

# Perfusion patterns in postictal $^{99m}\text{Tc}$ -HMPAO SPECT after coregistration with MRI in patients with mesial temporal lobe epilepsy

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## Abstract

**Objectives**—To assess patterns of postictal cerebral blood flow in the mesial temporal lobe by coregistration of postictal  $^{99m}\text{Tc}$ -HMPAO SPECT with MRI in patients with confirmed mesial temporal lobe epilepsy.

**Methods**—Ten postictal and interictal  $^{99m}\text{Tc}$ -HMPAO SPECT scans were coregistered with MRI in 10 patients with confirmed mesial temporal lobe epilepsy. Volumetric tracings of the hippocampus and amygdala from the MRI were superimposed on the postictal and interictal SPECT. Asymmetries in hippocampal and amygdala SPECT signal were then calculated using the equation:  
 $\% \text{ Asymmetry} = 100 \times (\text{right} - \text{left}) / (\text{right} + \text{left})/2$ .

**Results**—In the postictal studies, quantitative measurements of amygdala SPECT intensities were greatest on the side of seizure onset in all cases, with an average % asymmetry of 11.1, range 5.2-21.9. Hippocampal intensities were greatest on the side of seizure onset in six studies, with an average % asymmetry of 9.6, range 4.7-12.0. In four scans the hippocampal intensities were less on the side of seizure onset, with an average % asymmetry of 10.2, range 5.7-15.5. There was no localising quantitative pattern in interictal studies.

**Conclusions**—Postictal SPECT shows distinctive perfusion patterns when coregistered with MRI, which assist in lateralisation of temporal lobe seizures. Hyperperfusion in the region of the amygdala is more consistently lateralising than hyperperfusion in the region of the hippocampus in postictal studies.

(*J Neurol Neurosurg Psychiatry* 1997;63:235-239)

Keywords: temporal lobe epilepsy; mesial temporal sclerosis; SPECT; magnetic resonance imaging; cerebral blood flow

Ictal and postictal single photon emission computed tomography (SPECT) scanning is very helpful in localising the epileptogenic focus, especially in patients with temporal lobe epilepsy.<sup>1,2</sup> There are different patterns of perfusion during ictal and immediate postictal  $^{99m}\text{Tc}$ -hexamethylpropyleneamine oxime (Tc-HMPAO) SPECT scans. However,

ictal studies more consistently lateralise the epileptogenic temporal lobe than do postictal studies.<sup>2</sup>

Imaging the brain using different imaging modalities, which provide either structural or function information, offers the opportunity to investigate the functional attributes of anatomical brain structures. Conventional MRI provides detailed information about brain anatomy, whereas SPECT provides information about brain function. Because anatomical detail is poor in SPECT due to the low resolution of this imaging modality, coregistration with MRI has the potential to produce clinically useful information. Because the correlation of anatomical and functional information is of critical importance in the localisation of the epileptogenic focus, there are possible applications for coregistration of MRI with SPECT in patients with epilepsy.

We coregistered postictal and interictal SPECT in 10 patients with confirmed mesial temporal lobe epilepsy. These coregistered studies have shown distinctive patterns of perfusion which help in lateralising the side of mesial temporal seizure onset. These patterns were uncertain on SPECT studies not coregistered with MRI.

## Methods

Only patients with a confirmed diagnosis of mesial temporal seizures were included in the study. Postictal SPECT was obtained in 10 patients admitted for continuous 24 hour, 16 channel EEG video telemetry monitoring with scalp or scalp and sphenoidal electrodes. All postictal studies were obtained within two minutes of the cessation of the seizure. Postictal Tc-HMPAO injections were given as previously described by Newton *et al.*<sup>3</sup> Interictal SPECT studies were obtained after a seizure free period of at least 12 hours.

## IMAGE ACQUISITION

Brain MRI was performed on a 1.5T Signa, General Electric scanner (Milwaukee, WI, USA). Whole brain acquisitions were obtained in the coronal plane with a fast spoiled grass technique (FSPGR), TR = 14, TE = 3, flip angle = 30°. Voxel dimensions were 0.859 mm × 0.859 mm × 1.5 mm. The SPECT studies were performed on a Siemens Multispect 3 triple headed gamma camera with high resolution parallel hole collimators (Hoffman Estates, IL, USA). Each detector rotated through a circular

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Received 1 July 1996  
and in revised form  
13 January 1997  
Accepted 27 January 1997

Table 1 Hippocampal and amygdala volumetric measurements, EEG, and postsurgical pathological data

Patient No	Hippocampal volumes right/left (mm <sup>3</sup> )	Amygdala volumes right/left (mm <sup>3</sup> )	Side of initial temporal or frontotemporal EEG slowing	Pathology of postsurgical cases	Months after surgery	Engel classification postoperative outcome <sup>6</sup>
1	1060/2420	970/1540	Non-lateralising	Right MTS	18	IA
2	2400/1710	2000/1390	Left	Left MTS	20	IA
3	2660/1900	1980/1370	Left	Left MTS	16	IB
4	2280/2400	1730/1800	Left	Left MTS	24	IA
5	2620/1740	1930/1600	Non-lateralising	Left MTS	14	IA
6	2330/1910	1730/1520	Left	Left MTS	17	IA
7	1880/2220	1650/1950	Right	Right MTS	5	IA
8	2700/1950	1940/1270	Left	Left MTS	21	IA
9	2970/2300	2100/1870	Left	No surgery	—	—
10	1300/1850	960/1260	Right	No surgery	—	—

MTS = mesial temporal sclerosis.

arc of 120° at 13 cm radius of rotation. In total 96 frames of 128 × 128 word data were acquired over 360°. Each frame was acquired for 80 seconds with a zoom factor of 1.45. Tomographic reconstruction was performed on a Siemens Icon workstation using the filtered backprojection technique. Filtering incorporated a Shepp-Logan-Hanning filter with a cut off of 0.65 cycles/cm. Chang's first order attenuation correction was performed on the transaxial slices. The cubic voxel dimension of acquired and reconstructed data was 2.46 mm. Data were converted to an unsigned character 8 bit format.

#### COREGISTRATION OF DATA

The MRI and SPECT studies were coregistered by the method described by Hogan *et al.*<sup>4</sup> During this process, all data was integrated into an independent computer workstation using the ANALYZE™ version 7.5 image analysis software.

In all MRI studies, which were rendered to voxel dimensions, hippocampus and amygdala volume tracings were performed using the technique described by Cook *et al.*<sup>5</sup> These tracings were then superimposed on the coregistered postictal and interictal SPECT. In the process of coregistration, the SPECT studies were interpolated to match the voxel dimensions of the MRI studies. The average signal intensities of the SPECT within the volume of the hippocampal or amygdala tracings were then calculated. Asymmetries in hippocampal and amygdala SPECT signal were then calculated using the equation:

$$\% \text{ Asymmetry} = 100 \times (\text{right} - \text{left}) / (\text{right} + \text{left})/2$$

Table 2 Quantitative Tc-HMPAO SPECT intensity measurements

Patient No	Interictal hippocampal intensities (% asymmetries)	Interictal amygdala intensities (% asymmetries)	Postictal hippocampal intensities (% asymmetries)	Postictal amygdala intensities (% asymmetries)	Postictal time of Tc-HMPAO injection (s)
1	-4.3	8.0	-10.1	11.8	115
2	3.2	1.8	10.7	-5.7	95
3	-6.6	9.5	-15.5	-21.9	65
4	-3.1	-1.0	-6.7	-11.7	45
5	4.3	0.2	4.7	-8.7	40
6	3.2	2.4	-14.1	-5.2	35
7	1.7	-9.4	11.3	17.8	30
8	-1.1	-1.0	-5.7	-12.7	45
9	-3.0	-0.3	-7.9	-8.2	45
10	-7.0	4.5	-12.0	11.5	110

% Asymmetry = 100 × (right I - left I) / ((right I + left I)/2). This formula yields positive values for relative right sided hyperperfusion, and negative values for relative left sided hyperperfusion.

#### Results

All patients had hippocampal and amygdala volume loss as determined by MRI based hippocampal and amygdala volume measurements. Eight patients had pathologically confirmed mesial temporal sclerosis after anterior temporal lobectomy and hippocampectomy. The remaining two patients have not undergone epilepsy surgery. Data from EEG was lateralising during eight of the postictal SPECT studies. Although lateralising EEG discharges in individual seizures were not definitive on two of the EEG recordings during the postictal SPECT studies, all patients showed a majority of seizures propagating to one temporal lobe. None of the recorded seizures in this patient group showed initial propagation to the temporal lobe with a greater mesial temporal lobe volume. All postictal SPECT studies followed complex partial seizures without secondary generalisation.

The postoperative course in the patients who underwent epilepsy surgery averaged 17 months, and ranged from five to 24 months. All patients were Engel classification stage 1<sup>6</sup> in postoperative outcome.

Table 1 presents the results of hippocampal and amygdala volumetric measurements, ictal EEG results, postsurgical pathological data, and postoperative course.

In the postictal SPECT studies, quantitative analysis of amygdala region SPECT intensities were greatest on the side of seizure onset in all cases, with an average % asymmetry of 11.1 (range 5.2-21.9). Hippocampal intensities were greatest on the side of seizure onset in six studies, with an average % asymmetry of 9.6 (range 4.7-12.0). In four scans the hippocampal intensities were less on the side of seizure onset, with an average % asymmetry of 10.2 (range 5.7-15.5). There was no consistent localising quantitative pattern in the interictal SPECT studies. Table 2 presents the quantitative hippocampal and amygdala % asymmetry results.

Figure 1 shows an MRI and coregistered postictal SPECT. The patient had confirmed left sided onset of her seizures. The region of the hippocampus clearly shows hypoperfusion on the left side.

Figure 2 shows coregistered MRI and postictal SPECT, with cross section through the region of the amygdala. There is persistent postictal hyperperfusion over the left amygdala

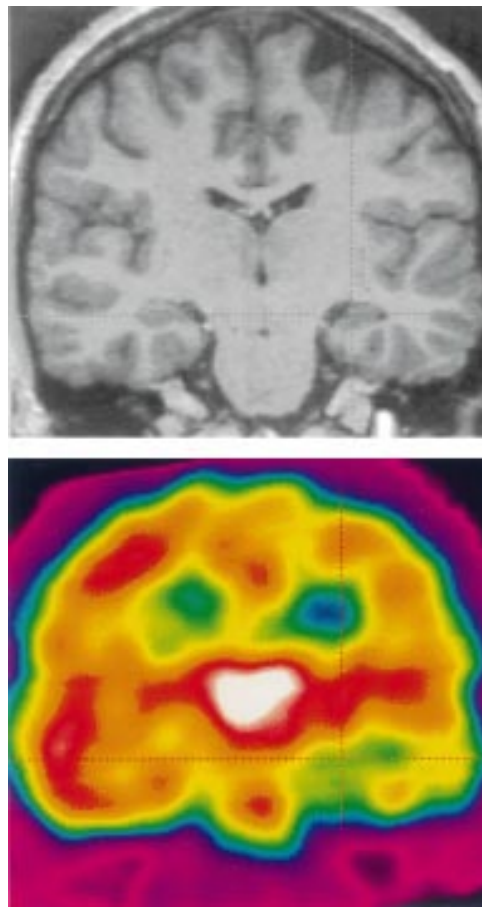


Figure 1 Top, MRI, and bottom, a coregistered postictal SPECT. The patient had confirmed left sided onset of her seizures. The region of the hippocampus clearly shows hypoperfusion on the left side.

region in this patient with left mesial temporal lobe epilepsy.

### Discussion

Ictal Tc-HMPAO SPECT is a useful test in the localisation of epileptic seizures in patients with temporal lobe epilepsy. Newton *et al*<sup>6</sup> published the results of qualitative analysis of ictal, postictal, and interictal Tc-HMPAO SPECT in 119 cases with proved unilateral temporal lobe epilepsy. Ictal SPECT correctly lateralised the side of seizure onset in 97%, was inconclusive in 3%, and was incorrect in 0%. Ictal studies showed hyperperfusion diffusely in the involved temporal lobe.<sup>7</sup> Postictal SPECT correctly lateralised in 71%, was inconclusive in 25%, and incorrectly lateralised in 4%. Postictal SPECT perfusion patterns showed persistent anterior mesial temporal hyperperfusion and lateral temporal hypoperfusion, which lasted for one to five minutes postictally. The anterior mesial temporal hyperperfusion then resolved, but lateral temporal hypoperfusion persisted for 10 to 20 minutes. Interictal studies showed correct lateralisation in only 48%, were inconclusive in 42%, and were incorrect in 10%.

The findings of Duncan *et al*<sup>1</sup> showed similar patterns of ictal and postictal perfusion in patients with temporal lobe epilepsy.

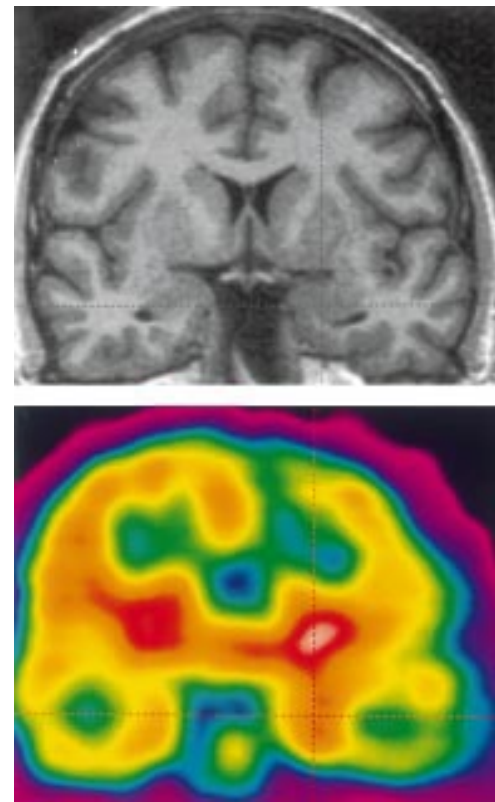


Figure 2 Top, MRI and bottom, a coregistered postictal SPECT, with cross section through the region of the amygdala. There is persistent postictal hyperperfusion over the left amygdala region in this patient with left mesial temporal lobe epilepsy.

In our series of postictal SPECT coregistered with MRI, it is possible to more precisely define the anatomical areas of perfusion changes. The postictal studies showed persistent hyperperfusion of the region of the amygdala in all cases, whereas hyperperfusion in the hippocampal region persisted in six of 10 cases. Duncan *et al*<sup>1</sup> considered postictal mesial temporal hyperperfusion to represent the area of the hippocampus. Berkovic *et al*<sup>7</sup> noted that the persistent postictal mesial temporal hyperperfusion was anterior. Whereas the hippocampus was hyperperfused postictally in some of our cases, the amygdala showed more consistent postictal hyperperfusion.

Our coregistration technique is accurate to about 4 mm,<sup>4</sup> as documented with scalp fiducial markers. As rotations around the x axis cause the greatest error in coregistration of the brain surface,<sup>8</sup> the position of our markers on the scalp produce a greater error measurement than at structures near the centre of the brain. Therefore, the coregistration mismatch of the hippocampal and amygdala tracings is probably less than 4 mm.

The limiting factor in interpretation of the regional patterns of perfusion on the coregistered SPECT is SPECT resolution. When considering this factor, the hippocampal and amygdala tracings should be thought of as volumetric structures. Volumes for the structures measured in this study ranged between 1 and 3 ml. Given that the initial SPECT voxel dimension was 2.46 mm, voxel counts for the small-



est volumes of 1 ml would be about 400 before coregistration, providing adequate data for signal measurement. Because the resolution of the SPECT in one dimension is 1 cm, signal averaging from structures in a 1 cm radius of any given point on SPECT will affect the intensity of that point. This makes it possible that the signal changes seen within the volumetrically measured regions of the hippocampus and amygdala on the SPECT may actually represent intensity changes in surrounding structures. However, given the established patterns of electrophysiological involvement of the hippocampus and amygdala in mesial temporal lobe epilepsy,<sup>9, 10</sup> and the link between epileptiform discharges and cerebral blood flow,<sup>11-13</sup> we think that these signal changes most likely represent changes in blood flow in the hippocampus and amygdala. Studies of blood flow in mesial temporal lobe seizures with modalities of greater temporal and spacial resolution than these SPECT images will be necessary to further investigate this hypothesis.

Because the patients in this series have concordant scalp EEG and MRI localisation of their seizures, they represent a group of patients with well established mesial temporal lobe epilepsy. The side of initial ictal lateralising scalp EEG discharges is highly predictive of the side of origin of mesial temporal lobe seizures.<sup>14</sup> Patients with scalp lateralisation have better results after surgery for epilepsy than patients who require invasive EEG monitoring to confirm the side of origin of their seizures.<sup>14, 15</sup> Loss of hippocampal volume is also a very specific lateralising finding in patients with mesial temporal lobe epilepsy.<sup>5, 16, 17</sup>

Eight of the 10 patients studied had pathologically confirmed mesial temporal sclerosis after temporal lobectomy. All postoperative patients had Engel stage I outcome with an average of 17 months postoperative follow up. This favourable outcome conforms with other larger studies of patients with concordant scalp EEG lateralisation of mesial temporal lobe seizures and MRI based hippocampal volumetric measurements.<sup>18, 19</sup> Jack *et al*<sup>18</sup> showed satisfactory postoperative seizure free rates in 97% of patients with lateralising ictal EEG recordings with concordant lateralising hippocampal volume loss. Although not pathologically confirmed, hippocampal volume loss in the two patients who have not undergone epilepsy surgery very likely represents mesial temporal sclerosis.<sup>20</sup> Because of the EEG, MRI, and postoperative findings in our patients, we think that they represent a group of patients with lateralised seizures of mesial temporal lobe origin due to mesial temporal sclerosis.

Asymmetries in SPECT signal intensities between mesial temporal lobe structures have been previously quantified in 10 normal subjects, using the same formula for percentage asymmetry as in this series.<sup>21</sup> The mean  $\pm$  2 SD was  $-1.0\% \pm 4.6\%$ . All of the postictal amygdala region intensities in our study showed asymmetries greater than 2 SD calculated for normal subjects. This suggests that the amygdala region signal asymmetry is significant. The range of postictal asymmetries

in the hippocampal area is also outside the 2 SD range in both the studies which showed relative hyperperfusion or hypoperfusion in the hippocampal region. This suggests that hyperperfusion of the hippocampal region may switch to hypoperfusion within the first two minutes postictally. The quantitative results showed no consistent patterns in the interictal SPECT studies. This is consistent with other studies which show that perfusion patterns on interictal SPECT are often discrepant with other data which lateralise the side of onset of temporal lobe seizures.<sup>1, 2</sup>

The reason that the amygdala region remained perfused longer than the hippocampal region is not clear. However, unlike the hippocampus, the amygdala has many connections with the neocortex and subcortical structures.<sup>22</sup> Perhaps the role of the amygdala in propagation of mesial temporal seizures is the reason it is perfused for a longer period postictally. It is important to realise that our studies were all immediately postictal, with injection within two minutes of the electrographic end of the seizure. The relative hyperperfusion to the amygdala region may not persist in later postictal injections.

We think that coregistration of postictal SPECT with MRI assists in interpretation of SPECT studies. One of the major difficulties in using SPECT is injecting the radioisotope during a seizure.<sup>23</sup> Often, injections are postictal. Using visual interpretation, the diagnostic yield of postictal Tc-HMPAO SPECT is considerably lower than in ictal studies.<sup>2</sup> Coregistration of postictal SPECT and MRI, using quantitative measurements of SPECT intensities over the hippocampus and amygdala, will improve the diagnostic yield of postictal Tc-HMPAO SPECT studies.

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## NEUROLOGICAL STAMP

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### Karl Friedrich Gauss (1777-1855)

Gauss came from a German peasant background. By the age of 3 he was able to correct his father's calculations when he heard him working out the wages for his labourers. At the age of 10 he astonished his teacher by discovering for himself the formula for the sum of an arithmetical progression. As a result of this mathematical precocity the Duke of Brunswick paid for Gauss to attend University and continued to support him until his death in 1806. After this Gauss accepted the directorship of the Observatory of Göttingen and he remained rector there for the rest of his life, only rarely leaving Göttingen. He also had a great linguistic ability and was able to teach himself fluent Russian in under two years.

His contribution to mathematics was profound but he had a reluctance to publish his discoveries. His interest was not confined to pure mathematics and he made contributions to many areas of applied mathematics and mathematical physics. By introducing what is now known as the Gaussian error curve, he showed how probability could be represented by a bell shaped curve, commonly called the normal distribution curve, which is basic to the description of statistically distributed data. His interest in mathematical astronomy resulted in many valuable innovations and he also made improvements in the design of astronomical instruments in use at his laboratory. His work transformed mathematics and he is generally



considered to be, with Newton and Archimedes, one of the greatest mathematicians of all time. The cgs unit of magnetic flux density is named in his honour. Soon after his death coins were struck in his honour.

He was honoured philatelically by the German Federal Republic on the centenary of his death in 1955 (Stanley Gibbons No 1130, Scott No 725).

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