Comparison of [^{18}F]FDG-PET, [$^{99\text{m}}\text{Tc}$]-HMPAO-SPECT, and [^{123}I]-iomazenil-SPECT in localising the epileptogenic cortex

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Abstract

Objectives—Firstly, to compare the findings of interictal ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) and of single photon emission computed tomography (SPECT) using $^{99\text{m}}\text{Tc}$ -hexamethyl propylene-amine-oxime (HMPAO) and ^{123}I -iomazenil in localising the epileptogenic cortex in patients who were candidates for epilepsy surgery, but in whom clinical findings, video EEG monitoring (V-EEG), MRI, and neuropsychological evaluations did not give any definite localisation of the seizure onset. Secondly, to assess the ability of these functional methods to help in the decision about the epilepsy surgery.

Methods—Eighteen epileptic patients were studied with FDG-PET and iomazenil-SPECT. HMPAO-SPECT was performed in 11 of these 18 patients. Two references for localisation was used—ictal subdural EEG recordings (S-EEG) and the operated region.

Results—Fifteen of 18 patients had localising findings in S-EEG. FDG-PET findings were in accordance with the references in 13 patients and iomazenil-SPECT in nine patients. HMPAO-SPECT visualised the focus less accurately than the two other methods. In three patients S-EEG showed independent bitemporal seizure onset. In these patients FDG-PET showed no lateralisation. However, iomazenil-SPECT showed temporal lobe lateralisation in two of them.

Conclusion—FDG-PET seemed to localise the epileptogenic cortex more accurately than interictal iomazenil-SPECT in patients with complicated focal epilepsy.

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Keywords: PET; SPECT; epilepsy; epilepsy surgery

Functional imaging is widely used in presurgical evaluation of medically intractable complex partial seizures. It reduces the number of invasive intracranial EEG recordings and is helpful in planning such recordings if necessary.

^{18}F -fluorodeoxyglucose (FDG) positron emission tomography (PET) studies in patients

with temporal lobe epilepsy show interictal areas of decreased cerebral glucose metabolism near the primary epileptic focus.¹⁻³ The congruence of the area of hypometabolism in PET with temporal lobe EEG abnormalities is 62%-89%.⁴⁻⁹

$^{99\text{m}}\text{Tc}$ -hexamethyl propyleneamine-oxime (HMPAO) shows the regional cerebral blood flow (rCBF). Interictally, HMPAO single photon emission tomography (SPECT) shows hypoperfusion of the whole temporal lobe in patients with medically intractable complex partial seizures of the temporal lobe.¹⁰⁻¹¹ The sensitivity of interictal HMPAO-SPECT, however, varies from 20%-83%.¹²⁻¹⁶ A few comparative studies have suggested that FDG-PET can demonstrate epileptic abnormalities more reliably than HMPAO-SPECT.¹⁶⁻¹⁹

Iomazenil (Ro 16-0154) is an iodine containing analogue of the benzodiazepine (BZ) receptor antagonist flumazenil (Ro 15-1788). Reduced uptake by BZ receptors in the epileptic focus has been shown both with PET (^{11}C -labelled flumazenil) and SPECT (^{123}I -labelled iomazenil).²⁰⁻²⁶ Iomazenil-SPECT was found to be comparable or even better in some ways than HMPAO-SPECT in localising epileptic foci.²⁰⁻²²⁻²³⁻²⁷ Iomazenil presumably reflects primary pathophysiological changes in the epileptic focus, compared with secondary changes in glucose consumption and rCBF seen with FDG and HMPAO, respectively. However, there is only one previous study comparing interictal iomazenil-SPECT with FDG-PET. The sensitivities of iomazenil-SPECT and FDG-PET were 80%.²⁴

There are no comparative studies of imaging with rCBF, benzodiazepine receptor uptake, and glucose consumption in the same epileptic patient population. The purpose of this study was firstly to compare the utility of interictal HMPAO-SPECT, iomazenil-SPECT, and FDG-PET in localising the epileptogenic cortex in a small subgroup of epileptic patients who are candidates for epilepsy surgery, but in whom the presurgical evaluation did not give definite localisation of the epileptic focus. Secondly, it was to assess the ability of these non-invasive functional methods to help in the decision to perform surgery in this patient group in whom the epileptogenic region really needed to be confirmed after the routine

Table 1 Clinical data of the patients studied

Patient	Age/sex	Medication
1	34/M	CBZ, CLO, PHT
2	44/F	CBZ, CLO, VGB
3	25/F	CBZ, CLO
4	42/F	CBZ, PHT, VGB
5	29/M	CBZ, PHT
6	27/M	CBZ, CLO
7	26/F	CBZ, CLO
8	20/M	CBZ, CLO, PHT
9	23/M	CBZ, CLO, TIAG
10	28/M	CBZ
11	46/M	No medication
12	22/F	CBZ
13	13/F	CBZ
14	21/F	CBZ, VPA
15	40/F	CBZ, VPA
16	25/M	CBZ
17	44/M	CBZ
18	16/F	CBZ, PHT

CBZ = carbamazepine; CLO = clonazepam; PHT = phenytoin; VPA = valproate; VGB = vigabatrin; TIAG = tiagabine.

presurgical evaluation. Thus ictal subdural-EEG (S-EEG) and the operated region were used as the references.

Methods

PATIENTS

Eighteen patients (nine women, nine men) from the epilepsy surgery programme in Kuopio University Hospital with drug resistant focal epilepsy were studied. The median age of the patients was 26.5 years. The antiepileptic medication (table 1) was kept unchanged between PET and SPECT investigations.

The primary presurgical methods (MRI, conventional EEG, video EEG monitoring (V-EEG) with sphenoidal electrodes, neuropsychological test) were inconclusive in this patient population and thus S-EEG was considered necessary. Brain MRI was performed in all patients with a 1.5T Magnetom (Siemens, Erlangen) with a standard head coil and a tilted coronal 3D gradient echo sequence (MP-RANGE: TR 10 ms, TE 4 ms, TI 250 ms, flip angle 12°, FOV 250 mm, matrix 256 × 192, 1 acquisition). This gave 128 T1 weighted partitions with a slice thickness of 1.5–1.8 mm, which were oriented at right angles to the long

axis of the hippocampus. The assessment of MRI was qualitative. PET and SPECT were carried out as ancillary investigations and were not considered in the decision to perform the operation. The decision was based on the clinical and ictal S-EEG findings, MRI, and neuropsychological data (including the WADA memory test). Fifteen patients were operated on, of whom 13 underwent temporal lobectomy. In one patient (4, table 2) a cyst in the occipital lobe was operated on and in one patient (6) the operation was performed in the parietal lobe. Table 1 shows the clinical data of the patients.

The study was approved by the ethics committee of Turku University Central Hospital, and all patients and controls gave their informed consent.

SUBDURAL EEG RECORDING

All patients had intracranial continuous EEG recordings with multiple subdural electrodes. Four to 11 strip electrodes were implanted bilaterally on the frontal and temporal cortex and below both temporal lobes, so that the tips of electrodes reached the hippocampal gyrus. Additional electrodes with individual localisations were used when needed in the case of extratemporal lesions. Antiepileptic medication was tapered off, if needed, during V-EEG monitoring until a sufficient number of seizures had been recorded. The electrodes were inserted through burr holes during general anaesthesia three days before the recording and were removed afterwards; the mean recording time was nine days. There were no haematomas or infections as complications of the procedures. S-EEG was performed after the functional imaging investigations.

PET

The PET and SPECT investigations were carried out in Turku University Central Hospital before the invasive recording. The patients were positioned in the PET scanner with the orbitomeatal line parallel to the detector rings in a dimly lit and quiet room. To ensure that the PET was interictal, scalp EEG was recorded for 15 minutes before the injection of the tracer, and throughout the 55 minute PET examination with an eight channel cassette EEG-recorder. The bipolar montage adopted, with standard 10-20 system electrode placement, covered the frontal-central, lateral frontal, and temporal areas on both sides. The EEG recordings and analyses were done with Medilog 9000 equipment (Oxford Medical Systems, UK).

The PET was performed with an eight ring whole body PET scanner (ECAT 931/08-12, Siemens/CTI, Knoxville, TN, USA) using 2-[¹⁸F]-fluoro-2-deoxy-D-glucose (FDG). The in plane resolution of the scanner was 6.5 mm full width at half maximum (FWHM) and axial resolution was 6.8 mm.²⁸ True resolution after reconstruction was 8 mm. Fifteen continuous transaxial slices (6.75 mm) were acquired. The images were reconstructed in 256 × 256 matrices using a Hann filter with a cut off frequency of 0.5. The data were corrected for decay of the

Table 2 Results of the presurgical methods

Patient No	MRI	S-EEG	HMPAO-SPECT	Iomazenil SPECT	FDG-PET	Operation
1	N	LT	—	LT	LT	LT
2	N	LT/LF	—	LT	—	ND
3	N	RT Mesial	RT	RT	RT	RT
4	Cyst/OL	RT/LT/OL	—	—	—	OL*
5	N	LT Mesial→LF	—	LT	LT	LT
6	Atr/RP	RT/RP	—	RT	RT/RP	RP
7	N	RT	—	RT	RT	RT
8	N	LT→LF	—	LT	LT	LT
9	MTS	RT	ND	—	RT	RT
10	N	RT	—	—	—	RT
11	nspec	RT	—	—	RT	RT
12	N	RF→RT RT→RF	—	RF	RT	RT
13	Cyst/LT	RT/LT	ND	RT	—	RT
14	N	RT Mesial	ND	RT Mesial	RT	RT
15	MTS	LT	ND	LT	LT	LT
16	N	LT/LF	ND	LT	LT	LT
17	N	RT Mesial	ND	RF/RT	RT	RT
18	N	RT/LT	ND	RT	—	ND

* Lesionectomy.

S-EEG = ictal subdural EEG; RT = right temporal; LT = left temporal; RF = right frontal; LF = left frontal; RP = right parietal; OL = occipital lobe; atr = atrophy; MTS = mesial temporal sclerosis; nspec = non-specific findings; N = normal; ND = not done; — = no lateralisation.

tracer, dead time, and photon attenuation with a measured attenuation correction.

The FDG was prepared by the methods of Hamacher *et al.*²⁹ and Solin *et al.*³⁰ The radiochemical purity exceeded 99% and the specific radioactivity at the time of injection was about 75 GBq/μmol (2 Ci/μmol). A bolus of 3.7 MBq/kg of FDG was injected intravenously and 21 venous blood samples were drawn from the preheated arm during the investigation to measure plasma activity. Regional cerebral glucose metabolic rate ($rCMR_{gluc}$) values were obtained drawing elliptical regions of interest (ROIs) with an average size of 0.5 cm×2 cm to the cortical grey matter areas: the frontal, sensorimotor (precentral and postcentral gyri), temporal, parietal, and the occipital lobe in addition to the subcortical structures (thalamus, brainstem, striatum, and cerebellum). The total number of ROIs was 70–100. $rCMR_{gluc}$ values were calculated according to Patlak *et al.*³¹ Left-right asymmetry (asymmetry index=AZ) was calculated for all pairs of symmetrical regions using the formula:

$$AI = (L - R) \times 100 / ((L + R) / 2).$$

In a series of seven healthy male volunteers (median age 26 years) studied in our PET centre the 95% confidence interval (95% CI) for the asymmetry index was 98.4%–104.3%. Thus the left-right asymmetry of the controls was negligible, which was in line with other quantitative studies.^{4 32–34} As suggested earlier,³ metabolic asymmetries of 15% or greater were considered significant in epileptic patients. The $rCMR_{gluc}$ were analysed without any knowledge of the results of the other investigations.

SPECT

In the interictal SPECT investigation with [^{99m}Tc]-HMPAO or [¹²³I]-iomazenil, the tracer was injected slowly with the patient lying in a supine position, eyes open, in a quiet room. The average [^{99m}Tc]-HMPAO and [¹²³I]-iomazenil doses were 740 MBq and 160 MBq respectively. Image acquisition was performed with a Siemens Orbiter gamma camera (Siemens Gammasonics, IL, USA) and started 15 minutes after HMPAO and two hours after iomazenil administration. Sixty four projections (30–35 s each) in a 64×64 matrix were collected over 360°. Using the LEAP collimator, the total number of counts was >5 million in HMPAO and 3.5 million in the iomazenil investigation. The acquisition time was 35–40 minutes. The projections were filtered with a Wiener filter and were reconstructed into orbitomeatal transversal, coronal, and sagittal slices. The spatial resolution of the filtered images was 16 mm FWHM and the slice thickness was 6 mm. No attenuation correction was applied.

The data were analysed by qualitative visual interpretation of focal defects and asymmetries without any knowledge of the results of the other investigations.

Results

EEG

In all patients ictal scalp EEG with sphenoidal electrodes posed a problem in lateralisation: seven patients had bitemporal seizure onsets, six patients had non-localising and non-lateralising surface EEG, three patients had seizures with fast generalisation, and two patients had temporal and extratemporal EEG discharges. Thus the localisation of the seizure onset needed to be confirmed with video EEG monitoring with subdural electrodes. It localised seizure onset in the temporal lobe in nine patients and showed bitemporal seizure onsets in two patients (13, 18; table 2). In addition, six patients (2, 5, 6, 8, 12, 16) had two foci in which the primary focus situated in the temporal lobe in four patients (5, 8, 12, 16), in the frontal lobe in one (2) and in the parietal lobe in one patient (6). Patient 4 had epileptiform activity in both temporal lobes and also in the occipital lobe.

MRI

Twelve patients had a normal MRI, and mesial temporal sclerosis was seen in two patients (9, 15). Two patients had a cyst, which was situated in the left temporal lobe in patient 13 and in the occipital lobe in patient 4. Patient 6 had atrophy in the parietal lobe and one patient (11) had non-specific findings in MRI.

PET

In nine patients with unilateral temporal lobe S-EEG seizure onset, PET showed an ipsilateral decreased glucose metabolic rate in the same temporal lobe as in S-EEG in eight patients (1, 3, 7, 9, 11, 14, 15, 17). In addition, four of the six patients (5, 8, 12, 16) with two foci in S-EEG had a hypometabolic area in the temporal lobe, which was considered the primary focus by S-EEG and was later operated on. Patient 6 with two foci in S-EEG had decreased glucose consumption in the right temporal and right parietal lobe also in PET. The parietal lobe was operated on. One of the patients (2) with primary focus in the frontal lobe in S-EEG had no significant changes in glucose consumption in the PET. Because the corticography during the operation did not localise the onset of epileptic activity, she was not operated on. None of the three patients with bitemporal S-EEG findings showed any lateralisation in PET imaging. Patient 10 had a normal PET investigation regardless of the temporal findings in S-EEG and had a temporal lobectomy.

SPECT

Eleven of the 18 patients were investigated with both HMPAO-and iomazenil-SPECT. As primary analysis of HMPAO-SPECT showed hypoperfusion of the temporal area only in one patient (3), and thus showed lateralisation less often than iomazenil-SPECT, HMPAO-SPECT was considered unnecessary for the rest of the patients to avoid excessive doses of radioactivity.

Iomazenil-SPECT was performed in all 18 patients. In visual assessment, asymmetry in

iomazenil uptake was found in five of the nine patients (1, 3, 7, 14, 15) with unilateral temporal lobe seizure onset. In addition, three of the six patients (5, 8, 16) with two foci in S-EEG had reduced uptake of iomazenil in the subsequently operated temporal lobe. In patient 6 with the temporal and parietal foci and in patient 2 with the temporal and frontal foci in S-EEG iomazenil-SPECT showed decreased uptake in the non-operated temporal lobe. Iomazenil-SPECT showed decreased BZ receptor binding in the temporal lobe in two of the three patients (13, 18) who had bitemporal epileptiform activities in S-EEG. Patient 4 with the operation in the occipital lobe had a normal iomazenil-SPECT investigation. Iomazenil-SPECT disclosed asymmetry in both the right temporal and the right frontal lobe in one patient (17), but the S-EEG showed the region of the seizure onset only in the operated temporal lobe. In patient 12 iomazenil-SPECT showed asymmetry only in the frontal lobe instead of the frontal and temporal lobe foci in S-EEG. She had temporal lobectomy. In three patients (9, 10, 11) iomazenil-SPECT was normal regardless of the unilateral S-EEG abnormalities.

PET AND SPECT COMPARISON

The results of the PET data were in agreement with S-EEG and the operated region in 13 of the 15 patients with unilateral S-EEG focus (1, 3, 5, 6, 7, 8, 9, 11, 12, 14, 15, 16, 17) and in addition, PET showed no asymmetry in the glucose consumption in one of the non-operated patients (18) with bitemporal findings in S-EEG data. Thus the agreement between PET, S-EEG, and operated region was 77% (14 of 18). Congruence of iomazenil-SPECT and S-EEG result and the operated region was found in nine of the 15 patients with unilateral (1, 3, 5, 7, 8, 14, 15, 16, 17) and in one of the three patients with bitemporal findings in S-EEG (13). Iomazenil-SPECT disclosed decreased uptake only in the non-operated lobe in patients 6 and 12, and thus iomazenil-SPECT was not considered to give any useful information about making the decision on which region to operate. The agreement of iomazenil-SPECT and references was therefore 55% (10 of 18).

Table 3 shows the results of S-EEG, PET, and iomazenil-SPECT collectively. PET showed no false lateralising findings, but false negative results were seen in two patients. On the other hand, SPECT disclosed false lateralising findings in two patients and in three

patients it was non-localising instead of localising S-EEG.

Discussion

To our knowledge this is the first study in which the usefulness of interictal HMPAO and iomazenil-SPECT and FDG-PET has been compared in localising the epileptogenic cortex in the same subgroup of epileptic patients, in whom the routine presurgical evaluations were not conclusive.

Mesial temporal sclerosis is found in 50%–75% of the temporal lobes resected in epilepsy surgery.³⁵ Brain MRI discloses findings in about 70% of those patients with mesial temporal sclerosis and in nearly all patients with foreign tissue lesions.^{36, 37} Ryvlin *et al*¹⁶ found that 80% of the patients with normal MRI, however, exhibited hypometabolism on PET, and the sensitivity of PET was even higher, reaching up to 100% when MRI was abnormal. Thus the structural findings in MRI must be taken into consideration when comparing the sensitivities of the different functional imaging methods obtained in different studies. Our patients belong to the difficult group of patients with temporal lobe epilepsy in whom MRI discloses only mild changes or is normal and in whom conventional non-invasive presurgical evaluation was not localising. In most of the patients (about 50 in the course of the two year study) operated on in Kuopio University Hospital, presurgical evaluations disclosed seizure onset without any invasive recordings. However, the localisation of the epileptogenic cortex needed to be confirmed before the decision about the operation in our patients could be made. This is the patient group who would really benefit from functional imaging investigations which might reduce the need of the invasive EEG recordings. We found functional imaging to be a useful presurgical method even in this complicated patient group.

The congruence of FDG-PET and our references, S-EEG and the operated region, in our study was 77%, which is still in line with the results of other studies,^{4–9} although most of the earlier FDG-PET studies have been done in patients with clearly lateralising scalp-EEG findings and usually abnormal MRI. PET also showed no false positive findings, which emphasises the usefulness of PET in preoperative evaluation.

The outcome and the pathological findings of the surgically removed tissue would surely provide the best measure of the congruence, but in most of the patients it is too early to tell the prognosis. On the other hand, we wanted to compare the presurgical methods with each other and especially their ability to help to make the decision on the operation and that is why we chose two references. In this study the SPECT investigations were performed with a single head gamma camera and image resolution of 16 mm. We do not know whether the results would be improved by using a more complex SPECT system. However, at present the device applied in this study is the system most widely available and thus the method

Table 3 Summary of the results of S-EEG, FDG-PET, and iomazenil-SPECT

	FDG-PET		Iomazenil-SPECT	
	Loc	Non-loc	Loc	Non-loc
S-EEG:				
Loc	13	2	12	3
Non-loc	0	3	2	1

Loc = localising; non-loc = non-localising; S-EEG = ictal subdural EEG.

would be easily accessible in most centres. For the same reason the analysis of SPECT images was qualitative. The antiepileptic drugs vigabatrin, benzodiazepines, and tiagabine might affect the uptake of iomazenil. One of our patients (2) had vigabatrin and clonazepam, one had tiagabine (9), and seven other patients (1, 3, 6, 7, 8, 9, 18) had clonazepam in their medication. Despite these common antiepileptic drugs in the patients with intractable epilepsy, iomazenil-SPECT disclosed the focus in most of these patients. By contrast with results of PET, iomazenil-SPECT showed false lateralising findings in two patients. Both of these patients had bitemporal epileptic discharges in S-EEG.

HMPAO-SPECT was performed in 11 of the 18 patients. As it showed the area of hypoperfusion only in one patient, we decided not to perform HMPAO-SPECT on the rest of the patients to minimise the dose of radioactivity. In our patients the ability of HMPAO-SPECT to localise the seizure onset was not as good as reported in previous studies.^{12–14 16 38 39} However, unlike in our study the patients in the previous studies had CT^{12–14} or MRI abnormalities in at least 50% of the cases.^{16 38} In accordance with our findings, Ryvlin *et al.*¹⁶ found interictal HMPAO-SPECT to show hypoperfusion in only 20% of the patients with normal MRI, but when MRI was abnormal, the sensitivity of HMPAO-SPECT was 90%. Jack *et al.*³⁹ also agreed that SPECT was prone to give incorrect results in patients in whom MRI showed no abnormalities. PET studies,⁴⁰ on the other hand, have also shown that measurements of rCBF are less potent in lateralising and localising the epileptic focus than measuring the cerebral glucose metabolism with FDG. In the present study, iomazenil-SPECT lateralised the focus much more accurately than HMPAO-SPECT. As SPECT is cheaper, less complicated, and more easily accessible than PET, comparative studies with these methods in the same populations are needed. Van Huffelen *et al.*²⁴ compared iomazenil-SPECT with FDG-PET and found the sensitivity of iomazenil-SPECT to be 85%. As in our study, they showed reduced benzodiazepine receptor uptake in SPECT to be less accurate than the measurements of glucose metabolism in PET.

Because it takes up to 40 minutes for the FDG to be taken up by the brain, ictal scanning is seldom possible with FDG-PET, by contrast with HMPAO-SPECT, the kinetics of which are faster than that of FDG. Ictal or postictal scanning increases the sensitivity of HMPAO-SPECT to that of FDG-PET.^{17 41–43} However, ictal scanning requires admission to hospital with long term monitoring and often drug withdrawal.

In summary, we found that in our patient population benzodiazepine receptor imaging with interictal ¹²³I-iomazenil-SPECT is more sensitive in the detection of the epileptogenic focus in the temporal lobe than rCBF imaging with ^{99m}Tc-HMPAO. Both interictal iomazenil-SPECT and FDG-PET are appropriate methods for localising the epileptic focus within the temporal lobe and thus help to make the deci-

sion on the operated region. At least with the instrumentation applied in this study and using S-EEG and the operated region as references, we found FDG-PET to be superior to interictal SPECT investigations.

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