Amygdala pathology in psychosis of epilepsy
A magnetic resonance imaging study in patients with temporal lobe epilepsy

L. Tebartz van Elst,1,2,3 D. Baeumer,1,2,3 L. Lemieux,2 F. G. Woermann,2 M. Koepp,2 S. Krishnamoorthy,1,2 P. J. Thompson,2 D. Ebert3 and M. R. Trimble1,2

1Raymond Way Research Group, 2Epilepsy Research Group, Institute of Neurology, University College London, UK and 3Department of Psychiatry, Albert-Ludwigs-University, Freiburg, Germany

Correspondence to: Dr L. Tebartz van Elst, Department of Psychiatry, Albert-Ludwigs UniversitaÈt, Hauptstrasse 5, 79104 Freiburg, Germany
E-mail: ludger_vanelst@psyallg.ukl.uni-freiburg.de

Summary
Psychosis of epilepsy (POE) has been recognized as a severe complication of chronic intractable epilepsy for more than a century. Most of the clinical symptoms of POE are reminiscent of schizophrenia. Nevertheless, there is general agreement that the phenomenology of POE differs from classical schizophrenia. The temporal lobe hypothesis of schizophrenia put forward in the 1960s notes that episodes with paranoid psychoses are more prevalent in temporal lobe epilepsy (TLE). However, the aetiology and pathogenesis of POE are poorly understood. One of the strongest biological findings in schizophrenia is volume loss of temporal lobe structures and the hippocampus in particular. In order to test the hypothesis that atrophy of the hippocampus and the amygdala is found in patients with TLE and POE, we performed a retrospective study of all patients with TLE who were admitted to the assessment unit of the Chalfont Centre for Epilepsy from 1995 until 1999.

Twenty-six (2.6%) of these 1008 patients fulfilled inclusion criteria and were compared with 24 patients with TLE without psychopathology and 20 healthy volunteers. All patients underwent extensive MRI investigations, including volumetric data sets and quantitative T2 relaxometry. We found that patients with TLE and POE differed from patients with TLE alone and healthy volunteers in that the total brain volumes were significantly smaller. While there were no differences in hippocampal volumes between the three study groups, there was a significant 16±18% enlargement of the amygdala on both sides in patients with POE. Our findings support the notion that POE is a distinct nosologic entity differing from schizophrenia not only in clinical details but also in neurobiological aspects. The finding of amygdala enlargement agrees with the observation of an association between dysphoric disorders of epilepsy and POE described nearly 100 years ago.

Keywords: amygdala; schizophrenia; psychosis of epilepsy; MRI; temporal lobe epilepsy

Abbreviations: AT2 = amygdala T2; PIP = postictal psychosis; POE = psychosis of epilepsy; SLPE = interictal schizophrenia-like psychosis of epilepsy; TLE = temporal lobe epilepsy

Introduction
The psychoses of epilepsy (POE)

Psychosis is an uncommon, but severe, complication of epilepsy. Figures of between 0.5% and 9% have been found by the small number of population-based epidemiological surveys looking at the prevalence of mixed psychosis in epilepsy (Schmitz and Wolf, 1995; Gudmundsson, 1966; Bredkjaer et al., 1998).

The phenomenology of POE is often reminiscent of schizophrenia. However, it is distinguished clinically by the absence of negative symptoms, better premorbid functions and a rare deterioration of the patient’s personality (Toone et al., 1982). In contrast to schizophrenia, genetic factors seem to play a minor role in POE (Slater et al., 1963).

There is no generally accepted classification of POE (Schmitz and Wolf, 1991). In the international classification systems of psychiatric disorders [ICD-10 (The International Statistical Classification of Diseases and Related Health Problems) and DSM-IV (Diagnostic and Statistical Manual of Mental Disorders)], there are no specific subcategories relating to the psychopathological syndromes seen in epilepsy. A recent suggestion is to distinguish episodic psychosis of epilepsy from non-episodic or chronic psychosis of
epilepsy (Toone, 2000; Rayport and Ferguson, 2001). Another possibility is to classify POE according to the most dominant clinical feature into (i) affective psychosis or (ii) schizophrenia-like psychosis of epilepsy. In clinical practice, POE is generally classified according to the temporal relationship of the psychotic episode to the seizure.

Ictal psychosis can be distinguished from postictal and interictal psychosis. Ictal psychosis is typically an expression of non-convulsive status epilepticus, including simple partial status, complex partial status and absence status (Wolf and Trimble, 1985). Postictal psychosis (PIP) accounts for approximately 25% of POE (Dongier, 1959). It often follows clusters of complex partial or secondarily generalized seizures (Kanner et al., 1996). Classically there is a lucid interval between seizure and psychosis lasting from 1 to 6 days (Trimble, 1991). The relationship to the type of epilepsy is unclear. While Dongier (1959) found a preponderance of generalized epilepsies, Logsdail and Toone (1988) noted a higher prevalence in focal epilepsy. Most patients with PIP present with abnormal mood and delusions, which are often grandiose, religious and mystic in nature (Slater et al., 1963; Kanemoto et al., 1996). Psychotic symptoms often remit spontaneously within days or weeks, but chronic psychosis sometimes develops from recurrent or even one single postictal psychosis (Logsdail and Toone, 1988; Savard et al., 1991). PIP is a risk factor for mood disorders after temporal lobe surgery (Kanemoto et al., 1998). Intercital schizophrenia-like psychosis of epilepsy (SLPE) occurs between seizures and cannot be linked directly to the ictus. While less frequent than PIP, clinically SLPE is significant in terms of its severity and duration (Slater et al., 1963; Wolf, 1976). SLPE generally presents as a paranoid hallucinatory syndrome similar to schizophrenia (Slater et al., 1963). However, there is controversy as to whether the absence of negative symptoms and formal thought disorder, and the better preserved personality function might distinguish SLPE clinically from schizophrenia (Perez and Trimble, 1980). SLPE typically begins 10–15 years after the onset of the epilepsy (Trimble, 1991) and sometimes develops out of PIP (Savard et al., 1991).

Aetiology of POE
The aetiology and pathogenesis of psychotic episodes in epilepsy are poorly understood. Some believe it is closely related to the seizure disorder (Kanner, 2000). Psychotic episodes classically follow the onset of epilepsy with a latency of 11–15 years (Trimble et al., 1996). This observation has led to the postulation of a kindling hypothesis of POE (Smith and Darlington, 1996). The observation that POE is more common in temporal lobe epilepsy (TLE) led Slater and his colleagues to challenge the old notion of a pathogenic antagonism between epilepsy and psychosis (Slater et al., 1963). Subsequently, the temporal lobe hypothesis of psychosis and schizophrenia was influential in neuropsychiatric research (Perez and Trimble, 1980). However, later studies did not always replicate this association. POE has been related to early onset of the epilepsy (Briellmann et al., 2000), bitemporal seizure foci and clustering of seizures (Umbricht et al., 1995), temporal lobe dysplasias (Adachi et al., 2000) and foreign body lesions (Andermann et al., 1999). In schizophrenia, volume loss of the hippocampus/amygdala complex is one of the strongest and most consistent biological findings (Lawrie and Abukmeil, 1998). Since it is even found in unaffected first-degree relatives of patients with schizophrenia, it has been proposed as a possible trait marker for schizophrenia (Lawrie et al., 1999). In POE, there are only two studies specifically investigating temporal lobe structures. Briellmann et al. (2000) studied six patients with postictal psychoses but did not find any evidence of volume loss of the hippocampus. Maier et al. (2000) used MRI volumetry and magnetic resonance spectroscopy to compare patients with POE with patients with epilepsy alone, with schizophrenic patients and with healthy controls. They did not find any convincing volumetric group differences when measuring the hippocampus/amygdala complex as a single structure (Maier et al., 2000). Both patient groups with epilepsy had reduced neurometabolite concentrations compared with healthy controls. However, this did not distinguish patients with POE from patients with epilepsy alone.

Recently, POE has been associated with the dysphoric disorder of epilepsy (Blumer, 2000a,b). In fact, Kraepelin pointed out such an association nearly 100 years ago (Kraepelin, 1913). The dysphoric disorder of epilepsy is characterized by affective symptoms such as brief episodes with depressed or euphoric mood, irritability, anergia, insomnia, anxiety and fears. These symptoms are known to be common in TLE in general and POE in particular (Blumer, 1991). In a previous study, we were able to demonstrate significant amygdala enlargement in patients with the dysphoric disorder of epilepsy (Tebartz van Elst et al., 1999).

To our knowledge, there is no other published study looking specifically at possible amygdala pathology in patients with POE.

Rationale for our study
While volume loss of the hippocampus/amygdala complex has been reported as a consistent finding in schizophrenia, the only studies investigating hippocampal volumes in patients with POE did not find convincing evidence of hippocampal volume loss. So far, there are no studies specifically investigating amygdala pathology in POE using modern MRI technology. In this work, we have tested the hypothesis that there is hippocampal and amygdala volume loss in patients with chronic intractable TLE and POE by comparing their volumes with those of healthy volunteers and those of patients with TLE but without psychopathology.
Patients and methods

Patient identification

Approval for this study was obtained from the Ethics Committee of the National Hospital for Neurology and Neurosurgery, University College London Hospitals, Queen Square, London, UK. Our study used a retrospective approach to identify patients with temporal lobe epilepsy at a tertiary referral centre (National Society for Epilepsy, Chalfont Centre for Epilepsy, Chalfont, St Peter, Bucks, UK). The clinical syndrome of interest was defined as complex partial seizures with clinical features, EEG and MRI findings compatible with temporal lobe epilepsy. Diagnoses were made by neurologists not involved in this study.

Patients with extratemporal or generalized epilepsy were excluded, as were patients with a full IQ below 70 on the Wechsler Adult Intelligence Scale—Revised. All discharge summaries of the Chalfont Centre for Epilepsy from August 1995 until April 1999 were scrutinized for evidence of psychotic episodes, and full hospital notes were obtained for relevant cases. Patients were then classified into groups of postictal and interictal psychosis on the basis of the notes made by consultant psychiatrists working in the Department of Neuropsychiatry, National Hospital for Neurology and Neurosurgery, and/or discharge summaries from in-patient stays at psychiatric hospitals.

Psychotic episodes were defined according to ICD-10 criteria for the paranoid subtype of schizophrenia with the exception of the time criterion (World Health Organization, 1991). The minimum requirement for a diagnosis of ‘psychosis’ was the presence of delusions and/or hallucinations. Confusional states or depressive symptoms alone were not regarded as sufficient. The temporal relationship of the psychotic mental state to the ictus was noted, and patients with psychopathology present independent of seizures were classified as suffering from SLPE, while psychotic episodes that appeared in a clear temporal relationship to a cluster of seizures (mostly being separated from it by a lucid interval) were said to represent PIP. Episodes that seemed to be drug-induced provoked by excessive consumption of alcohol or represented complex partial status were excluded. These criteria closely follow the description of postictal psychosis by Logsdail and Toone (1988). To keep the study groups homogeneous, patients with a history of any other first axis psychiatric disorder were excluded from the study. However, minor affective symptoms reminiscent of dysthymia or cyclothymia were allowed, since they are common in patients with TLE. The control group consisted of 20 healthy volunteers and 24 randomly chosen cases of TLE without any psychopathology except dysthymia, who were matched for age, sex, duration of epilepsy and antiepileptic medication. All patients and volunteers have given informed consent to take part in the study.

MRI assessment

MRI images were obtained at the Chalfont Centre for Epilepsy on a 1.5 T GE Signa scanner (GE Medical Systems, Milwaukee, Wis., USA) using a $T_1$-weighted inversion-recovery prepared volume acquisition [IRSPGR: TI (inversion time) = 450 ms, TR (repetition time) = 15 ms, TE (echo time) = 4.2 ms, flip angle = 20°; $124 \times 1.5$ mm thick contiguous coronal slices; matrix $256 \times 192$, $24$ cm $\times 18$ cm field of view]. For computation of $T_2$, relaxation time values, a conventional spin echo sequence [TR = 2000 ms, TE1 = 30 ms, TE2 = 120 ms, NEX (number of excitations) = 1, $256 \times 192$ matrix, $24 \times 18$ cm field of view, $5$ mm thick coronal slices with no gap; scan time $10$ min] was obtained by two interleaved acquisitions to cover the entire brain. In the latter, the slices were acquired in a tilted coronal plane perpendicular to the long axis of the hippocampi.

Radiological diagnosis was made by two neuroradiologists following visual assessment of the MRI scans.

Volumetric measurements

A locally developed software package MRreg (http://www.erg.ion.ucl.ac.uk/MRreg.html) was used for measurements (Lemieux et al., 1998, 2000). Intensity windowing was monitored consistently. The brain volume was calculated by outlining in every 10th slice (no magnification) using the semi-automatic threshold and region growing tool to delineate the cerebrum, cerebellum and brainstem superior to the pons. The number of voxels was then multiplied by the voxel volume to give the slice brain volume (in cm$^3$). The total brain volume was obtained by multiplying the sum of the slice volumes by 10. The images were then zoomed by a $\times 4$ magnification factor for hippocampal and amygdala volume measurements. Hippocampal and amygdala volumes were measured by manually outlining the boundaries of each structure separately following a well-established and validated protocol (Watson et al., 1992, 1997). The volume of each structure was calculated by multiplying the number of voxels within each trace by the voxel volume and dividing by the magnification factor; the structure volume was obtained by summing the in-slice volumes. The hippocampal and amygdala volumes were corrected for total brain size by dividing by the cerebral volume. The person carrying out the rating (the ‘rater’) was blind to the subject grouping by random mixing and ordering of the patients, and normal controls. Reliability between raters was assessed by calculating an intraclass correlation coefficient from repeated measurements of 20 randomly chosen scans (Norman and Streiner, 1994).

$T_2$ mapping

Pixel-by-pixel $T_2$ maps were calculated from coronal images using a region of interest approach identical to the one described previously (Tebartz van Elst et al., 2000). Briefly,
amygdala T₂ (AT₂) relaxation time values were measured by the same observer (F.G.W.) using DisplImage image analysis software (Plummer, 1992) by placing the largest possible elliptic region of interest within the amygdala while avoiding anatomical boundaries. For hippocampal T₂ relaxation time values, regions of interest were placed on four to six consecutive slices, the first being the one anterior to the slice in which the fornix was seen in its greatest length (Tebartz van Elst et al., 2000). Intra-rater variability of AT₂ relaxation time measures using this method were assessed by calculating the limit of agreement and the coefficient of repeatability (Bland and Altman, 1986).

Data analysis
All quantitative data were analysed for differences in variance using Levene’s test (Norman and Streiner, 1994); the two primary contrasts of interest being possible differences between patients with TLE with and without psychosis on the one hand and differences between patients with PIP and SLPE on the other hand. In order to test our main hypothesis of altered mesial temporal volumes in patients with TLE and psychosis, we performed an ANOVA (analysis of variance) comparing total brain, amygdala and hippocampal volumes and T₂ relaxation times of patients with TLE and POE, non-psychotic patients and healthy controls. Results were corrected for multiple comparisons using the Bonferroni correction method. Post hoc group comparison was also performed using the Bonferroni correction method. To test possible influences of the factors, gender and age, we performed a factorial ANOVA using study groups and gender as factors and age as covariate.

In a second step, we divided patients with TLE and psychosis into those with PIP and those with SLPE, and repeated all analyses to assess whether there were differences between the two groups.

We repeated all analyses after excluding all patients with a history suggestive of the dysphoric disorder of epilepsy in order to assess a possible influence of this syndrome on our findings.

Finally, to test a possible influence of antipsychotic medication on our findings, we reanalysed the data after excluding all patients who were receiving such medication.

T₂ values were compared using one-way ANOVA for the amygdala and Kruskal–Wallis one-way ANOVA for hippocampal values, which were not normally distributed. Categorical data, such as laterality of EEG and MRI abnormalities, were analysed using the appropriate contingency test.

Results
Study group structure
Figure 1 shows the selection process used for this study. A total of 1008 patients who underwent assessment at the Chalfont Epilepsy Centre between 1995 and 1999 were surveyed. Sixty-eight patients (6.8%) suffered from major depression, 56 (5.6%) displayed severe aggressive behaviour and 46 (4.6%) suffered from psychotic disorders. Of these, 20 had to be excluded for the following reasons: in six cases the documentation was insufficient; four patients suffered from a primary generalized epilepsy; two cases were clearly drug-induced; two episodes of altered mental state were merely affective in character; two developed after temporal lobectomy; two patients had been operated on; one patient had a learning disability (IQ 60); and in one case the MRI study was not available. Fifteen of the remaining 26 patients with psychosis suffered from postictal psychosis and 11 had a chronic interictal psychosis. Twenty-four patients with TLE without any major psychopathology and 20 healthy volunteers were identified. The groups were matched with respect to age, gender and duration of epilepsy. There was no significant group difference with respect to the history of encephalitis or status epilepticus. In the group of patients with PIP, however, there was a remarkable absence of febrile convulsions (none out of 15 patients) compared with the other groups of TLE-patients (four out of 11 patients with TLE and SLPE, and nine out of 24 patients with TLE alone (χ² = 7.534, P = 0.02). However, following correction for multiple comparison, this difference failed to reach significance level.

Twelve of the 26 patients with POE (46%) compared with six out of 24 patients in the control group (25%) had a history of minor affective symptoms suggestive of the dysphoric disorder of epilepsy [seven with PIP (44%) and five patients with SLPE (46%)]. Even though dysphoric symptoms were more common in the psychotic group, this group difference was not significant.

Eleven of the 26 patients with POE received antipsychotic medication at the time of the study (42%) and 15 did not (58%).

Reference data and reliability
Amygdala, hippocampal and total brain volumes of the group of 20 healthy volunteers served as a reference (Table 4).
intraclass correlation coefficient as calculated from repeated measurements of random images of the whole study group was 0.99 for the hippocampi and 0.88 for the amygdala. This compares favourably with published data (Watson et al., 1992; Tebartz van Elst et al., 2000).

Intra-rater reliability of hippocampal T2 measurements showed a mean difference of 0.25 ms (1% of the mean T2 value of the healthy controls), a limit of agreement of 3.0 ms and a coefficient of repeatability of 3.5%. Corresponding values for AT2 measurements were a mean difference of 1.2 ms (1.4% of the mean AT2), a limit of agreement of 4 ms and a coefficient of repeatability of 4.7%.

All quantitative relaxometric and volumetric data except for the hippocampal T2 relaxation times were normal in distribution, thus allowing us to proceed with ANOVA. The hippocampal relaxation times were compared using Kruskal–Wallis one-way ANOVA.

### EEG and MRI abnormalities

There was no difference in the distribution of EEG abnormalities between the groups with respect to laterality. While hippocampal sclerosis was more common in patients without POE, there were no significant differences in term of nature and laterality of the neuropathology as diagnosed by visual assessment of MRI scans (Tables 1 and 2).

### Neuropsychological profile

While there were no differences in performance IQ (Wechsler Adult Intelligence Scale—Revised) between psychotic and non-psychotic patients, verbal IQ was significantly lower in the psychotic group [mean verbal IQ: POE: 86.4, SE (standard error, 2.3); TLE–Controls: 95.1 (3.0); T = 2.307, \( P = 0.02 \); mean performance IQ: POE: 89.7 (2.6); TLE–Controls: 90.8 (4.7); T = 0.203, \( P = 0.8 \); mean total IQ: POE: 86.5 (2.3); TLE–Controls: 93.6 (2.9); T = 1.902, \( P = 0.06 \); \( P \)-values not corrected for multiple comparisons]. Comparing patients with PIP and SLPE, it was evident that all IQ figures were lower in patients with interictal psychosis; however, this difference did not reach significance level.

### T2 measurements

Comparison of hippocampal and amygdala T2 measurements did not reveal any evidence of increased values in the psychotic group. Table 3 summarizes our findings.

### Volumetric measurements

Table 4 summarizes our volumetric findings. Patients with POE had significantly smaller total brain volumes compared with both healthy controls and patients without psychopathology [ANOVA \( F(2) = 11.750, P < 0.001 \); factorial ANOVA \( F(6) = 6.656, P < 0.000 \)]. Post hoc sub-group comparison (Bonferroni correction) showed that this overall group difference was due to significantly reduced cerebral volumes of patients with POE (mean volume 1056.5 cm³; SD 114.1 cm³) compared with the patient control group [mean volume 1168.3 cm³; SD 111.3 cm³; (I–J) = 111.8, \( P = 0.003 \)] and with healthy controls [mean volume 1214.8 cm³; SD 114.1 cm³; (I–J) = 158.3, \( P < 0.001 \)].

While there were no significant differences in hippocampal volumes, group comparison revealed a highly significant 16–
18% enlargement of both right \[ ANOVA \ F(2) = 8.211, \ P = 0.001; \] factorial ANOVA \[ F(6) = 2.930; \ P = 0.01 \] and left amygdala volumes \[ ANOVA \ F(2) = 9.079, \ P < 0.001; \] factorial ANOVA \[ F(6) = 4.207; \ P = 0.001 \] in patients with POE. The factor gender and the covariable age did not contribute significantly to the variance of either hippocampal or amygdala volumes. Post hoc sub-group analysis using Bonferroni correction proved that a bilateral enlargement of the amygdala of psychotic patients was responsible for the overall significant finding in the factorial ANOVA (see Fig. 2).

Sixteen of the psychotic patients suffered from PIP and 11 from chronic SLPE. Table 5 summarizes our volumetric findings for these sub-groups. Even though cerebral volume loss was more pronounced in the SLPE sub-group, there were no significant volumetric differences distinguishing these two sub-groups.

Following exclusion of patients with a history of dysphoric symptoms, there were minor changes in the degree of cerebral volume loss and amygdala enlargement. However, the overall finding of cerebral volume loss \[ ANOVA \ F(2) = 7.478; \ P = 0.001 \] and amygdala enlargement in psychotic patients remained unchanged and was still significant for both sides \[ right: ANOVA \ F(2) = 6.452; \ P = 0.003; \] left: \[ ANOVA \ F(2) = 5.144; \ P = 0.009 \].

To test a possible influence of antipsychotic medication on our findings, we repeated our analyses after exclusion of those 11 psychotic patients who had received antipsychotic medication. Again, there were minor changes in the degree of cerebral volume loss \[ ANOVA \ F(2) = 6.866; \ P = 0.002 \] and amygdala enlargement in patients with POE with the overall findings being unchanged \[ right side: ANOVA \ F(2) = 16.747; \ P < 0.001; \] left side: \[ F(2) = 7.771; \ P = 0.001 \].

**Discussion**

In our study, we investigated a possible role of mesial temporal structures, in particular the hippocampus and amygdala, in the aetiopathogenesis of POE in patients with TLE. Methodological limitations of our study should be considered before embarking on an interpretation of our findings.

**Methodological issues**

**Patient selection**

First, our study is retrospective in nature. All patients with chronic intractable TLE who had been referred to the Chalfont Epilepsy Centre from 1995 until 1999 (\( n = 1008 \)) were surveyed and a total number of 2.6% or 26 patients with POE were included. All these patients had been seen and diagnosed by a neuropsychiatrist who was an expert in epilepsy (M.R.T). All three study groups were matched for age and sex, and the two patient groups were matched with respect to the duration of epilepsy. Unfortunately, we were not able to obtain an elaborate psychometric assessment of these patients retrospectively since the patients had been referred from all over the UK. Patients with any DSM-IV axis one disorder (except for psychosis of epilepsy) were excluded from further analysis. Minor psychiatric disorders and, in particular, the dysphoric disorder of epilepsy were not excluded since this disorder is common in epilepsy.

**Neurological and neuropsychological assessment**

Only patients with temporal lobe epilepsy were included in our study. All patients received a thorough neurological,
psychiatric and neuropsychological work-up. Patients with extratemporal or generalized epilepsies were excluded, as were those with a full-scale IQ <70 or with first axis psychiatric diagnoses other than psychosis. Thus, our study groups are homogeneous and our findings should relate to the group-defining variable.

Neuroimaging

The methodology we used in terms of MRI acquisition and volumetric measurements was identical to previous studies (Tebartz van Elst et al., 1999).

Mesial temporal lobe pathology in POE

In our study, we were able to demonstrate an association between cerebral volume loss, amygdala enlargement and schizophrenia-like psychotic disorders in temporal lobe epilepsy. Clear-cut hippocampal sclerosis was more common in the non-psychotic patient group; however, there were no significant differences in terms of EEG or MRI pathology between patients with POE and patients with TLE alone. Furthermore, there were no differences with respect to the T2 relaxation times as an indicator of gliosis between the different study groups.

There were no significant differences between the psychotic sub-groups of patients with PIP and SLPE. Both subgroups displayed significant cortical volume loss and bilateral amygdala enlargement.

Our result of preserved hippocampal volumes and amygdala enlargement contrasts strongly with the numerous studies of patients with schizophrenia where a significant volume loss of these mesial temporal lobe substructures presents a rather homogeneous finding (Lawrie and Abukmeil, 1998; Nelson et al., 1998; Harrison, 1999).

Mesial temporal lobe structures and schizophrenia

Despite almost 100 years of research since Kraepelin first described schizophrenia (calling it dementia praecox), the precise neuropathology of schizophrenia remains obscure (Toone, 2000). Forty years ago, Slater’s work pointing out a relationship between the temporal lobes and schizophrenia-like psychosis in epilepsy led to the temporal lobe hypothesis of schizophrenia (Slater et al., 1963; Slater and Moran, 1969). Subsequently, considerable evidence for the preferential involvement of the temporal lobes in the pathogenesis of schizophrenia emerged. Beside decreased cerebral cortical volumes, one of the most consistent structural findings in imaging studies confirmed by meta-analyses is ventricular enlargement, and hippocampal and probably amygdala volume loss (Lawrie and Abukmeil, 1998; Nelson et al., 1998; McCarley et al., 1999; Gur et al., 2000; Wright et al., 2000). While there are several candidates for the histological and molecular correlates of these abnormalities, their precise nature is not yet clear (Harrison, 1999).

Mesial temporal lobe structures and POE

Ever since Slater and his colleagues published their study of a series of 69 patients with epilepsy and schizophrenia-like psychosis (Slater et al., 1963), mesial temporal lobe structures and, in particular, the hippocampus were thought to play a crucial role in the development of psychotic episodes in TLE. Some authors have pointed to a possible role of the amygdala in the pathogenesis of psychotic syndromes (Smith and Darlington, 1996; Stevens, 1999). However, there are only a few imaging studies that have specifically looked at hippocampal and amygdala pathology in POE; most did not find significant differences or were confined to small numbers of patients (Conlon et al., 1990; Jibiki et al., 1993; Fong et al., 2000). Mellers et al. (1998) found a reduced activation of the left temporal lobe during neuropsychological testing in patients with SLPE compared with schizophrenic patients and non-psychotic patients with epilepsy. This suggested that, in SLPE, the pathophysiology may be relatively confined to the dominant temporal lobe. This finding corresponds well with our observation of a significant reduction in verbal IQ in our sample of patients with POE, since verbal IQ represents dominant and, thus, generally left hemisphere functions.

Briellmann et al. (2000) did not find evidence of hippocampal volume loss in six patients with postictal psychosis. Maier et al. (2000) did not find any overall group differences when they compared the hippocampus/amygdala complex of 12 patients with POE with schizo-
Amygdala abnormalities in psychosis of epilepsy 147

Psychosis of epilepsy—a distinct nosological entity?
A number of research groups have reported amygdala enlargement in different affective disorders ranging from dysthymia in patients with TLE (Tebartz van Elst et al., 1999) to bipolar disorder (Altshuler et al., 1998; Strakowski et al., 1999; Bremner et al., 2000) and generalized anxiety disorder in children (De Bellis et al., 2000).

Thus amygdala enlargement is common to POE and a range of different affective disorders, while in schizophrenia, if anything, there is amygdala volume loss. Patients with major depression or bipolar disorder were excluded from our study. However, patients with symptoms of the dysphoric disorder of epilepsy (Blumer, 2000b) were allowed. When excluding these patients from analysis, we still found significant amygdala enlargement in the psychotic patient group even though to a lesser degree. Thus, our results may support the notion of Blumer (2000a), who recently pointed to an association between the dysphoric disorder of epilepsy and POE. He drew to attention an observation first published by Kraepelin nearly 100 years ago (Kraepelin, 1913). In his famous textbook of psychiatry, Kraepelin stressed the point that psychotic disorders in patients with epilepsy often develop against a background of affective symptomatology. Blumer evolved this concept and defined clinical criteria for the dysphoric disorder of epilepsy (Blumer, 2000a, b). He has published his experiences with a series of eight patients with SLPE, who were successfully treated with a combination of antidepressant and antipsychotic drugs, thus supporting his view that interictal psychoses can be viewed as severe interictal dysphoric disorders with psychotic features. Other authors supported this view by pointing out that a history of depression predicts the occurrence of postictal psychotic symptoms (Kanner, 2000).

From a morphological point of view, our patients with POE resembled patients with schizophrenia in that they displayed reduced cortical volumes, even though this was probably a non-specific finding. They resembled patients with dysphoric disorder of epilepsy (Tebartz van Elst et al., 1999) in that they had normal hippocampal and enlarged amygdala volumes. Our findings are in agreement with the assumption that psychoses of epilepsy develop on the background of dysphoric disorder of epilepsy (Kraepelin, 1913; Blumer, 2000a).

From a morphological point of view, there were no major differences between patients with PIP and SLPE. Both tend to develop late in the course of chronic intractable TLE, and PIP sometimes evolves into SLPE (Trimble, 1991, 1996). Since an association with the dysphoric disorder of epilepsy also seems to be common to both clinical syndromes (Blumer 2000a, b), one might speculate that they represent different clinical aspects of one nosological entity.

Clinical relevance of the findings
Our findings are of clinical relevance in that they support the view that POE might develop against the background of the dysphoric disorder of epilepsy. This condition is often missed clinically, since it does not fit easily into the classic nosological criteria of ICD-10 or DSM-IV (Blumer, 1991, 2000b). With POE being a severe complication of chronic TLE, these considerations add weight to the importance of a thorough psychiatric assessment of patients with chronic intractable epilepsy. Atypical forms of depression often fulfilling the criteria of the dysphoric disorder of epilepsy are easily missed and early therapeutic intervention might be important for the prevention of POE. Finally, for patients with POE, consideration should be given to an additional treatment with antidepressant medication, since affective symptoms might contribute to the pathogenesis of the psychotic syndrome.
Conclusions

In summary, we found clear evidence of cerebral volume loss and amygdala enlargement in patients with schizophrenia-like psychosis of epilepsy when compared with matched patients without psychosis and healthy volunteers. In contrast to patients with schizophrenia, hippocampal volumes were preserved in patients with POE. Cerebral volume loss was more pronounced in patients with SLPE compared with patients with PIP. Other than that, there were no morphological differences between these two patient sub-groups. Since amygdala enlargement has been reported in different patient groups with affective disorder, our findings support the notion that POE might develop on the background of the dysphoric disorder of epilepsy, which is often missed in clinical practice. This consideration gives weight to a call for thorough psychiatric assessment of patients with chronic TLE, since early treatment of affective disorder might prevent the development of psychotic syndromes in these patients.

While amygdala enlargement obviously is not specific for POE, the combination of amygdala enlargement and cerebral volume loss might be. Further research should be directed towards whether cerebral morphometry would enable vulnerability profiles for individual patients to be defined, i.e. the risk assessment of the development of affective or psychotic syndromes.

References


Andermann LF, Savard G, Meencke HJ, McLachlan R, Moshe S, Andermann F. Psychosis after resection of ganglioglioma or DNET: and amygdala enlargement in patients with schizophrenia-like psychosis of epilepsy when compared with matched patients with POE. Cerebral volume loss was more pronounced in patients with SLPE compared with patients with PIP. Other than that, there were no morphological differences between these two patient sub-groups. Since amygdala enlargement has been reported in different patient groups with affective disorder, our findings support the notion that POE might develop on the background of the dysphoric disorder of epilepsy, which is often missed in clinical practice. This consideration gives weight to a call for thorough psychiatric assessment of patients with chronic TLE, since early treatment of affective disorder might prevent the development of psychotic syndromes in these patients.

While amygdala enlargement obviously is not specific for POE, the combination of amygdala enlargement and cerebral volume loss might be. Further research should be directed towards whether cerebral morphometry would enable vulnerability profiles for individual patients to be defined, i.e. the risk assessment of the development of affective or psychotic syndromes.


Lawrie SM, Abukmeil SS. Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic
Theodore WH, editors. Epilepsy and behavior. New York: Wiley-
epilepsy: relation between ages of onset. Br J Psychiatry
1995; 8: 295±305.

Slater E, Moran PA. The schizophrenia-like psychoses of

Slater E, Beard AW, Glithero E. The schizophrenia-like psychosis

Smith PF, Darlington CL. The development of psychosis in
epilepsy: a re-examination of the kindling hypothesis. [Review].
Behav Brain Res 1996; 75: 59±66.

Stevens JR. Epilepsy, schizophrenia, and the extended amygdala.

Strakowski SM, Delbello MP, Sax KW, Zimmerman ME, Shear
PK, Hawkins JM, et al. Brain magnetic resonance imaging of
structural abnormalities in bipolar disorder. Arch Gen Psychiatry
1999; 56: 254±60.

Tebartz van Elst L, Woermann FG, Lemieux L, Trimble MR.
Amygdala enlargement in dysthymia—a volumetric study of
patients with temporal lobe epilepsy. Biol Psychiatry 1999; 46:
1614±23.

Tebartz van Elst L, Woermann FG, Lemieux L, Thompson PJ,
Trimble MR. Affective aggression in patients with temporal lobe
epilepsy: a quantitative magnetic resonance study of the amygdala.
Brain 2000; 123: 234±43.

Toone BK. The psychoses of epilepsy. [Review]. J Neurol
Neurosurg Psychiatry 2000; 69: 1±3.

Toone BK, Garralda ME, Ron MA. The psychoses of epilepsy and
the functional psychoses: a clinical and phenomenological

Trimble MR. The psychoses of epilepsy. New York: Raven Press;

Trimble MR. Biological psychiatry. 2nd ed. Chichester: Wiley;
1996.

Trimble MR, Ring HA, Schmitz B. Neuropsychiatric aspects of

Umbricht D, Dregger G, Barr WB, Lieberman JA, Pollack S, Schaul
N. Postictal and chronic psychoses in patients with temporal lobe

Watson C, Andermann F, Gloo P, Jones-Gotman M, Peters T,
Evans A, et al. Anatomic basis of amygdaloid and hippocampal
volume measurement by magnetic resonance imaging. Neurology

Watson C, Jack CR Jr, Cendes F. Volumetric magnetic resonance
imaging. Clinical applications and contributions to the
understanding of temporal lobe epilepsy. [Review]. Arch Neurol

Wolf P. Psychosen bei Epilepsie. Ihre Bedingungen und
Wechselbeziehungen zu Anfällen. Habilitationsschrift. Berlin:
Freie Universität Berlin; 1976

Wolf P. Psychosen bei Epilepsie. Ihre Bedingungen und

Wolf P, Trimble MR. Biological antagonism and epileptic

World Health Organization. International Klassifikation psychischer

Wright IC, Rabe-Hesketh S, Woodruff PW, David AS, Murray RM,
Bullmore ET. Meta-analysis of regional brain volumes in

Accepted August 20, 2001