British Journal of Psychiatry (1993), **163**, 32–36

A Pilot Study of Schizophrenia-Like Psychosis in Epilepsy Using Single-Photon Emission Computerised Tomography

E. JANE MARSHALL, G. M. S. SYED, P. B. C. FENWICK and W. A. LISHMAN

In a pilot study, SPECT was used to explore differences in rCBF between a group of patients with schizophrenia-like psychoses of epilepsy (SLPE) and a matched group of epileptic controls. Five patients in each group were investigated and those with SLPE showed significant reductions in the index of rCBF in the left medial temporal region. These differences are being investigated further.

The psychoses of epilepsy are of interest because they constitute a natural paradigm for schizophrenia, and could illuminate its pathogenesis. Early descriptions of the psychotic features highlighted paranoid symptoms and retention of affective warmth (Hill, 1953; Pond, 1957; Slater *et al*, 1963). An association between temporal lobe epilepsy, particularly left-sided lesions, and the nuclear schizophrenia (NS) CATEGO category (Wing *et al*, 1974) has been reported (Perez & Trimble, 1980; Perez *et al*, 1985).

Individuals with schizophrenia-like psychoses of epilepsy (SLPE) typically have little genetic predisposition to schizophrenia. The onset of the psychosis follows some 10–15 years after the onset of the epilepsy. Patients commonly have complex partial seizures, with a mediobasal-limbic focus, and the psychosis usually starts as the seizure frequency diminishes (Slater *et al*, 1963; Flor-Henry, 1969; Trimble, 1991).

Flor-Henry (1969) reported a possible association between SLPE and epileptic foci in the left temporal lobe. In a clinical series of patients who had undergone unilateral temporal lobectomy, Taylor (1975) reported that women, especially those who were left handed and had 'alien tissue lesions', appeared to be at special risk of developing SLPE. Lesions of the left hemisphere carried higher risk than those in the right hemisphere. Sherwin (1981), investigating patients who had undergone a temporal lobectomy, found that left-handed patients, with epileptogenic lesions in the left temporal lobe, seemed particularly predisposed to SLPE. However, these findings have not been substantiated by Kristensen & Sindrup (1978) or Jensen & Larsen (1979).

Several of the above studies incorporated air-encephalography (AEG) and computerised tomography (CT). The studies of Slater *et al* (1963) and Kristensen & Sindrup (1978) showed AEG evidence of deep midline or diffuse brain damage in epileptic patients with psychosis. Toone *et al*'s (1982) CT evaluation of SLPE reported an excess of abnormalities in the left hemisphere in the psychotic group, but this failed to reach significance. In a magnetic resonance imaging study of epileptic psychosis, Conlon *et al* (1990) found no significant differences in T_1 relaxation time between 12 patients with epilepsy and psychosis ('NS' subclass on the Present State Examination) and 17 patients with epilepsy and no psychiatric illness. However, patients experiencing hallucinations had a significantly higher T_1 value in the left temporal lobe compared with patients without hallucinations.

Positron emission tomography (PET) and single-photon emission computerised tomography (SPECT) allow the study of brain function as opposed to structure. In a PET study, using oxygen-15 inhalation, Gallhofer *et al* (1985) showed that individuals with SLPE had a lower regional oxygen extraction rate than epileptic and normal controls, especially in the frontal, temporal and basal ganglia regions. The psychotic group also had significantly lower regional cerebral blood flow (rCBF) and oxygen metabolism in the temporal areas on the left side.

The objective of this pilot study was to use SPECT to investigate rCBF in two groups of patients with epilepsy, one with a history of SLPE and one without. The aims were: (a) to ascertain whether there was any difference in rCBF between the two groups, (b) whether the epileptics with psychosis had more widespread dysfunction, and, if so, (c) whether this dysfunction was more pronounced in the left than the right hemisphere.

Method

The case notes of all patients attending the specialist Epilepsy Clinic at the Maudsley Hospital, a tertiary referral centre for epilepsy and related problems, were screened, with special attention being paid to the detailed clinical

https://doi.org/10.1192/bjp.163.1.32 Published online by Cambridge University Press

histories and results of electroencephalographic (EEG) studies, neuroradiological (CT) and neuropsychological investigations. Exclusion criteria for entry into the study included alcohol and drug abuse, a history of status epilepticus, progressive brain disease, space-occupying lesions on CT brain scan, and left handedness. Patients with a history of psychosis were not included if the psychotic illness was affective, of less than three months' duration, and only postictal. Ten men were selected.

The SLPE group consisted of five men with epilepsy and a diagnosis of schizophrenia by Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978). All five were on neuroleptic medication and none was psychotic at the time of the SPECT scan. The epileptic control group consisted of five men matched with the SLPE group for age, age at onset of epilepsy, type of epilepsy, and side of EEG focus. The mean (s.d.) age of the SLPE group was 37.6 (7.7) years and that of the control group was 38.0 (8.7) years. The mean age at onset of epilepsy was 12.5 (12.1) years and 9.95 (10.4) years respectively. All 10 patients were taking anticonvulsant medication of equivalent type and dose and had levels within the therapeutic range. The five men in the SLPE group were each interviewed with the Schizophrenia and Affective Disorders Schedule – Lifetime version (SADS-L; Spitzer & Endicott, 1978) to confirm the RDC diagnosis of schizophrenia. All patients were right handed (Annett Handedness Schedule; Annett, 1970). Verbal and performance IQ were rated using the Wechsler Adult Intelligence Scale (WAIS-R; Wechsler, 1981).

Interictal rCBF was evaluated with SPECT following an intravenous injection of the single-photon tracer technetium-99m-labelled HMPAO (Ceretec, Amersham, UK). Within minutes, ^{99m}Tc-HMPAO crosses the blood–brain barrier and is taken up by brain cells in proportion to blood flow (Lassen *et al*, 1988). Once in the brain, it becomes lipophobic, and there is insignificant washout during scanning. It thus gives a 'snapshot' of the rCBF for the two to four minutes after the injection (Sharp *et al*, 1986). Each patient was resting supine, with eyes closed at the time of injection with 550 MBq of ^{99m}Tc-HMPAO. The ^{99m}Tc-HMPAO for injection was freshly prepared and administered within 10 minutes. The lipophilic component was assessed using the chromatography (ITLC) method.

An SME-810 multidetector head-dedicated SPECT system, based in the Department of Nuclear Medicine at King's College Hospital, was used to obtain images. This system has a spatial resolution of approximately 7.5 mm at full-width half-maximum. At least eight overlapping slices, each 15 mm thick, were acquired in the horizontal plane, using the orbito–meatal (OM) line as baseline. Reconstruction was carried out using Wiener filters and the iterative method. Coronal sections were generated from the transverse sections using the related software package (SME 2.51).

Image analysis

Analysis was carried out blind to patient/control status. Regions of interest were outlined by hand, tracing on the transverse and the reconstructed coronal sections, with computer guidance for the peripheral regions in order to standardise a width of five to six pixels over cortical areas. Four transverse slices were chosen for analysis. The first was at the level of the OM line where the cerebellum was outlined. The second slice, 10 mm above the OM line, was used to outline inner and outer temporal regions. The third slice was midventricular and was located about 40–55 mm above the OM line. It was divided into four equal parts on the brain convexity bilaterally (as described by Lewis *et al*, 1992) and a strip of mesial frontal cortex was outlined on either side of the midline within the first segment. Two subcortical regions, the caudate and thalamus, were measured bilaterally on this slice. Finally, a slice at the supraventricular level (60 mm above the OM line) was divided into two equal portions bilaterally. Two regions of interest, each five pixels in width, were outlined on either side, and were termed 'high frontal' and 'high parietal' regions. The frontal poles and anterior temporal lobes were outlined on reconstructed coronal sections, and the temporal lobes were further divided into equal thirds on either side (medial, mid and lateral regions).

All measurements were performed using an Apple-Mackintosh analysis package. The software calculated the mean uptake per pixel in each region. The measurement of relative rCBF by normalising the mean count per unit volume in each region of interest to a reference region, usually the cerebellum, has been used in investigations of Alzheimer's disease (Montaldi *et al*, 1990) and schizophrenia (Bajc *et al*, 1989). In this study epileptic patients were on anticonvulsant medication, which can cause cerebellar atrophy; therefore the mean count per unit volume for each region could not be normalised against the cerebellum. Because three patients in the SLPE group (cases 2, 4 and 5) had some brain atrophy on their CT scans (visible right temporal horn, cerebellar atrophy and right hemiatrophy respectively) the rCBF index for each region could not be expressed as a percentage of the total uptake in the relevant slice. Instead, the following normalisation procedure was used. The mean value of counts per unit volume in each region of interest was taken as the numerator. This was divided by the unweighted mean of the average values of counts per unit volume in each region of interest, using all regions of interest in the relevant slice. This normalised count rate was termed the 'normalised rCBF index' and is used as our indicator, indirect though it is, of rCBF.

The data were analysed using the SPSS-PC program. The Wilcoxon matched-pairs signed-ranks test was used to test the difference in ratios of regional uptake between the two groups.

Results

Clinical data on the two groups are shown in Table 1, with information on each matched pair being presented together. Three pairs had predominantly right-sided lesions and two pairs had predominantly left-sided lesions. Tables 2 and 3 show the results of the normalised rCBF index on transverse sections and reconstructed coronal sections respectively for the matched groups. Analysis of transverse slices (Table 2) reveals a significant between-group difference for the right thalamus only ($P=0.04$), the

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Table 1
Clinical features of five men with schizophrenia-like psychosis (SLPE) and five controls (C)

	Control or SLPE	Age: years	Age at onset of seizures: years	Age at onset of SLPE: years	Seizure type	Seizure frequency	EEG	CT	Verbal IQ	Performance IQ
1	C	40	10	–	CPS GTC	1 per 3 months (occasional)	L	N	110	111
	SLPE	40	5	32	CPS GTC	1 per 3 months (occasional)	L	N	97	96
2	C	31	12	–	CPS GTC	1 per 3 months (occasional)	R>L	N	94	90
	SLPE	29	18	18	GTC	Seizure free for 2 years	R>L	RTH	–	–
3	C	28	1.5	–	CPS GTC	1 per month (occasional)	L	N	111	118
	SLPE	31	0.75	17	CPS GTC	1–2 per month (occasional)	L	N	98	107
4	C	45	33	–	GTC	3 per month	N	N	96	76
	SLPE	39	24	29	GTC	Seizure free for 1 year	R;FT	CA	89	80
5	C	44	6	–	CPS	4 per month	R	N	116	115
	SLPE	51	2	50	CPS	Seizure free for 1 year	R	RH	85	92

CPS = complex partial seizure; GTC = generalised seizure; FT = fronto-temporal; RTH = right temporal horn visible; CA = cerebellar atrophy; RH = right hemiatrophy; N = normal; R = right-sided; L = left-sided; IQ = measured on WAIS-R.

Table 2
Group means (s.d.) of normalised count rates (normalised rCBF index) on transverse slices, comparing matched epileptic control group with schizophrenia-like psychosis of epilepsy group using the Wilcoxon matched-pairs signed-ranks test

	Epileptic controls ($n=5$)	Schizophrenia-like psychosis group ($n=5$)	
Cerebellum			
right	1.005 (0.005)	1.019 (0.024)	NS
left	1.010 (0.025)	1.002 (0.014)	NS
Outer temporal			
right	0.252 (0.015)	0.250 (0.024)	NS
left	0.254 (0.009)	0.256 (0.012)	NS
Inner temporal			
right	0.246 (0.010)	0.251 (0.011)	NS
left	0.249 (0.004)	0.243 (0.007)	$P=0.07$
Caudate			
right	0.075 (0.005)	0.079 (0.005)	NS
left	0.075 (0.004)	0.078 (0.015)	NS
Thalamus			
right	0.083 (0.003)	0.078 (0.005)	$P=0.04$
left	0.086 (0.003)	0.079 (0.008)	$P=0.07$
Medial frontal			
right	0.071 (0.008)	0.071 (0.003)	NS
left	0.072 (0.007)	0.073 (0.004)	NS
High frontal			
right	0.239 (0.016)	0.248 (0.010)	NS
left	0.243 (0.005)	0.250 (0.021)	NS
High parietal			
right	0.262 (0.013)	0.248 (0.042)	NS
left	0.256 (0.014)	0.255 (0.022)	NS

Table 3
Group means (s.d.) of normalised count rates (normalised rCBF index) on reconstructed coronal slices, comparing matched epileptic control group with schizophrenia-like psychosis group using the Wilcoxon matched-pairs signed-ranks test

	Epileptic control group ($n=5$)	Schizophrenia-like psychosis group ($n=5$)	
Frontal pole			
right	0.509 (0.024)	0.487 (0.013)	NS
left	0.491 (0.024)	0.513 (0.013)	NS
Medial temporal			
right	0.153 (0.017)	0.160 (0.012)	NS
left	0.179 (0.009)	0.158 (0.009)	$P=0.04$
Mid temporal			
right	0.170 (0.011)	0.170 (0.010)	NS
left	0.165 (0.017)	0.170 (0.011)	NS
Lateral temporal			
right	0.169 (0.017)	0.171 (0.011)	NS
left	0.163 (0.010)	0.171 (0.015)	NS

SLPE group showing a lower normalised rCBF index. Two other regions almost reach significance, the left thalamus ($P=0.07$) and left inner temporal region ($P=0.07$), where the SLPE group again show a lower normalised rCBF index. On the reconstructed coronal slices, the normalised rCBF index is significantly reduced in the left medial temporal region ($P=0.04$) in the SLPE group.

https://doi.org/10.1192/bjp.163.1.32 Published online by Cambridge University Press

Discussion

This study is the first to use SPECT to compare rCBF in epileptic patients with and without a schizophrenia-like psychosis. The hypothesis that patients with SLPE would have reduced left-sided blood flow was upheld in part, and this was despite the fact that two patients in the SLPE group had some right-sided brain atrophy (cases 2 and 5). Significant reduction in the normalised rCBF index in the left hemisphere was circumscribed to the medial temporal region.

The results are in keeping with the other functional imaging (PET) study of SLPE (Gallhofer *et al*, 1985) and with Roberts *et al*'s (1990) clinicopathological study of temporal lobe epilepsy and schizophrenia-like psychosis. They also support post-mortem and MRI reports of structural abnormalities implicating the left temporal lobe in the pathogenesis of schizophrenia (Crow, 1991). The somewhat higher normalised rCBF index in the caudate nuclei of the SLPE group relative to the control group is in keeping with the fact that these patients were on neuroleptic drugs. However, it does not rule out the possibility that the caudate nuclei are implicated in the psychotic process.

We could not explain the reduced normalised rCBF index in the thalami of the SLPE group. Lewis *et al* (1992) reported increased caudate and thalamic rCBF in their schizophrenic group, which they considered to be due to neuroleptic medication.

Conclusions are tentative because: (a) the numbers in the study were small; (b) the SLPE patients were not psychotic at the time of investigation and were receiving neuroleptics; and (c) the epileptic controls, although strictly matched for seizure type, differed from the SLPE patients with respect to gross brain damage (as measured by IQ and CT scan) and seizure frequency. Although matching of the two groups was done to eliminate any bias in the type of epilepsy, it meant that the epileptic controls had potential risk factors for developing psychosis. This might explain why differences in the normalised rCBF index between the two groups were so small. The normalised rCBF index in the group with SLPE is reduced despite their having rather less frequent seizures, where one might have perhaps expected the reverse, as reduced rCBF has been reported to be especially prominent postictally (Engel, 1984). The apparently substantial differences between the two groups in IQ raises the possibility that there are systematic differences between groups in brain atrophy. Three of the SLPE patients did have CT scans indicating atrophy, but in two of the three (cases 2 and 5) the atrophy was right sided and this would not explain the reduction in rCBF in the left inner and medial temporal regions.

We are also cautious about our conclusions because of the technical limitations of SPECT. Quantitative analysis of rCBF with PET is superior when intra-arterial blood sampling is used. Also, sophisticated methods of analysis, such as statistical parametric maps, have been developed for PET (Friston *et al*, 1991; Liddle *et al*, 1992). However, SPECT and PET have one methodological problem in common, and that is the anatomical definition of regions of interest. We did not carry out MRI on our patients, and thus could not use MRI templates to assist with outlining the regions of interest. Although the regions of interest were drawn manually, they were standardised by using a grid in the midventricular and supraventricular slices and by drawing the regions of interest five to six pixels in width in cortical areas.

This study supports the hypothesis that damage to limbic-related cortex in epilepsy may predispose to psychosis. Further functional imaging research on SLPE should aim to correlate the various psychotic syndromes of SLPE with patterns of cerebral blood flow. Such a study is presently being carried out in our department.

Acknowledgements

This work was carried out with the assistance of a grant from the Mason Medical Research Fund. We would like to thank all the patients who took part and Dr Graham Dunn for statistical advice. We are also grateful to Dr John Mellers for reading earlier drafts of the paper and for his helpful comments.

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*E. Jane Marshall, MRCPI, MRCPsych, *Lecturer, Sections of Genetics and Neuropsychiatry, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, and formerly Senior Registrar, Epilepsy Unit and Neuropsychiatry, Maudsley Hospital, Denmark Hill, London SE5 8AZ*; G. M. S. Syed, MB, BS, MSc, PhD, *Research Fellow, Department of Nuclear Medicine, King's College Hospital, Denmark Hill, London SE5*; P. B. C. Fenwick, FRCPsych, *Senior Lecturer, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, and Consultant Psychiatrist, Maudsley Hospital, Denmark Hill, London SE5 8AZ*; W. A. Lishman, BSc, MD, DSc, FRCP, FRCPsych, *Professor of Neuropsychiatry, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, and Honorary Consultant, Maudsley Hospital, Denmark Hill, London SE5 8AZ*

*Correspondence

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