Perfusion patterns during temporal lobe seizures: relationship to surgical outcome

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Summary
We sought to determine whether patterns of ictal hyperperfusion demonstrated using [99mTc]HMPAO (hexamethylpropylene amine oxime) single photon emission computed tomography (SPECT) predict outcome of temporal lobectomy; in particular, whether the more extensive patterns of ictal hyperperfusion are associated with poor outcome. We studied 63 patients who had ictal SPECT studies prior to temporal lobectomy. Hyperperfusion on ictal SPECT scans was lateralized, and classified into: (i) ‘typical’, (ii) ‘typical with posterior extension’, (iii) ‘bilateral’ and (iv) ‘atypical’ patterns. Outcome (minimum of 2 years follow-up) was classified as either seizure free, or not seizure free. Actuarial analysis was used to test the relationship of SPECT patterns with outcome. There were 35 cases with the typical ictal SPECT pattern, 13 posterior, nine bilateral and six atypical cases. The atypical pattern was associated with lack of pathology in the surgical specimen. Outcome was similar for the typical, posterior and bilateral with 60%, 69% and 67% seizure free, respectively. In contrast, the atypical group had a worse outcome with only 33% seizure free. Actuarial analysis showed a significant difference in outcome between patients with the typical pattern, and patients with the atypical pattern (P = 0.04). We conclude that extended patterns of ictal perfusion in temporal lobe epilepsy do not predict poor outcome, indicating that extended hyperperfusion probably represents seizure propagation pathways rather than intrinsically epileptogenic tissue. Atypical patterns of hyperperfusion are associated with poor outcome and may indicate diffuse or extra-temporal epileptogenicity.

Keywords: epilepsy; temporal lobe; neurosurgery; SPECT

Abbreviation: HMPAO = hexamethylpropylene amine oxime; SPECT = single photon emission computed tomography

Introduction
Temporal lobectomy is a widely practised treatment for refractory temporal lobe epilepsy. Unfortunately this operation is not always successful in achieving seizure control, as ~20% of patients fail to achieve a major reduction in seizures. Findings using MRI have emerged as a useful preoperative predictor of outcome (Jack et al., 1992; Kuzniecky et al., 1993; Garcia et al., 1994; Berkovic et al., 1995), but other neuroimaging modalities have not been well studied as yet.

Ictal [99mTc]HMPAO (hexamethylpropylene amine oxime) single photon emission computed tomography (SPECT) shows increased cerebral blood flow in the ipsilateral temporal lobe in ~95% of patients with temporal lobe epilepsy (Berkovic et al., 1991; Newton et al., 1992, 1994). Typically, ictal hyperperfusion involves the anteromesial temporal region and the anterolateral and inferior temporal neocortical areas. This pattern is easily recognizable, provides valuable data for presurgical localization of the epileptogenic region, and is seen particularly in patients with hippocampal sclerosis or other mesial temporal lesions (Ho et al., 1996). We have observed other patterns of cerebral hyperperfusion on ictal SPECT during temporal lobe seizures, usually in association with lateral temporal lesions or no lesion on the MRI scan, and sometimes in cases with mesial temporal pathology. These patterns include bilateral temporal involvement, or more limited hyperperfusion changes in the ipsilateral temporal lobe (Ho et al., 1996).

Temporal lobectomy is usually restricted to the anterior
5–6 cm. We therefore questioned whether the more extensive ictal perfusion patterns are predictive of poor post-operative seizure outcome. In particular, we investigated bilateral hyperperfusion, extensive ipsilateral posterior hyperperfusion and atypical patterns of hyperperfusion in order to ascertain whether they predict poor outcome. We also examined the relationship of the various ictal SPECT patterns to the pathology of surgical specimens.

We used actuarial analysis as it is the preferred method of analysing seizure outcome. Variable lengths of follow-up and changing seizure status over time can be taken into account using this method (Elwes et al., 1991; Rougier et al., 1992; Berkovic et al., 1995).

Methods

We studied retrospectively 63 patients (30 males; mean age at operation 31 years, SD 10, range 14–55 years) selected from a larger population undergoing temporal lobectomy for refractory complex partial seizures at the Austin Hospital between October 1989 and April 1993. Subjects were selected if they had an ictal [99mTc]HMPAO SPECT scan performed during a complex partial seizure as part of presurgical investigations. We excluded ictal injections during secondarily generalized partial seizures and post-ictal studies because these are known to have perfusion patterns different to ictal studies of complex partial seizures (Newton et al., 1992).

As part of pre-surgical investigation all patients underwent pre-operative localization of seizure focus by the use of ictal SPECT, video-EEG monitoring, neuropsychological studies, and MRI. Ten patients had intracranial EEG studies. Clinical seizure characteristics in all patients were typical of temporal lobe onset, with behavioural arrest, staring and automatisms, seizure characteristics in all patients were typical of temporal lobe onset, with behavioural arrest, staring and automatisms, frequently preceded by an aura.

Temporal lobectomy was performed on the right in 28 patients and on the left side in 35 patients. For those undergoing dominant temporal lobe removals, 3.5 cm of the lateral temporal lobe was excised, for those undergoing non-dominant removals, 5.0 cm was excised. The hippocampus was excised microsurgically, usually to the level of posterior midbrain. Mass lesions were completely excised where possible and the anterior 2 cm of hippocampus removed. When the lesion was located in the lateral temporal region, the hippocampus was not resected unless it appeared abnormal on MRI.

All subjects gave informed consent for SPECT studies and the protocol was approved by the Austin Hospital Human Ethics Committee.

Ictal perfusion and surgical outcome

[99mTc]HMPAO SPECT studies

Patients underwent continuous video-EEG monitoring and were injected with 550–700 MBq (15–20 mCi) of [99mTc]HMPAO during ongoing seizure activity according to methods previously described (Newton et al., 1993). All were scanned within 2 h of [99mTc]HMPAO injection. Scans were performed using a single head rotating gamma camera (GE Starcam 400 AC). SPECT data acquisition was performed as previously described (Rowe et al., 1989, 1991a). Optimal display of the temporal lobes was achieved by identification of the midsagittal image, and generation of axial slices in the plane of a line drawn from the inferior surface of the frontal lobe to the most posterior aspect of the occipital pole (Rowe et al., 1989, 1991a). Coronal images were reconstructed perpendicular to this plane.

Qualitative analysis

Transaxial and coronal images were presented on colour scale film for visual analysis. Ictal SPECT scans of all 63 patients were presented in random order to two observers (S.F.B. and M.R.N.) who were blinded to patient identity and localizing information. The observers were first required independently to lateralize the seizure foci as left or right temporal. For determination of sensitivity a true positive result was recorded if both observers correctly lateralized the scan. A study was considered non-lateralizing when observers disagreed on lateralization. Inter-observer reliability was tested with Cohen’s kappa (κ) (Cohen, 1960).

Observers then independently classified the perfusion patterns into four groups (see Fig. 1) as follows:

(i) ‘Typical’ perfusion pattern; this comprises a pattern of ipsilateral anteromesial and anterolateral temporal hyperperfusion. This group was subdivided into a ‘mesial’ perfusion pattern where mesial hyperperfusion was greater than lateral and a ‘lateral’ perfusion pattern, where lateral hyperperfusion was greater than mesial.

(ii) ‘Posterior’ perfusion pattern; the typical pattern [see group (i) above] plus posterior extension. Posterior extension was defined as temporal lobe hyperperfusion involving greater than two thirds of the antero-posterior distance from the temporal pole to the most posterior aspect of the occipital pole on the transaxial slice of interest.

(iii) ‘Bilateral’ perfusion pattern; defined as typical anteromesial and anterolateral temporal hyperperfusion in both temporal lobes.

(iv) ‘Atypical’ perfusion pattern; defined as hyperperfusion not predominantly involving the anteromesial and anterolateral temporal regions.

Fig. 1 Ictal SPECT perfusion patterns in temporal lobe epilepsy. ‘Typical’ (mesial > lateral) pattern with hyperperfusion predominantly in the anteromesial temporal region. ‘Typical’ (lateral > mesial) pattern with hyperperfusion predominantly in the anterolateral temporal region. ‘Posterior’ pattern: typical pattern of hyperperfusion plus posterior extension. ‘Bilateral’ pattern: typical anteromesial and anterolateral temporal hyperperfusion in both temporal lobes. ‘Atypical’: two examples of an ‘atypical’ pattern, showing hyperperfusion which was not predominantly in the ‘typical’ anteromesial and anterolateral areas.
Where there was disagreement between the two observers as to the classification of the perfusion pattern, the scans were reviewed and consensus obtained.

Quantitative analysis
Quantitative analysis of scans in each of the perfusion pattern groups was performed using methods previously described (Rowe et al., 1991a, b). Comparison of flow changes between temporal lobes were carried out by comparing activity in the area of seizure focus with the homologous region in the opposite side.

This was done by placing a 5 × 8 pixel (15 × 25 mm) rectangle over the right mesial temporal region, and 3 × 12 pixel (9 × 38 mm) rectangles over the right posterior and lateral temporal regions on a 1 cm thick slice at the midtemporal level. These were then mirrored across to homologous regions in the left side, with minor adjustments if necessary. The mean count in each region was then normalized to the cerebellum by dividing the counts by the average cerebellar counts in that study. We chose the cerebellum as the best surrogate reference for normalization as there are no significant changes in the side to side cerebellar perfusion ratio in complex partial seizures (changes are seen in secondarily generalized seizures, therefore this seizure type was excluded from the study) (Newton et al., 1992). This normalization step assumes that absolute cerebellar blood flow does not change significantly from the interictal to the ictal state in partial seizures. The normalized counts in each region of interest in the epileptic side were compared to the normalized counts in the homologous regions in the contralateral side. Student’s paired t-test was used to compare the means of the epileptic and contralateral side for each region of interest.

Neuropathology
Surgical specimens were classified into three categories: (i) mass lesions, (ii) hippocampal sclerosis, (iii) no significant pathological abnormality (includes minor dysplasias). In the latter two groups, all specimens included sufficient hippocampus to assess for sclerosis.

Association between SPECT patterns and pathology were tested using the χ² statistic with Yates’ correction for 2 × 2 tables. Where more than one cell in a 2 × 2 table had an expected frequency of less than five a Fisher’s exact test was used.

Postoperative seizure outcome
Postoperative seizure outcome was assessed as part of the regular Comprehensive Epilepsy Programme follow-up described previously (Bladin, 1992; Berkovic et al., 1995). Those unable to attend appointments were contacted by telephone. The remainder had follow-up within the previous 2 years. All patients had at least 2 years postoperative follow-up. One patient had died of an illness unrelated to epilepsy; outcome was included to the time of last follow-up.

Patients were designated either seizure free or not seizure free according to the outcome at most recent follow-up. The definition of seizure free was based on Engel’s postoperative seizure classification (Engel, 1993). Patients who had immediate post-operative neighbourhood seizures, non-disabling simple partial seizures, and atypical generalized convulsions with antiepileptic drug withdrawal are included in the seizure free group. Two patients had undergone a second operation (extension of lobectomy) due to poor seizure control but continued to have seizures. They were classified as ‘not seizure free’ from time of first postoperative seizure until time of last follow-up.

Actuarial analysis of outcome for the different perfusion patterns was performed using Kaplan–Meier estimated survival curves (SPSS-PC version 4.0) as previously described (Berkovic et al., 1995). Comparison of ‘survival’ curves were performed using Lee-Desu statistic (Norušis, 1990) using SPSS.

Results
Ictal SPECT
[99mTc]HMPAO was injected during ongoing seizure activity in all cases. Mean duration of seizures studied was 108.5 s (range 47–312 s); isotope was injected 40–200 s after seizure onset and 0–234 s before seizure termination. There was no significant difference in the mean duration of the seizures studied in the four groups (typical pattern = 102.7 s, typical plus posterior extension = 109.2 s, bilateral pattern = 100.3 s, atypical pattern = 154.7 s; ANOVA, P = 0.07), or the mean injection time of isotope (typical pattern = 86.8 s, typical plus posterior extension = 71.9 s, bilateral pattern = 83.2 s, atypical pattern = 97.2 s; ANOVA, P = 0.55).

Qualitative analysis
On blinded visual analysis, both observers correctly lateralized 58/63 (92%) scans. There was excellent inter-observer agreement for scan lateralization (κ = 0.97). Three studies were incorrectly lateralized by both observers, and two were incorrectly lateralized by one observer. Scans were classified into SPECT perfusion patterns as follows: typical in 35 (mesial 10, lateral 25), posterior extension in 13, bilateral in nine, and atypical in six. Of the five studies where errors were made by one or both observers, two showed an atypical perfusion pattern and three showed a bilateral pattern.

Quantitative analysis
Semi-quantitative analysis of regions of interest for each perfusion pattern group (Table 1) supported the blinded visual interpretation of perfusion patterns. Results for the typical
Ictal perfusion and surgical outcome

Table 1 Ictal SPECT semi-quantitative analysis

<table>
<thead>
<tr>
<th>Regions of interest</th>
<th>Typical (n = 35)</th>
<th>Posterior extension (n = 13)</th>
<th>Bilateral (n = 9)</th>
<th>Atypical (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesial temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ipsilateral*</td>
<td>0.954</td>
<td>1.172</td>
<td>0.873</td>
<td>1.021</td>
</tr>
<tr>
<td>Mean contralateral†</td>
<td>0.754</td>
<td>0.946</td>
<td>0.822</td>
<td>0.933</td>
</tr>
<tr>
<td>Mean difference‡</td>
<td>0.2</td>
<td>0.227</td>
<td>0.051</td>
<td>0.088</td>
</tr>
<tr>
<td>P-value§</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ipsilateral</td>
<td>0.971</td>
<td>1.257</td>
<td>0.883</td>
<td>0.856</td>
</tr>
<tr>
<td>Mean contralateral</td>
<td>0.774</td>
<td>0.93</td>
<td>0.815</td>
<td>0.957</td>
</tr>
<tr>
<td>Mean difference</td>
<td>0.197</td>
<td>0.328</td>
<td>0.068</td>
<td>–0.099</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td>0.0001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Posterior temporal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ipsilateral</td>
<td>0.757</td>
<td>1.175</td>
<td>0.789</td>
<td>0.945</td>
</tr>
<tr>
<td>Mean contralateral</td>
<td>0.777</td>
<td>0.923</td>
<td>0.822</td>
<td>0.962</td>
</tr>
<tr>
<td>Mean difference</td>
<td>–0.02</td>
<td>0.252</td>
<td>–0.033</td>
<td>–0.016</td>
</tr>
<tr>
<td>P-value</td>
<td>NS</td>
<td>0.0001</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Mean counts (normalized to the cerebellum) in the epileptic side; † mean counts (normalized to the cerebellum) in the contralateral side; ‡ mean difference between epileptic and contralateral side in each region-of-interest; § Student’s paired t-test was used to compare means in the epileptic and contralateral sides.

Neuropathology
Forty patients had mesial temporal sclerosis, 10 had mass lesions (six ganglioglioma, two cavernous angioma, one dysembryoplastic neuroepithelial tumour, one epidermoid cyst), and 13 had no significant pathological abnormality in the resected temporal tissues.

Neuropathology and associated SPECT patterns (Table 2)
The majority of cases with hippocampal sclerosis had ictal SPECT patterns of typical (25 cases, 60%) or posterior hyperperfusion (10 cases, 25%). Interestingly, in the 24 patients with hippocampal sclerosis and a typical pattern, a predominantly mesial pattern was seen in five, whereas 19 cases had a lateral predominance. Mass lesions had a variety of perfusion patterns (typical 50%, bilateral 30%). Cases without significant temporal lobe pathology also had a variety of perfusion patterns, but atypical patterns were seen most often in this group (31%). The association between the atypical SPECT pattern, and absence of temporal lobe pathology was significant (P = 0.01, Fisher’s exact test).

Seizure outcome (Fig. 2)
The mean period of follow-up was 49 months (range 24–74 months). Sixty percent of patients were seizure free, and forty percent had experienced seizures post-operatively by...
the time of most recent follow-up. Of those with a typical hyperperfusion pattern, 60% (21/35) were seizure free. Patients with posterior hyperperfusion, were 69% (9/13) seizure free, and those with bilateral hyperperfusion were 67% (6/9) seizure free. Of those with the atypical pattern, only 33% (2/6) were seizure free.

A plot of the cumulative percentage of seizure freedom for each of these groups (Fig. 2) showed that the typical, posterior and bilateral patterns had a similar outcome. In the typical group, there was no difference between the mesial and lateral patterns (data not shown). In contrast the atypical group showed a poorer outcome. The difference in outcome between the typical and atypical groups was significant (Lee Desu statistic; 0.04). There was no significant difference between the bilateral and posterior groups compared with the atypical group, probably reflecting the small numbers.

Four patients without significant temporal lobe pathology had an atypical pattern and only one was seizure free. In contrast, of the nine other patients without significant temporal lobe pathology, where ictal SPECT showed typical or extended patterns, five (55%) were seizure free.

Of the 25 patients who had seizures postoperatively, three eventually became seizure free for 2 years or longer (one mesial, one lateral, one posterior pattern).

### Discussion

The findings of this study confirm the high degree of accuracy of ictal SPECT for the lateralization of temporal lobe epilepsy (Berkovic et al., 1991; Stefan et al., 1990; Duncan et al., 1993; Harvey et al., 1993; Markand et al., 1994; Newton et al., 1994). We found that particular perfusion patterns on ictal SPECT had prognostic importance. The presence of typical, posterior or bilateral ictal patterns correlated with good outcome after temporal lobectomy, using the strict criterion of seizure freedom. In contrast, atypical hyperperfusion patterns were associated with poor outcome. Duration of seizures and time delay from seizure onset to isotope injection did not differ for the hyperperfusion patterns suggesting the patterns reflect other biological features of the seizures.

The observation that bilateral hyperperfusion or posterior hyperperfusion did not adversely affect outcome may appear surprising. Ictal SPECT provides information about the individual seizure event, reflecting acute functional changes in the epileptogenic region and probably also in areas of seizure spread. Thus even though ictal SPECT shows changes distal to the area of resection, our follow-up data imply that those regions do not have intrinsic epileptogenicity. This is in contrast to interictal [18F]fluorodeoxyglucose PET studies, which suggest that bilateral or extensive temporal hypometabolism predicts poor postoperative outcome (Theodore et al., 1992; Radtke et al., 1993). PET measurements reflect the chronic interictal state, rather than acute effects of seizures, and extensive interictal changes may be indicative of widespread epileptogenicity.

The hippocampal sclerosis group provides some insight into the relative contribution to ictal hyperperfusion by the epileptogenic region versus the areas of spread. There is good evidence that seizure origin in hippocampal sclerosis is from mesial temporal structures (Wieser et al., 1993). However, ictal SPECT showed predominantly a lateral temporal hyperperfusion pattern rather than mesial hyperperfusion. This disparity between the site of the epileptogenic focus and the site of maximum temporal hyperperfusion may be contributed by the relatively low spatial resolution of SPECT, where partial volume effects can result in underestimation of activity in relatively small regions of epileptogenic tissue such as the mesial temporal cortex. In addition, extensive seizure propagation between the mesial temporal structures and the lateral temporal neocortex may also account for the prominent lateral and even posterolateral hyperperfusion in seizures with mesial temporal onset. There are reciprocal multisynaptic pathways between the hippocampal formation and the ventrolateral temporal lobe via the subicular and parahippocampal gyrus (Van Hoesen et al., 1979, 1982; Nieuwenhuys et al., 1988) and ictal depth electrode studies show that the lateral temporal cortex is extensively involved in mesial onset seizures (Wieser 1983; Spencer et al., 1993).

The bilateral hyperperfusion pattern is uncommon, but was seen in all the pathological subgroups. We have previously shown that this pattern is more common in patients with lateral temporal rather than mesial temporal seizure foci (Ho et al., 1996). These findings may be explained by known anatomical connections. Mesial temporal structures project to the ipsilateral temporal neocortex (Amaral and Price, 1984). There are no direct connections between the two mesial temporal regions, but the lateral temporal neocortex is connected to the contralateral temporal lobe by anterior

### Table 2 Pathology and associated ictal SPECT patterns

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Typical</th>
<th>Posterior</th>
<th>Bilateral</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS (n = 40)</td>
<td>5</td>
<td>19</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Mass lesions (n = 10)</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>NL (n = 13)</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>n = 63</td>
<td>10</td>
<td>25</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

HS = Hippocampal sclerosis; NL = no significant temporal lobe pathology.
commissural fibres (McCulloch and Garol, 1941; Turner et al., 1979).

Another important finding was that patients with atypical SPECT patterns were more likely to have postoperative seizure recurrence in comparison with patients who have any variation of the typical pattern. Atypical patterns may be due to unsuspected foci outside the area of resection or more diffuse pathology. This is supported by the significant association between lack of major temporal lobe pathology in our surgical specimens and the atypical pattern.

Cases without significant temporal lobe pathology showed a variety of ictal SPECT patterns and did not invariably have a bad outcome. This group is likely to have different aetiologies. Amygdaloïd sclerosis could account for some of these cases (Hudson et al., 1993), but our pathological material did not include sufficient amygdaloïd tissue to confirm this. We previously speculated that cases with anteromesial temporal hyperperfusion and good outcome could be due to this pathological subgroup (Ho et al., 1996).

Ictal SPECT can add complementary information to structural neuroimaging. A negative MRI scan is a predictor of poor outcome. Our data suggest that cases with a typical ictal SPECT and negative MRI may do well, whereas the combination of an atypical ictal SPECT and negative MRI is associated with a poor outcome.

In conclusion, ictal SPECT patterns in temporal lobe epilepsy reflect both the epileptogenic region and, to a lesser extent, pathways of spread. Knowledge of ictal hyperperfusion patterns has important implications for selection of patients for temporal lobe surgery. Extended typical hyperperfusion patterns, involving posterior temporal cortex or the contralateral anterior temporal lobe, appear to indicate seizure pathways rather than intrinsically epileptogenic tissue, and have no adverse effect on seizure outcome after surgery. The presence of an atypical hyperperfusion pattern is predictive of poorer outcome and warrants additional consideration before proceeding to surgery.

Acknowledgements
We wish to thank Dr Michael Saling for statistical advice and the technical staff of the Nuclear Medicine Department for their skilled assistance. Dr Ho was the recipient of a Ciba-Geigy (Australia) Epilepsy Fellowship and a National Health and Medical Research Council Postgraduate Medical Scholarship.

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Received March 12, 1997. Revised June 2, 1997. Accepted June 23, 1997