PAPER

Schizophrenia-like psychosis arising de novo following a temporal lobectomy: timing and risk factors

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Objectives: To clarify risk factors for the development of schizophrenia-like psychotic disorders following temporal lobectomy, and to explore the possibility that the early postoperative period is a time of high risk for the onset of such chronic psychotic disorders.
Methods: Patients who developed schizophrenia-like psychosis were identified from a series of 320 patients who had a temporal lobectomy for medically intractable epilepsy. The relationship of their disorders to both the operation and subsequent seizure activity was examined. Using a retrospective case–control design, risk factors for the development of schizophrenia-like psychosis were established.
Results: Eleven patients who developed schizophrenia-like psychosis postoperatively were identified and compared with 33 control subjects who remained free of psychosis postoperatively. The onset of de novo psychotic symptoms was typically in the first year following the operation. No clear relationship between postoperative seizure activity and fluctuations in psychotic symptoms emerged. Compared with the controls, patients who become psychotic had more preoperative bilateral electroencephalogram (EEG) abnormalities, pathologies other than mesial temporal sclerosis in the excised lobe and a smaller amygdala on the unoperated side.
Conclusions: Temporal lobectomy for medically intractable epilepsy may precipitate a schizophrenia-like psychosis. Patients with bilateral functional and structural abnormalities, particularly of the amygdala, may be at particular risk for the development of such psychoses.

INTRODUCTION

Several forms of psychotic disorders arise in association with epilepsy, including episodic seizure related psychoses and chronic interictal psychotic disorders which phenomenologically resemble schizophrenia. Psychotic disorders which follow a chronic interictal course and arise for the first time following a temporal lobectomy are of interest both as a potentially serious complication of the operation and for the insights they might provide into more common psychoses such as schizophrenia.

To date there are reports of just over 50 patients who developed de novo psychotic disorders following surgical treatment for medically intractable epilepsy.[1–16] Although interpretation of the literature is complicated by the different definitions of psychosis used, several key issues of practical and theoretical importance have emerged. Firstly, several studies report a preponderance of congenital lesions, such as dysembryoblastic neuroepithelial tumours, in the excised lobe rather than the typical pathology of mesial temporal sclerosis which underlies most cases of temporal lobe epilepsy.[6 13 17 18] There is also evidence of a clustering of the onset of the psychotic disorders in the early postoperative period. A review of studies done before 1997 reports that 11 of 23 cases of de novo psychosis started within six months of the temporal lobectomy.[19] More recent work has confirmed this: Blumer *et al*[12] describe six patients who developed psychosis within the first two postoperative months and Inoue and Mihara[14] detail five cases that all arose in the first two years after the operation. Such temporal links provoke concerns about possible aetiological links between this operation and the development of psychosis. The pathophysiology of such an association could relate to changes in postoperative seizure activity. In a recent report of three patients who developed purely postictal psychosis, the psychosis followed the emergence of a new seizure type originating from the side contralateral to the operation.[15] In all these cases there were preoperative bilateral electroencephalogram (EEG) abnormalities and the excision of the temporal lobe and development of new seizure activity may have acted upon a bilaterally compromised functional substrate prone to developing psychosis. We speculate that similar functional bilateral anomalies may be associated with the development of postoperative chronic schizophrenia-like psychosis. We also extend the previous work by examining patients for the presence of bilateral structural abnormalities.

The identification of risk factors for the development of psychosis post temporal lobectomy has potential therapeutic benefit as it would aid the early identification of those at high risk for developing the disorder.

We report on 11 subjects who developed psychotic disorders de novo following temporal lobectomy. We confined our study to patients who developed a chronic schizophrenia-like disorder and thus excluded purely postictal psychosis and depressive disorders with psychotic features. We describe the phenomenology of their disorders; the relationship between their surgery, subsequent seizure activity and psychotic symptoms; and identify risk factors for the development of psychosis.

METHODS

The study included 320 patients who underwent surgical treatment for medically intractable epilepsy at the Maudsley Hospital and King's College Hospital in London between 1978 and 2001. The preoperative protocols used in the epilepsy surgery centre have been described in detail elsewhere.[20] In addition to interictal and awake EEG, most patients proceeded to ictal video-EEG recordings. Formal psychiatric evaluation is requested if there is evidence of a mental disorder either in the past or during the preoperative investigation period. In the patients with temporal lobe

Abbreviations: CI, confidence interval; DNET, dysembryoblastic neuroepithelial tumour; EEG, electroencephalogram; MTS, mesial temporal sclerosis; OR, odds ratio

Table 1 Clinical features of patients who developed schizophrenia-like psychoses following surgical treatment for epilepsy

Subject	Age/sex	Delusions	Hallucinations	First rank symptoms	Thought disorder	Negative symptoms	Course of disorder	Duration of symptoms
P1	22/M	Persecutory	Auditory (2nd person)	Thought insertion	Present	Apathy	Chronic continuous (no response to treatment)	10 yrs
P2	20/F	Persecutory	Auditory (2nd person)	None	Present	Social withdrawal	Chronic continuous (partial control by antipsychotics)	14 yrs
P3	21/M	Persecutory reference	None	None	Present	None	Chronic continuous (partial control on antipsychotic)	8 yrs
P4	39/F	Persecutory	None	Somatic passivity	None	None	Episodic with chronic residual delusions (partially responsive to treatment)	3 yrs
P5	39/M	Persecutory	None	None	Present	Social withdrawal	Chronic continuous (refused treatment)	9 yrs
P6	18/M	Persecutory	Auditory (2nd person)	None	None	Emotional flattening	Chronic continuous (poorly responsive to antipsychotics)	8 yrs
P7	19/M	Persecutory	Somatic	Thought insertion	None	None	Chronic continuous (refused medication)	4 yrs
P8	33/F	Persecutory	Auditory (2nd person)	None	None	None	Episodic with minimal symptoms between episodes on mediation	Episodes last 3–8 mths
P9	19/F	Persecutory	Auditory (2nd person)	Somatic passivity	None	None	Episodic with complete recovery between episodes on antipsychotic medication. Intermittently compliant with medication.	16 yrs
P10	34/F	Persecutory and reference	Auditory (2nd person)	None	Present	None	One prolonged episode (partially responsive to antipsychotics)	2 yrs
P11	18/F	Persecutory	Auditory (3rd person)	Commentary hallucinations	Present	None	One prolonged episode (responsive to medication)	8 mths

M, male; F, female; yrs, years; mths, months.

epilepsy, a standardised en bloc resection involves excision of the anterior part of the anterior part of the temporal lobe—typically extending 3.5 cm from the tip of the temporal lobe on the left and 4.5 cm on the right. A small number of patients had selective amygdalo-hippocampectomy in which the resection was limited to the mesial structures.

Follow up assessments are routinely conducted at 2, 6, and 12 months postoperatively. Further appointments are usually then made annually or more frequently, according to clinical need. All of the patients who developed chronic psychosis postoperatively received specialist neuropsychiatric evaluation and all but one were hospitalised in a specialist neuropsychiatric unit at the Maudsley Hospital. Such patients are typically followed up at this centre until stable where practical or by another regional neuropsychiatric unit.

Cases

The cases met the DSM-IV diagnosis of a psychotic disorder due to a general medical condition, specifically fulfilling the criteria for schizophrenia. We thus excluded three subjects who had purely postictal psychosis, which tended to be of short duration and two subjects with affective psychoses. All data were entered into OPCRIT (operational criteria for psychotic and affective illness), a well validated operationalised diagnostic tool to establish the diagnosis which would be reached if the presence of epilepsy and surgery were discounted.[21 22] This enabled a check that the psychoses were indeed ''schizophrenia-like''.

For each case the next three consecutive patients who had a temporal lobectomy but did not develop psychosis were selected as controls. Two potential postoperative psychotic subjects and eight controls were excluded due to insufficient data.

Neuroimaging

Many of the subjects had their operations before the advent of clinical magnetic resonance imaging (MRI) and thus structural analyses were confined to postoperative imaging. This was obtained for seven subjects in the psychotic group and 21 subjects in the non-psychotic group. Images were obtained on a 1.5 Tesla GE N/Vi Signa System (General Electric, Milwaukee, MI, USA) scanner using a 3-D inversion recovery. Prepared fast spoiled GRASS T1-weighted dataset was obtained in the coronal plane with 1.5 mm contiguous sections. The volumes of the amygdala and hippocampus of the unoperated side were measured by two independent raters using criteria developed by Watson *et al* and adjusted for total intracranial volume.[23] The posterior to anterior distribution of the hippocampus and amygdala were presented graphically. Interrater reliabilities for the volumetric analyses (expressed as intraclass correlations) were 0.94 for the amygdala, 0.98 for the hippocampus, and 0.97 for total intracranial volume.

Ethical approval was obtained from the Ethics Committee of the Institute of Psychiatry.

Statistical analysis

To identify potential risk factors for the development of psychosis, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous categorical variables, and the χ^2 test applied to non-dichotomous categorical variables. Continuous variables were analysed using *t*-tests.

RESULTS

Demographic and clinical details

Eleven patients were identified who developed de novo postoperative schizophrenia-like psychotic disorders (see table 1). The disorders were dominated by persecutory delusions and auditory hallucinations; thought disorder was present in six and schneiderian first rank symptoms present in five patients. Negative symptoms were infrequent, and although subjects often showed affective symptoms these did not dominate the clinical presentation.

There was little evidence of any association between postoperative seizure activity and the development of psychotic symptoms (see table 2). Of the six subjects who had persistent seizures, only one showed a clear worsening of his chronic psychotic symptoms postictally. There were no associations between symptoms and demographic or clinical features such as the aetiology, type, and duration of the epilepsy or side, extent, or outcome of the operation.

Table 3 shows the anticonvulsant treatment that patients were taking at the time of the development of the psychotic symptoms. Nearly all subjects were taking the same medication in the period before their operation and in only one case (subject P2) had an alteration in medication preceded the development of psychosis (the withdrawal of adjunctive agents). Blood levels of medication in the postoperative period were available for seven of the subjects and all were within the therapeutic range with no cases of toxicity.

There was a close temporal link between the recurrence of seizures postoperatively and the first appearance of psychotic symptoms in two subjects. In the remainder either the psychosis arose despite cessation of clinically overt seizures or there was a long time difference between the recurrence of seizures and onset of psychosis. Fluctuations in the course of the schizophrenia-like psychosis were closely related to ongoing seizure activity in only one patient.

The postoperative EEG abnormalities among the psychotic patients whose seizures persisted postoperatively showed clear epileptiform activity. These abnormalities were typically similar to the abnormalities seen preoperatively, with the focus of activity shifting anterior or posterior to the excised region. In one case there was a clear increase in the epileptiform activity in the side contralateral to the excised lobe. Three of the five psychotic patients who experienced a cessation of seizure activity had no definite epileptiform activity on EEG recordings (sleep and wake surface EEGs in all cases). The other two patients who had no recurrence of seizures showed some EEG anomalies. Subject P3's tracing demonstrated very infrequent sharp waves in the region of the excised temporal lobe. Subject P9, who had no clinically overt seizure activity, had however a highly abnormal EEG, which was taken while she was experiencing psychotic symptoms. The abnormalities were not thought to be attributable to her medication at the time of the recording, which included pimozide.

Table 2 Details of epilepsy and underlying pathology in the 11 subjects

Subject	Age of onset of habitual seizures(years)	Side of operation	Preoperative EEG abnormalities	Pathology
P1	3	L	Unilateral	MTS
P2	8	R	Bilateral	Vascular hamartoma
P3	9	R	Unilateral	MTS
P4	12	L	Unilateral	DNET
P5	23	L	Bilateral	No definite pathology
P6	3	R	Bilateral	MTS
P7	2	R	Bilateral	No definite pathology
P8	19	R	Unilateral	Abscess
P9	6	L	Bilateral	MTS
P10	14	R	Bilateral	Ganglioglioma
P11	7	R	Unilateral	DNET

EEG, electroencephalogram; L, left; R, right; MTS, mesial temporal sclerosis; DNET, dysembryoblastic neuroepithelial tumour.

Relationship of the psychosis to operation

As can be seen from fig 1, eight patients developed their initial symptoms within a year of the operation.

Risk factors

None of the demographic, neuropsychological, or operative variables studied differentiated those who developed psychosis postoperatively from those who did not (see table 4). However, it emerged that psychotic patients were more likely to have pathologies other than mesial temporal sclerosis identified in the resected tissue (with the entire 95% CI of the odds of having a pathology other than sclerosis lying above 1.0). The psychotic patients were also more likely to have had bilateral EEG abnormalities on their preoperative EEGs.

The only neuroanatomical difference between the groups on the postoperative MRI was a significantly smaller amygdala on the unoperated side (fig 2).

DISCUSSION

We report on 11 patients who, following surgical treatment for epilepsy, developed de novo psychotic illnesses which phenomenologically resembled schizophrenia with persistent persecutory delusions, auditory hallucinations, and, in some cases, schneiderian first rank symptoms. Negative symptoms were not prominent, although this could in part reflect the length of the follow up period. We did not confirm previously reported associations between particular psychotic symptoms and clinical features such as the age of onset of epilepsy. Although as in previous reports the majority of the patients had right sided temporal lobectomies this did not emerge as a significant risk factor for the development of psychosis.[19]

Blumer *et al* have recently argued that there is a causal link between temporal lobectomy and psychosis.[12] Our confirmation of a clustering of cases of new onset psychosis in the year after the operation appears to support this position. However, part of the association could arise from factors such as the age of operation. The mean age of operation in our subjects was 25 years which lies near the peak age onset of schizophrenia.[24] In the cohort of patients who underwent temporal lobectomy from 1978 to 2001 there were also seven subjects who were psychotic prior to the operation (details available from PS), and the median age of onset of their psychosis at 26 years did not differ significantly from that of the postoperative psychotic group. The only difference between the groups was in the later age at operation of 32 years among those who were psychotic prior to surgery. It seems most likely that the operation acts as a stressor, precipitating psychosis in vulnerable subjects during a high risk period.

The presence of pathologies other than mesial temporal sclerosis emerged as a significant risk factor for the development of postoperative psychosis. The prominence of congenital lesions such as dysembryoblastic neuroepithelial tumours and gangliogliomas has been reported by other groups.[6 13 25] The significance of this association is unclear but it could reflect the presence of aberrant prenatal neurodevelopment which may contribute to a vulnerability to the development of a psychotic disorder in adult life.

Our results echo other findings implicating bilateral abnormalities in the pathogenesis of postlobectomy psychosis. Functionally, this is apparent from our finding of higher

Table 3 Relationship between postoperative seizures and psychotic symptoms and details of EEG abnormalities

Subject	Postoperative medication	Relationship between onset of psychosis and recurrence of seizures	Relationship between ongoing seizure activity and fluctuations in psychotic symptoms	Postoperative EEG
P1	Carbamazepine Sodium valproate	Psychosis appeared same time as recurrence of seizures (early postoperative period)	None	Spikes and sharp waves over L posterior temporal region
P2	Carbamazepine	Psychosis appeared 5 years prior to recurrences of seizures	None	Spikes over R posterior temporal region
P3	Phenytoin Mysoline	Seizures abolished	N/A	Infrequent sharp waves in R temporal region
P4	Carbamazepine Gabapentin	Seizures abolished	N/A	No definite epileptiform activity
P5	Carbamazepine Sodium valproate Lamotrigine	Psychosis appeared same time as recurrence of seizures (early postoperative period)	Psychotic symptoms more intense for a week following cluster of seizures, but also present interictally	Spikes over frontotemporal regions bilaterally, more prominently on R (abnormalities from unoperated side more prominent than preoperatively)
P6	Carbamazepine Phenytoin	Psychosis appeared 5 years prior to recurrence of seizures	Depression postictally, but psychotic symptoms chronic	Spikes over frontotemporal regions bilaterally
P7	Carbamazepine	Psychosis appeared 6 years prior to recurrence of seizures	None	N/A
P8	Carbamazepine Sodium valproate	Seizures abolished	N/A	No definite epileptiform activity
P9	Phenytoin	Seizures abolished	N/A	L frontal sharpened spike waves and some R midtemporal sharp waves. Persistent focal slow rhythms
P10	Lamotrigine Topiramate	Seizures abolished	N/A	No definite epileptiform activity
P11	Carbamazepine Primidone Lamotrigine	Psychosis appeared 1 year after recurrence of seizures	None	Sharp waves in R frontotemporal and sylvian regions

EEG, electroencephalogram; L left; R, right; N/A, not available.

rates of preoperative bilateral EEG abnormalities. The presence of preoperative bilateral EEG anomalies in this group has been reported by others[4] and the postoperative emergence of new seizures from the unoperated lobe has been found to be associated with de novo episodic postictal psychosis.[15] A similar clear temporal link between the recurrence of seizures and onset of de novo chronic psychotic symptoms was apparent in only two of the patients. In both cases the seizures were similar in semiology to preoperative seizures, although an increase in abnormal epileptiform activity in the unoperated lobe was noted in one patient. Additionally there is no simple link between ongoing seizure activity and fluctuations in the intensity of the chronic psychotic symptoms. Only one patient showed a definite deterioration in psychotic symptoms following a cluster of seizures and none of the patients demonstrated an alternating pattern of seizure remittance and psychotic exacerbations.

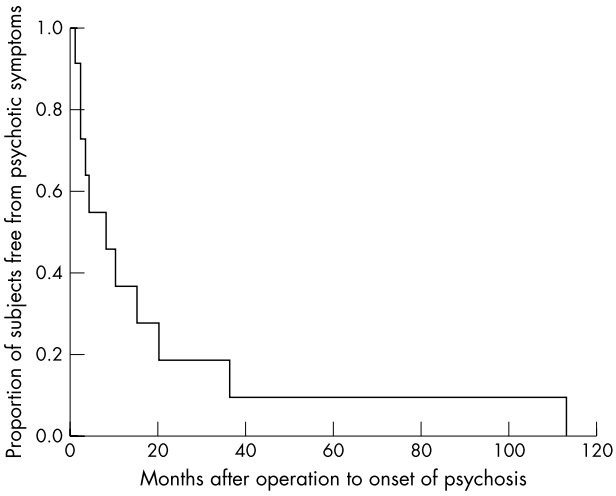

Figure 1 Time in months from the operation until the onset of psychotic symptoms.

It is also possible that subclinical ictal activity—either ipsilateral or contralateral to the excised lobe—may contribute to the development of psychosis. Among the five subjects who had no clinically overt seizure activity two had abnormal EEGs—which in one case were relatively minor but in the other included bilateral frontal sharp waves and focal slow rhythms. Although it is plausible that in this subject the subclinical ictal activity may have contributed to the onset and maintenance of psychotic symptoms, this would appear to be an exceptional case.

The functional bilateral abnormalities are complemented by the evidence we report for specific bilateral structural abnormalities, reflected in the decreased volume of the amygdala on the unoperated side. Another recent study emphasised the possible pathogenic role of the amygdala in the psychoses of epilepsy, however, this study found an

Table 4 Risk factors for the development of postoperative schizophrenia-like psychosis

	Patients who developed psychosis after TL	Patients free of psychosis after TL	Test of significance
Demographic factors			
Sex			
Male	5	20	OR (male) 0.54 (95% CI 0.13 to 2.14)
Female	6	13	
Age at operation (mean (SD))	25 (8)	27 (8)	$t=-0.63$, df 42, p=0.53
Follow up in years (mean (SD))	8 (5)	10 (6)	$t=-0.89$, df42, p=0.37
Neuropsychological factors			
Handedness			
Right	10	28	$\chi^2=1.14$, df 2, p=0.56
Left	1	2	
Ambidextrous	0	3	
IQ			
Verbal	93 (18)	96 (13)	$t=-0.51$, df 42, p=0.61
Performance	95 (20)	96 (12)	$t=-0.16$, df 42, p=0.87
Clinical factors			
Age in years of onset of habitual seizures (mean (SD))	10 (7)	9 (6)	$t=-0.25$, df42, p=0.80
History of febrile convulsions	3	7	OR (history of febrile convulsions) 1.39 (95% CI 0.29 to 6.6)
History of status epilepticus	2	2	OR (status) 3.4 (95% CI 0.42 to 28.1)
Preoperative EEG findings			
Unilateral abnormalities	4	25	OR (bilateral abnormalities) 5.45 (95% CI 1.26 to 23.6)
Bilateral abnormalities	7	8	
Operation			
Side			
Right	7	16	OR (right side) 1.6 (95% CI 0.4 to 6.4)
Left	4	17	
Extent			
Anterior temporal lobectomy	9	32	OR (temporal lobectomy) 0.14 (95% CI 0.13 to 1.73)
Amygdalo-hippocampectomy	2	1	
Outcome			
Total cessation of seizures	5	23	OR (complete cessation) 0.36 (95% CI 0.08 to 1.45)
Partial improvement	1	4	
No improvement	5	6	
Pathology			
Mesial temporal sclerosis	4	25	OR (of pathologies other than mesial temporal sclerosis) 5.46 (95% CI 1.26 to 23.6)
Other pathologies			
Dysembryoblastic neuroepithelial tumours	2	1	
No definite abnormality	2	4	
Arteriovenous malformation	0	1	
Cavernous haemangioma	1	0	
Abscess	1	0	
Ganglioglioma	1	2	

TL, temporal lobectomy; OR, odds ratio; CI, confidence interval.

enlargement of the amygdala.[26] The discrepancy may reflect differences in the study populations as we included only surgically treated subjects who form a small and distinct group among all those with epilepsy and psychosis. Several strands of research implicate abnormalities of the amygdala in the pathogenesis of schizophrenia. Structurally, there are consistent reports using volumetric MRI of a more marked decline in the volume of the amygdala in patients with schizophrenia compared with other brain structures.[27] Some of the negative symptoms of schizophrenia such as flattened affect, thought disorder and abnormal processing of emotionally salient material have been linked to amygdala dysfunction.[28–31] In view of this evidence it is possible that among subjects who have a temporal lobectomy, if the remaining amygdala is structurally and functionally abnormal this may have critical effect, precipitating a chronic psychotic disorder.

There are several limitations to the study. Although all subjects underwent an intensive preoperative investigations and prolonged follow up, it is possible that some control subjects may have had undetected psychotic disorders. There were also some candidate cases and control subjects who were lost to follow up, although given the small numbers of such subjects their data are unlikely to influence the pattern of results greatly. The risk factors we examined were not exhaustive and had a bias towards biological variables. In the future we aim to collect data on the potentially critical variable of family history of mental illness using reliable techniques. We also did not systematically examine the possibility that psychosocial variables such as socioeconomic class may be risk factors for the development of psychosis. Similarly we do not have data on the psychosocial outcome of patients although the clinical impression is of an almost uniformly poor outcome among the group who developed psychosis (particularly if seizures persisted) compared with those who remained free of psychosis.

It is unlikely that the psychoses developed as a result of psychotogenic anticonvulsant medication as drugs are typically not changed in the first year after a lobectomy, which is the peak risk period for the development of psychosis. There was only one case in which an alteration of medication (the withdrawal of lamotrigine) preceded the onset of psychosis. Iatrogenic psychosis secondary to anticonvulsant toxicity is also unlikely in our cases as serum anticonvulsant levels during the postoperative period were all within the therapeutic range (although results were not

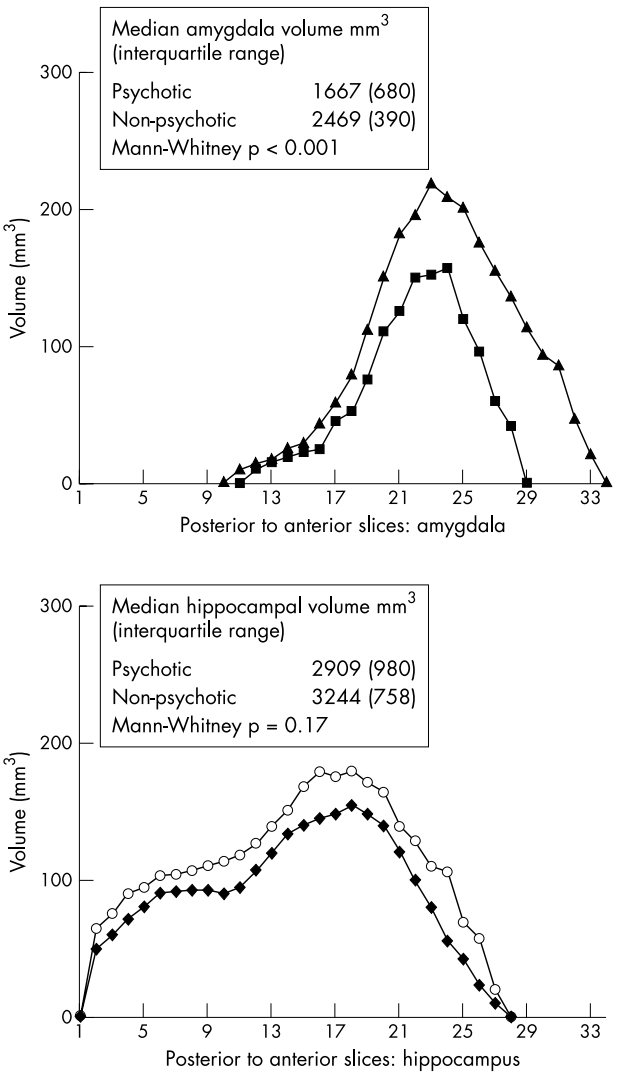

Figure 2 Posterior to anterior coronal slice by slice volumes of the amygdala (top graph) and the hippocampus (bottom graph) on the unoperated side in patients who developed psychosis and those who remained free from psychosis. The volume of the amygdala on the unoperated side was significantly smaller among the patients who became psychotic following temporal lobectomy (■) compared with the patients who remained free of psychosis (▲). There was no significant difference between the volume of the hippocampus for the psychotic group (◆) and non-psychotic group (○).

available on all cases). Additionally the case definition excluded patients whose psychosis occurred in the context of an acute organic brain syndrome.

Our study identifies both the characteristics of those patients at greatest risk for the development of schizophrenia-like psychosis following a temporal lobectomy and also the period of greatest risk. This may aid in the early identification and treatment of those who develop de novo psychotic disorders. We also find that bilateral temporal lobe abnormalities, particularly of the amygdala, may form part of the neural substrate of this disorder.

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