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A Study of Epileptic Psychosis Using Magnetic Resonance Imaging

P. CONLON, M. R. TRIMBLE and D. ROGERS

Magnetic resonance imaging (MRI) was used in patients with epilepsy and psychosis. From 50 patients with epilepsy, a subgroup of 12 patients were categorised by the Present State Examination (PSE) as having nuclear schizophrenia (NS) and then compared with an epileptic control group with no psychiatric history. Further, patients with hallucinations were compared with patients without hallucinations. No differences in T_1 relaxation times in any regions of interest were noted in the NS group compared with the other group. However, patients with hallucinations had a significantly higher T_1 value in the left temporal lobe. These findings support the concept that specific abnormalities in limbic system structures relate to the phenomenology of the psychoses of epilepsy, especially left temporal lobe epilepsy.

The relationship between epilepsy and psychosis has been of interest for over 150 years, one of the earliest pathological descriptions being that of Bouchet & Cazauveilh (1825), who noted an association between epilepsy and insanity, the common underlying pathology being noted in the "*cornes de Ammon*". Slater & Beard (1963) suggested that the two were causally associated, and that underlying structural pathology was related to the development of the psychosis. In their series of 69 patients, birth trauma head injury and abnormal air encephalograms were common findings. Four-fifths of their patients had "organic personality change". A similar view was taken by Kristensen & Sindrup (1978), who examined 96 patients with epilepsy and psychosis, comparing them with a matched control group without psychosis, and reported significantly more defined organic lesions in the psychotic group. Their psychotic group showed more abnormalities on clinical neurological examination, an increased frequency of ambidexterity or left handedness, and had more patients with abnormal neuro-otological impairments. However, in contrast to the findings of Slater and Beard, the number of patients with abnormal air encephalograms was no different between the psychotic group and controls.

Taylor (1975), following an analysis of the pathology of the temporal lobes of patients removed at temporal lobectomy, noted "alien tissue" lesions more commonly in psychotic patients. In this series, left-handed females were most likely to have developed a schizophrenic-like psychosis.

In contrast, other authors have failed to define such clear evidence of organic lesions in patients with epilepsy and psychosis. Using computerised tomography (CT), neither Toone *et al* (1982) nor Perez *et al* (1985) detected an excess of structural pathology in an epileptic psychotic group compared with controls, although Toone *et al* did report an absence of right-sided pathology in patients with hallucinations rated by the Syndrome Check-List, derived from the Present State Examination (PSE) of Wing *et al* (1974). Flor-Henry (1969) preferred the concept of some functional as opposed to structural change within the central nervous system that related to the psychosis. This was based in particular on observations of inverse relationships between the frequency of seizures and the onset of psychosis in some patients. He studied 50 patients with temporal lobe epilepsy who at some time had also been psychotic, and compared them with non-psychotic controls. He noted the psychotic group had fewer psychomotor–psychosensory attacks, and less frequent convulsive or ictal manifestations. Air encephalogaphic abnormalities were reported in 52% of psychotics and 58% of the controls, and other indices of brain damage were also equivalent. He concluded "that structural cerebral damage, in itself, is not aetiological for psychosis in temporal lobe epilepsy". The epileptic psychoses he suggested were truly "epileptic".

In early work at the National Hospitals we have used clinical, electroencephalographic (EEG), and radiological imaging techniques to define further the underlying pathogenesis of epileptic psychosis. First, using the PSE, we have identified a subgroup of patients classified by the CATEGO program as nuclear schizophrenia (NS), with a clinical presentation virtually identical to that seen in patients with schizophrenia in the absence of epilepsy (Perez & Trimble, 1980). Using clinical and electrophysiological data, patients with NS and epilepsy have been shown more likely to suffer from temporal lobe epilepsy, and have a left-sided temporal lobe focus. This issue of laterality was first clearly raised by Flor-Henry (1969), who reported that psychotics had an excess of

dominant-hemisphere foci, and this effect was predominantly related to schizophrenia-like psychosis. This has been confirmed by several other investigations (see Perez *et al*, 1985) even using depth electrodes to establish the site of the focus (Sherwin, 1981). However, this was not found by Slater & Beard (1963), nor by some other investigators (e.g. Kristensen & Sindrup, 1978).

When we quantitatively assessed the CT scans of patients with epileptic psychosis, we were not able to show any significant left–right differences, although the number of patients examined was small (Perez *et al*, 1985). Using positron emission tomography (PET) with oxygen-15, in a small sample of patients with temporal lobe epilepsy and psychosis (mostly schizophrenia-like, with first-rank symptoms) we found reduced regional oxygen extraction ratios (rOER), in particular in frontal, temporal, and basal ganglia regions of interest (ROIs), and significantly lower regional cerebral blood flow (rCBF) and oxygen metabolism ($rCMRO_2$) in temporal areas on the left side when compared with a matched non-psychotic control group (Gallhofer *et al*, 1985).

In this paper we present data on a group of patients with epilepsy and psychosis who have been examined using magnetic resonance imaging (MRI).

Method

Thirty-four epileptic patients (17 psychotic and 17 controls) formed the experimental groups. They were taken from a larger sample of 50 epileptic patients on whom MRI scans were carried out. The diagnosis of epilepsy was based on clinical and EEG findings, using the criteria of Hopkins & Scrambler (1977). Seizure type was assessed according to the international classification proposed by the International League Against Epilepsy (Dreyfuss, 1981), and localisation was supported by available EEG findings. The seizure type of the epileptic patients was as follows: 11 had primary or secondary generalised seizures, 22 had simple or complex partial seizures without secondary generalisation, and 14 had partial seizures with secondary generalisation. There were three who had other forms of seizures. The EEG identification of the abnormalities was as follows: left temporal 16, right temporal 11, bitemporal 10, generalised 7, other 3, normal 3. CT scans were obtained for all patients.

The MRI was carried out using an MD 800 Scanner of field strength 0.08 tesla with resonance frequency of 3.4 MHz. The standard pulse sequence for this scanner was used (Eastwood, 1984), which employs alternating saturation-recovery and inversion-recovery sequences, with a repetition time (TR) of 1 s and an inversion time (T_I) of 200 ms. The slice thickness was 12 mm. The calculated T_1 image was generated from a computed algorithm. Manipulation of the radiofrequency of the magnetic fields yields MRI variables of proton density, T_1 and T_2 relaxation times. T_1 represents relaxation along the longitudinal axis of protons recovering their original orientation in the static field after excitation by a 180 ° pulse. Images weighted for T_1 relaxation times depend on interactions of adjacent molecules (the lattice), thus giving biochemical information concerning the local environment.

Ten slices in three planes were taken, including one coronal (through the external auditory meatus), one sagittal (in the midline), and eight transaxial slices (from the level of the cerebellum moving cranially to a level above the lateral ventricles).

T_1 times were measured in multiple ROIs. These corresponded on transaxial slices to frontal grey (medial and lateral), frontal white, occipital grey (medial and lateral), occipital white, globus pallidus–putamen, thalamus, and temporal grey (medial, anterior, and lateral). On the coronal section, temporal grey (medial and lateral) and temporal white were measured. The ROIs contained between 10 and 20 pixels, the actual size being determined by the standard deviation of T_1 values, which were kept at less than 5% in order to ensure homogeneous tissue measurements. Occasional values were not obtained due to poor image quality. The daily reproducibility of T_1 measures using standard phantoms of copper sulphate in the relevant T_1 range had a standard deviation less than 5% of the mean (Richards *et al*, 1987). All values were determined blind to both the epileptic and the psychiatric diagnosis of the patients.

The psychiatric diagnosis was initially made on clinical grounds, and patients who were psychotic identified. These were then given a PSE as close in time as possible to scannings, and subgroups, for example those with a CATEGO subclass of NS or those with hallucinations determined by examining the relevant items on the PSE (60–70) and reviewing the case notes, were selected for further investigation. Seventeen patients were clinically psychotic and PSE profiles categorised 12 as having NS. Seven had psychosis with Schneiderian auditory hallucinations. Among the total sample there were 17 patients who had no current evidence or past history of any psychiatric disturbance.

Student's *t*-test (two-tailed) was used for statistical analysis of the independent ROIs.

Results

The epileptic sample comprised 28 males and 22 females, with mean age of 34.7 years (range 17–65). Clinical neurological examination was normal in 38. The mean duration of epilepsy was 20.3 years ($\pm$ 11.6) and all but two patients were on anti-epileptic medications (13 on a single drug and 35 on two drugs or more).

The CT scans were normal in 33 and abnormal in 17 patients, while visual inspection of the MRI scan showed 36 to be normal and 14 to be abnormal. Of the 12 psychotic patients with a CATEGO classification of NS, seven had a normal CT scan, five an abnormal scan (one right-sided angioma, one occipital infarct, and three generalised atrophy or ventricular enlargement). In the control group,

with no psychiatric disturbance, 14 of the scans were reported normal, and three were abnormal (one probable basal ganglia infarct, one right occipital lobe lesion, and one left hemisphere porencephalic cyst). All patients categorised with NS had a clinical diagnosis of temporal lobe epilepsy; on the EEG six had a right-sided focus, three a left-sided focus, and three had bilateral foci. In the control group, 12 had a diagnosis of temporal lobe epilepsy, four generalised epilepsy and one frontal lobe epilepsy.

Further details of the MRI scans with respect to epilepsy variables and comparison with a normal control group are presented elsewhere (Conlon *et al*, 1988). With regard to the data presented here, two separate analyses were carried out. In the first, patients with epilepsy and no psychiatric history were compared with those patients who have NS. Secondly, patients with hallucinations were compared with those without. All statistically significant results are reported, as well as data on selected ROIs for comparative purposes.

The analysis of the mean T_1 relaxation times showed no significant differences between patients with epilepsy and no psychiatric illness in comparison to those with epilepsy and NS (Table I). In order to control for the effect of gross structural lesions in our interpretation, data were reanalysed on patients who had normal CT scans, and again no significant differences for any area were reported.

Patients with hallucinations ($n=7$) had higher T_1 values than those without hallucinations ($n=10$) (Table II), predominantly in the white and grey matter of the frontal and temporal regions, a significant difference being noted in the left temporal white region.

Discussion

We have attempted to examine hypotheses relating to the underlying pathogenesis of this form of psychosis in patients with epilepsy, and the question of laterality with regard to the presentation of psychotic symptoms in epileptic patients. Of the imaging techniques available for examining the brain, MRI is very recent. Although there are several papers which have evaluated MRI in epilepsy, most of these rely on visual inspection of the generated images, rather than on quantitative evaluation of proton spin data. We have reported elsewhere the findings relevant to epilepsy using the MD 800 scanner (Conlon *et al*, 1988), in which we have shown the sensitivity of T_1 measurements to the detection of abnormalities in the temporal lobes of patients with temporal lobe epilepsy. Further, we have outlined its usefulness in detecting cerebral pathologies not identified by CT (e.g. cerebral tumours)

TABLE I

Mean T_1 values (±s.d.) for patients with epilepsy and no psychiatric illness and for those with nuclear schizophrenia (NS)

	Left		*Right*	
	Epileptic control (n = 17)	*NS (n = 12)*	*Epileptic control (n = 19)*	*NS (n = 12)*
Frontal grey, medial	400 ± 19	401 ± 27	398 ± 16	392 ± 20
Frontal white	281 ± 20	282 ± 13	293 ± 23	286 ± 12
Occipital grey	394 ± 12	390 ± 11	391 ± 12	389 ± 9
Temporal grey, medial	405 ± 15	402 ± 12	404 ± 11	398 ± 13
Temporal grey, anterior	414 ± 27	406 ± 13	418 ± 24	408 ± 14
Temporal white	330 ± 15	322 ± 13	327 ± 12	327 ± 18

TABLE II

Mean T_1 values (+s.d.) for patients with hallucinations compared with those without

	Left hemisphere		*Right hemisphere*	
	No hallucinations (n = 10)	*Hallucinations (n = 7)*	*No hallucinations (n = 10)*	*Hallucinations (n = 7)*
Frontal grey, medial	393 ± 12	406 ± 35	385 ± 14	396 ± 24
Frontal white	277 ± 11	282 ± 15	280 ± 13	288 ± 14
Occipital grey	389 ± 11	387 ± 10	385 ± 12	391 ± 9
Temporal grey, medial	399 ± 10	402 ± 14	395 ± 12	400 ± 21
Temporal grey, lateral	392 ± 14	389 ± 10	390 ± 16	395 ± 14
Temporal white	311 ± 18	329 ± 9*	319 ± 18	332 ± 21

*$P<0.05$.

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and in allowing the morphology of certain areas of the brain, for example the corpus callosum, to be identified and measured *in vivo* (Conlon & Trimble, 1988*a*).

In this paper we have explored the aetiopathogenesis of psychosis in epilepsy, particularly that form of psychosis which resembles NS. As in our previous publications (Perez & Trimble, 1980; Perez *et al*, 1985; Gallhofer *et al*, 1985), we have chosen to classify the phenomenology of our patients using the PSE, a valuable instrument for detecting first-rank symptoms of Schneider. Our failure to note differences in T_1 values when patients with NS were compared with a control group with epilepsy and no psychiatric history, as a whole group and in those who have normal CT scans, where the influence of gross structural lesions on T_1 times has been minimised, supports our contention from our CT scan studies that gross structural pathology, *per se*, is unlikely to be a significant link between epilepsy and an ensuing psychosis. The lack of structural pathology is in contrast to some earlier studies, most notably those of Slater & Beard (1963) and Taylor (1975). However, the latter series was selected for patients having temporal lobectomy, where the chance of finding gross pathology is obviously high. Our patients were taken from the clinic, and in that sense were unselected. Slater and Beard based their conclusions on air encephalographic data. They then noted essentially atrophic changes, not the kind of abnormalities that were sought in this investigation. The frequency of atrophy in psychotic and control groups is in fact found to be similar (Flor-Henry, 1969; Kristensen & Sindrup, 1978; Toone *et al*, 1982).

This is in contrast to the data which would support a functional change. This includes the earlier work of Flor-Henry (1969), in which an inverse relationship was shown between seizure frequency and psychosis, noted in many cases by several other authors before and since (Slater & Beard, 1963; Trimble, 1985), implying some physiological link between the two. Further, the psychosis in these patients tends to develop a number of years after the onset of seizures and not vice versa (Slater & Beard, 1963), suggesting that the continued, recurrent seizures may bring over time some functional change.

Of interest was the finding in our study that patients with hallucinations have a significant increase in the T_1 times in the left temporal region. Although the finding of a single significance of this value should be interpreted with caution, it is not out of keeping with the laterality data from several other studies (Flor-Henry, 1969; Perez *et al*, 1985; Gallhofer *et al*, 1985), including the study of Toone *et al* (1982), where patients with hallucinations were found not to have a right-sided focus. In our study the T_1 changes presumably reflect pathological or physiological alterations in these areas that may or may not be associated with the clinical phenomenology. However, they do suggest some association between limbic pathology and hallucinations, a hypothesis which arises from the work in temporal lobe epilepsy generally, which, when associated with psychosis, is a condition which may be seen as a model for Crow's type 1 (Crow, 1980), predominantly 'positive' symptom schizophrenia. In our analysis, the area of the temporal lobe particularly affected was the white matter precisely in the areas where pathological studies might suggest changes in patients with temporal lobe lesions responsible for epilepsy (for example mesial temporal sclerosis) (Stevens, 1986); this would therefore suggest some link between Schneiderian hallucinatory experiences and limbic pathology.

Although with regards to laterality there are some negative reports (e.g. Kristensen & Sindrup, 1978), the investigators have not used Schneiderian principles for classifying schizophrenia. However, studies with CT, looking for structural associations, have also tended to be negative (Perez *et al*, 1985; Toone *et al*, 1982). The fact that a laterality difference was not identified in the NS group as a whole in this investigation may reflect on the heterogeneity of Schneiderian symptoms that lead to a computer-diagnosed category of NS. It might be that only certain first-rank symptoms are related to dominant hemisphere dysfunction. This idea receives some support from our finding of a significant increase in the T_1 value of the white matter of the left temporal lobe in patients with Schneiderian auditory hallucinations. Further, in schizophrenia, using MRI, Besson *et al* (1987) noted an association between 'positive symptoms' that include hallucinations, and left temporal changes.

A final point should be made with regards to MRI techniques. This is the first study of MRI in epileptic psychosis, and the MD 800 machine has allowed us to examine T_1 data in relation to the clinical phenomenology of our patients. In general, raised T_1 values suggest underlying pathology, although the precise nature of the pathology is unclear. Nonetheless, it is hoped that the findings reflect upon the value of MRI in detecting subtle changes, suspected from pathological studies, within the brain *in vivo*, which may have particular importance with regard to psychiatry (Conlon & Trimble, 1988*b*). Thus, some crucial areas of brain anatomy thought to be of relevance for psychopathology, notably limbic system structures, including deep and medial temporal structures, are poorly visualised by current

scanning techniques, but may be well visualised by MRI. Further studies of MRI in allied psychiatric conditions, such as affective disorder and schizophrenia, are in progress, since studies in epilepsy, a natural model for chronic disturbed brain function, must be taken in conjunction with findings from patients who do not have epilepsy.

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