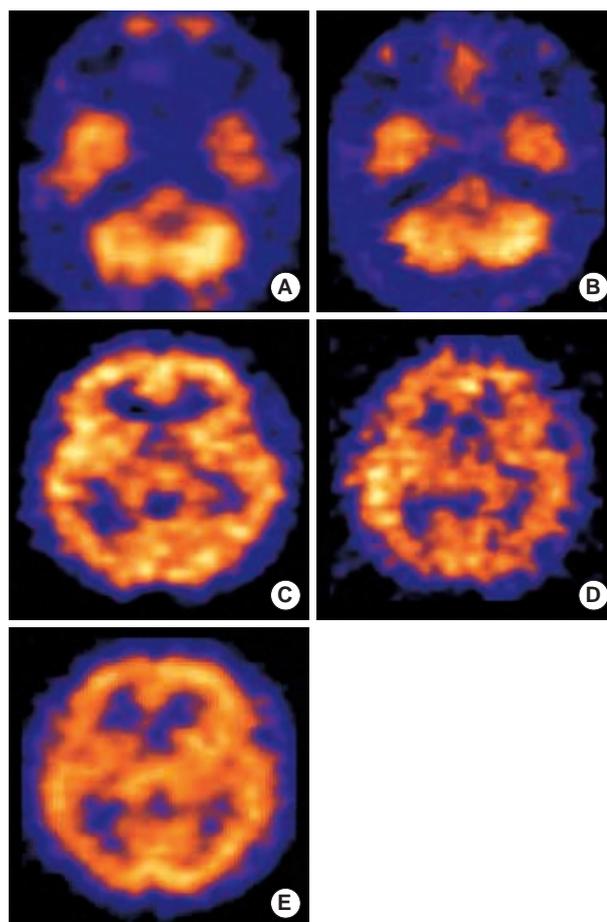


Fig. 7. Hyperperfusion on interictal SPECT (A, B) and delayed postictal hyperperfusion after ictus (C, D, E). In a patient with surgically confirmed right temporal lobe epilepsy, interictal SPECT (B) taken on the fourth day after ictal study (A), shows the same increased perfusion in the right temporal lobe and crossed cerebellar hyperperfusion. (C, D, E) Delayed hyperperfusion at the epileptogenic zones. In this patient with right temporal lobe epilepsy, perfusion is increased in the right temporal lobe on ictal SPECT (C) and also in 6-hr delayed SPECT (D). On interictal SPECT (E), perfusion is decreased in this temporal lobe (16).

normal controls (Fig. 6). After spatially transforming and smoothing the individual PET or SPECT data, using the general linear model, the voxel count of the individual patient is compared with that of the normal controls. This analysis method is easy to perform and very robust, and has recently become popular (16-18).

## QUANTIFICATION USING AUTOMATIC VOLUME OF INTEREST ON POPULATION BASED ATLAS

This method is based on the population-based standard anatomy, which was developed by Montreal Neurological Institute and named SPAM. SPAM, an abbreviation for 'sta-

tistical probabilistic anatomical map', differs from SPM. SPM is a voxel-based approach, whereas SPAM is an area-based approach. We have a population-averaged anatomical definition of gyri and lobes in MRI template format. To construct SPAM, the Montreal group collected, parceled, and segmented normal MR images from 152 young people. Original PET images are transformed to an MRI template and multiplied by the probabilities obtained from the SPAM template. For example, if the right hippocampus is chosen, the resulting image shows the counts in the probabilistic area of the right hippocampus. This method was first used by our group to quantify objectively the asymmetric index and these asymmetric indices could be used to localize epileptogenic zones on FDG PET (19).

## TECHNICAL ISSUES OF ICTAL SPECT

### Rapidity of radiotracer injection

Ictal hyperperfusion is followed by postictal hypoperfusion in epileptogenic zones. Whereas an ictal hyperperfusion could be revealed if the injection is delayed within 60 sec of the ictal EEG onset (20), the postictal perfusion decrease might be observed if the injection is delayed within 2 to 15 min of the ictal EEG onset. Postictal hypoperfusion in epileptogenic zones has been used to help identify epileptogenic zones. The semiology and EEG should be monitored with a video camera equipped with a continuous EEG monitoring system just to confirm the pertinence of ictal injection. Although referred to by earlier studies, the onset of clinical ictus is frequently different from that of ictal EEG. The latter is sure to be the earlier of the two, and video-EEG monitoring is indispensable to determine the injection delay.

A recent report (21) analyzed the relationships between the results of ictal SPECT and those of ictal EEG, placing an emphasis on the possibility of false lateralization. Low concordance rate was revealed to exist between peri-ictal EEG and ictal SPECT when the preinjection and postinjection epochs were different in terms of their lateralizations. Considering the spreading nature of ictal discharges associated with increased cerebral perfusion, this result seems reasonable, however we analyzed a larger group of patients (n=68) than in the previous study (21) and found that preinjection EEG, not postinjection EEG was significantly effective in determining the pattern of ictal SPECT (22). This result might be explained by the delayed perfusion change induced by ictal electrical discharges.

### HMPAO versus ECD

Both Tc-99m hexamethylpropylene amine oxime (HMPAO) ictal SPECT (5) and Tc-99m ethyl cysteinate dimer (ECD) ictal SPECT (23, 24) were reported to be helpful for the localization of epileptogenic zones, and one report concluded that Tc-99m ECD compares favorably with unstabilized Tc-99m HMPAO for peri-ictal SPECT studies. Since ECD is stable after labeling, the latter was believed to have a distinct advantage of rapid injection at the time of ictus. Recently, however, $CoCl_2$ has been used as a stabilizer for HMPAO, and when used along with $CoCl_2$, Tc-99m HMPAO was found to match Tc-99m ECD in terms of the rapidity of its injection at the time of ictus (26).

The distribution patterns of Tc-99m HMPAO and Tc-99m ECD were found to be very similar, although the identified differences may be significant (27, 28). When one considers the different cellular retention mechanisms of these compounds, a difference in their distribution at the time of ictus might be expected.

In an earlier study (29), we replaced Tc-99m HMPAO with Tc-99m ECD for a period of three months. Before this period, only Tc-99m HMPAO had been used for ictal perfusion SPECT. We compared the diagnostic performances of the two in terms of finding hyperperfused areas and epileptogenic zones and the degree of hyperperfusion. We found that the sensitivity of Tc-99m ECD ictal SPECT was similar to that of Tc-99m HMPAO ictal SPECT in temporal lobe epilepsy, however, ictal hyperperfusion was higher for Tc-99m HMPAO SPECT. In patients with neocortical epilepsy, Tc-99m HMPAO ictal SPECT also proved superior to Tc-99m ECD ictal SPECT in terms of sensitivity and the degree of hyperperfusion.

### Repeated ictal SPECT

For our clinical practice routine these days, the video monitoring of ictal semiology and EEG covers several episodes of ictus. This is partly because the ictal EEG at the start of the ictal discharge may be ambiguous in some episodes, and also because the observation of multiple episodes enhances the credibility of the localization of ictal scalp EEG. Ictal SPECT is usually associated with one ictal episode among these multiple episodes. It is also not infrequent that multiple foci are found in patients on ictal EEG monitoring.

Peri-ictal propagation of seizure activity complicates the interpretation of hyperperfused areas, because the seizure activity can spread to other brain areas within a relatively short period (30). It is inevitable that unexpected patterns of ictal hyperperfusion are observed on ictal SPECT. Sometimes no area of significant hyperperfusion is found on ictal SPECT. Reproducible observation of ictal cerebral blood flow may overcome the possible false lateralization or lack of sensitivity. Repeated ictal SPECT is expected to yield information that complements the ictal scalp EEG findings (31).

According to a previously reported reproducibility study, peri-ictal SPECT results were found to be reproducible in most patients, and this was also corroborated by quantitative subtraction ictal SPECT co-registered to MRI (SISCOM)

analysis (32). However, the authors considered that the peri-ictal SPECT images showed decreased perfusion repeatedly at the epileptogenic zones. Ictal SPECT is usually considered to be unreliable when it reveals only an area of decreased perfusion and not areas of increased perfusion. Efforts to shorten the injection delay should have been taken in these cases (20, 32).

Through the investigation on the utility of repeated ictal SPECT, we found that the repeated ictal SPECT was useful for yielding new or additional information about the epileptogenic zones by confirming that the region of interest was the epileptogenic zone (Fig. 8) or by suggesting that the epilepsy was of multifocal origin (31). We suggest that ictal SPECT should be repeated when the first SPECT findings are ambiguous. This strategy, which has been adopted in about 10% of the surgical candidates at our institution over the past 5 yr, proved to compliment definitely the other improved methodologies, such as the SISCOM or the closer control to shorten the injection time in epilepsy monitoring units.

## Subtraction SPECT and SPM

Subtraction SPECT (33) or difference SPECT (34) has re-cently evolved to SISCOM by various investigators (34-36). While we believe that ictal SPECT images should be closely compared with interictal SPECT images, traditional side-to-side visual comparisons of ictal and interictal images (Fig. 9A) may be difficult because of differences in the overall intensity of both images or differences in slice level and orientation (35). In this sense, computer-aided subtraction of the interictal SPECT from the ictal SPECT images, with subsequent co-registration to MRI (Fig. 9B), can overcome these limitations. Several reports (7, 35, 37) have suggested that SISCOM should be valid and superior to side-to-side interpretation.

However, a recent report (38) questioned the usefulness of ictal-interictal subtraction SPECT and suggested that a normal population database should be used in interpreting a patient's ictal SPECT. The authors used an automated voxel-based analysis method to find hyperperfused areas, and found that the voxel-based automated SPM determination of hyperperfused areas (Fig. 9C) was superior to the ictal-interictal subtraction SPECT. As is well known to its advocates, SISCOM might yield confusing data on areas of hyperperfusion in some cases. These findings are interesting but no definitive explanation has been given to them.

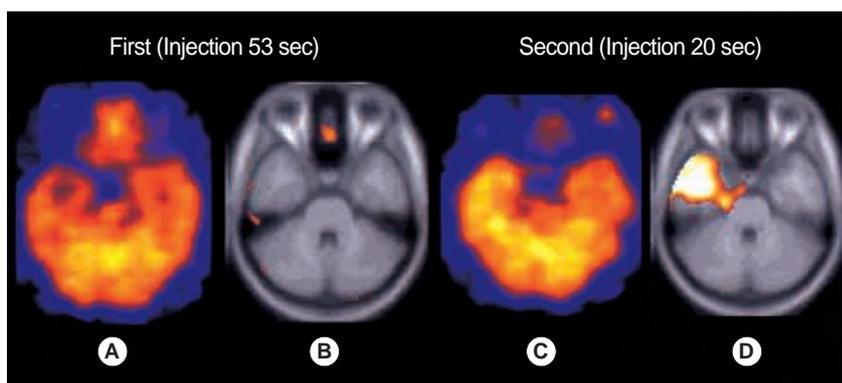However, there could be several reasons for this observa-



**Fig. 8.** Repeated ictal SPECT. (**A**) The first ictal SPECT. (**B**) Its SPM result dioes not reveal any area of increased perfusion. (**C**) The second ictal SPECT. (**D**) Its SPM result reveals an area of increased perfusion in the right temporal lobe.
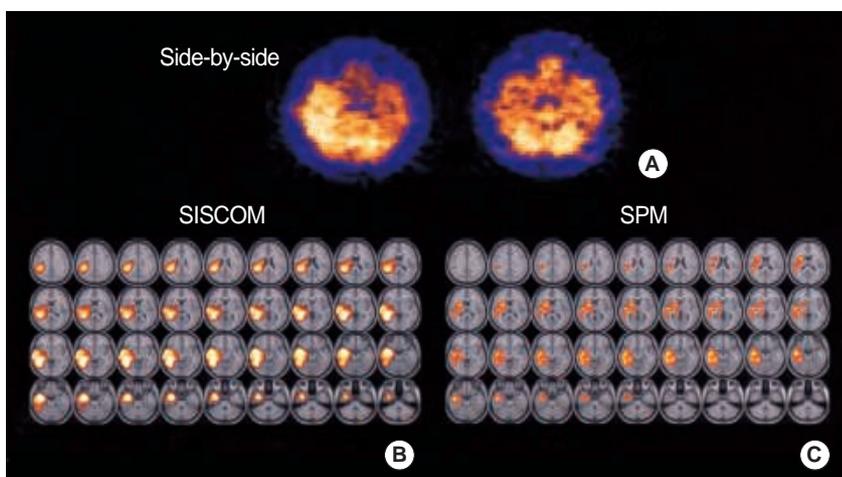


**Fig. 9.** (**A**) Side-by-side examination of ictal and interictal SPECT, (**B**) SISCOM and (**C**) SPM ictal SPECT result. The right temporal lobe was found to be epileptogenic.

tion. First, the interictal SPECT may not be actually interictal. True interictal scans do not always represent the actual interictal period, and this discrepancy may occur in as many as 5% of interictal scans, probably due to the injection during the subclinical ictal period (38). EEG monitoring and confirmation of interictal EEG during injection might overcome this problem, however, our recent investigation (16) proved that even the interictal injection of radiotracer several hours after an ictal episode cannot guarantee true interictal images. Late postictal hyperperfusion was found in more than a half of the patients. We believe that this is the reason for the prevalence of increased perfusion in the epileptogenic zones in interictal SPECT. To determine whether the interictal SPECT represent the true interictal perfusion, subtraction of interictal from ictal images would be helpful. EEG monitoring at the time of injection does not convince us that this SPECT image reflects the true interictal perfusion.

## CONCLUSION

Functional neuroimaging methods, such as FDG PET and ictal perfusion SPECT, are helpful to localize epileptogenic zones especially in patients with non-lesional epilepsy on MRI. Quantitative methods, such as SPM, SPAM, and SISCOM are believed to be able to enhance the objectivity of the analysis to find epileptogenic zones by revealing hypometabolic or hyperperfused areas.

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