Affective aggression in patients with temporal lobe epilepsy
A quantitative MRI study of the amygdala

L. Tebartz van Elst,[1,2,3] F. G. Woermann,[2] L. Lemieux,[2] P. J. Thompson[2] and M. R. Trimble[1,2]

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

Correspondence to: Dr L. Tebartz van Elst, Department of Psychiatry, Albert-Ludwigs-Universität, Hauptstrasse 5, D-79104 Freiburg, Germany

Summary
Recurrent episodes with interictal affective aggression are a rare but well-recognized problem in patients with temporal lobe epilepsy. They are referred to as episodic dyscontrol or, more precisely, as intermittent explosive disorder (IED). The amygdala play a crucial role in the affective evaluation of multimodal sensory input and the neurobiological mediation of aggressive behaviour. With hippocampal sclerosis, in the context of mesial temporal lobe sclerosis, being the most common cause of temporal lobe epilepsy, we hypothesized that the amygdala might be affected by the same pathogenic process in aggressive patients. We investigated 50 patients with temporal lobe epilepsy: 25 with and 25 without a history of IED. Data from clinical, electrophysiological, neuropsychological and psychometric investigations were obtained, as well as MRI scans for the quantitative assessment of possible amygdala pathology. We found no evidence of a higher prevalence of amygdala sclerosis in the aggressive patients. Hippocampal sclerosis was significantly less common in patients with temporal lobe epilepsy and IED. However, a significant subgroup of patients (20%) with temporal lobe epilepsy and aggressive behaviour had severe amygdala atrophy in the context of a history of encephalitis. Another subgroup of aggressive patients (28%) had different left temporal lesions affecting either the amygdala or periamygdaloid structures. IED was associated with left-sided or bilateral EEG and MRI abnormalities, low IQ and high scores in depression and anxiety.

Keywords: amygdala; aggression; intermittent explosive disorder; MRI; temporal lobe epilepsy

Abbreviations: AT2 = amygdala T_2; IED = intermittent explosive disorder

Introduction
Phenomenology and classification of aggression
Human aggression is an important social and clinical problem (Fenwick, 1986; Saver *et al.*, 1996; Trimble, 1996; Swartz *et al.*, 1998). The relationship between temporolimbic epilepsy and aggressive behaviour is a particularly controversial issue (Geschwind, 1975). While a history of complex partial seizures is reported to be common in patients with episodic affective aggression (Bach-Y-Rita *et al.*, 1971; Elliott, 1982), most of the community-based studies did not find an increased prevalence of aggressive behaviour in patients with epilepsy (Kligman and Goldberg, 1975; Lishman, 1998).

One problem with studying aggression is its phenomenological and probably neurobiological heterogeneity, leading to difficulties in assessment and classification. However, human data, in agreement with animal research, point to the existence of at least two different phenomenological and neurobiological subtypes of aggression: predatory and defensive aggression (Goldstein, 1974; Mungas, 1983; Moyer, 1987; Vitiello and Stoff, 1997). Predatory aggression is characterized phenomenologically as a well-structured and goal-directed behaviour performed in an emotionally calm and concentrated state of mind. In contrast, defensive aggression is seen typically in the context of high emotional arousal associated with vocalizations and signs of fear or anger. The behaviour itself is less structured and defensive (Valzelli, 1981). Apart from the planned and goal-directed aggression often seen in persons with antisocial personality disorder (predatory aggression), most forms of human aggression are thought to be a reaction towards a perceived threat, be it real or not (Albert *et al.*, 1993). Obviously, the perception as to whether a stimulus is threatening or not is decisive in the information processing leading to the aggressive behaviour.

Neurobiology of aggression

Various brain structures have been implicated in the mediation of aggressive behaviour in animals and humans, the most important being the periaqueductal grey (Brandao *et al.*, 1994; Behbehani, 1995), the hypothalamus (Andy and Jurko, 1972), the amygdala and associated limbic structures (Dicks *et al.*, 1968; Halgren, 1992; Kling and Brothers, 1992; Rolls, 1992; Aggleton, 1993) and the frontal lobes (Damasio *et al.*, 1990; Miller *et al.*, 1997; Raine *et al.*, 1998). Within this network of critical structures, the amygdala are thought to play a crucial role in the mediation of fear-induced aggression, a subtype of defensive aggression (Aggleton, 1993; LeDoux, 1995; Charney and Deutch, 1996; Gallagher and Chiba, 1996). They receive extensive input from various levels of sensory information processing and project to most of the other critical brain structures, i.e. the brainstem, hypothalamus, thalamus and frontal lobe (Amaral *et al.*, 1992; Alheid *et al.*, 1995). From a neurophysiological point of view, they are in a predestined position for the affective evaluation of multimodal sensory input. Thus pathology within the circuits affecting the amygdala might lead to mental states where the misinterpretation of sensory input as threatening leads to aggressive outbursts. In agreement with this assumption, electrical stimulation of the amygdala can lead to experiences such as fear, anxiety or anger (Chapman *et al.*, 1954; Gloor *et al.*, 1982), and lesioning of the amygdala severely impairs fear conditioning in animals (Davis *et al.*, 1994) and humans (LaBar *et al.*, 1995). Furthermore, in an open retrospective study of 481 cases of bilateral amygdalotomies performed for the control of conservatively untreatable aggressiveness, moderate to excellent improvement of aggressive behaviour was reported in 70–76% of cases (Ramamurthi, 1988).

Aggression and temporal lobe epilepsy

The prevalence of aggression in epilepsy in general, not taking into account the specific epileptic subsyndrome, varies between 4.8% (Rodin, 1973) and 50% (Gastaut *et al.*, 1955). In a large survey of 666 patients with temporal lobe epilepsy, Currie and co-workers reported aggression in 7% of the patients (Currie *et al.*, 1971). Falconer reviewed 100 patients from London's Maudsley Hospital referred for temporal lobectomy and found a prevalence of outbursts of aggressive behaviour in as many as 27% of the patients (Falconer, 1973). However, these studies were hampered by selection bias, and the real prevalence of aggressive behaviour in epilepsy remains controversial (Lishman, 1998).

In epilepsy, three different types of aggressive behaviours should be distinguished on the basis of their relationship to the seizures: ictal, post-ictal and interictal aggression. All three types of aggression are defensive, in that they are episodes of affective aggression, i.e. they occur in the context of high emotional arousal, anger or fear.

Ictal and post-ictal aggression are often associated with confusion or psychosis (Treiman, 1991). Interictal aggression, on the other hand, can be seen in the context of an antisocial personality disorder which, in turn, might be the consequence of the sometimes difficult psychosocial background of patients with epilepsy. However, an interictal syndrome of episodic affective aggression, independent of observable ictal activity, major psychiatric disorder or antisocial personality disorder, is well described and has been referred to as episodic dyscontrol (Bach-Y-Rita *et al.*, 1971; Maletzky, 1973; Ratner and Shapiro, 1979; Leicester, 1982; Elliott, 1984; Stone *et al.*, 1986). Episodic dyscontrol is characterized by several discrete episodes of failure to resist aggressive impulses that result in serious assaultive acts or destruction of property. The behaviour is out of proportion to any precipitating psychosocial stressor and is not due to substance abuse, another mental disorder such as personality disorder, any other first axis psychiatric disorder or a general medical condition such as head trauma or neurodegenerative diseases. The phenomenological criteria are those of intermittent explosive disorder (IED) according to DSM-IV (Elliott, 1984; American Psychiatric Association, 1994). Because of the emotional arousal typically seen in episodic dyscontrol, this behavioural syndrome has to be classified as a subtype of defensive aggression. The high level of arousal with signs of anxiety or fear is also the reason why amygdala pathology is thought to contribute to this behavioural syndrome (Fenwick, 1986; Elliott, 1992; Trimble *et al.*, 1996). In three past studies, the relationship between different psychobiological factors, e.g. brain pathology, IQ and demographical background, and aggression in epilepsy was addressed. While Rodin found more evidence of organic brain disease (Rodin, 1973), and Falconer reported an increased incidence of mesial temporal lobe sclerosis in aggressive patients with temporal lobe epilepsy (Falconer, 1973), Herzberg and Fenwick did not find any relationship between specific EEG or CT pathology and aggression in patients with temporal lobe epilepsy (Herzberg and Fenwick, 1988). All three studies found a relationship between low IQ and aggression, and two reported an association between male sex and aggression (Rodin, 1973; Falconer, 1973).

To our knowledge, there is no study investigating a possible association between aggressive behaviour and brain pathology using the modern technique of MRI and focusing on the amygdala as an important limbic brain structure for this condition.

MRI assessment of temporal lobe structures

The most common pathology underlying temporal lobe epilepsy is hippocampal sclerosis often in the context of mesial temporal sclerosis (Margerison and Corsellis, 1966; Wieser, 1983; Gloor, 1991). Some authors give a prevalence to hippocampal sclerosis in temporal lobe epilepsy as high as 65% (Babb and Brown, 1987). A radiological *in vivo* diagnosis of mesial temporal lobe sclerosis is possible by demonstrating atrophy of the mesial temporal lobe structures

on T_1-weighed anatomical MRI images and increased signal on conventional spin-echo T_2 MRI sequences (Jackson *et al.*, 1990; Duncan *et al.*, 1996; Woermann *et al.*, 1998). Since hippocampal sclerosis seems to be diffuse rather than focal in most of the cases (Kim *et al.*, 1995), an involvement of the amygdala by the pathological process underlying hippocampal sclerosis might be expected, and indeed is reported in the literature (Hudson *et al.*, 1993; Miller *et al.*, 1994).

In vivo identification of amygdala sclerosis by measuring the amygdala T_2 relaxation time has been reported in patients with temporal lobe epilepsy (Van Paesschen *et al.*, 1996; Kalviainen *et al.*, 1997). Furthermore, amygdala volumetry has been validated as a reliable method (Watson *et al.*, 1992; Cendes *et al.*, 1993; Soininen *et al.*, 1994; Kalviainen *et al.*, 1997).

Rationale for this study

The aim of our study was to investigate amygdala pathology in patients suffering from temporal lobe epilepsy and additional affective aggression, specifically IED. In particular, we hypothesized that, in patients with temporal lobe epilepsy and intermittent affective aggression, amygdala sclerosis in the context of hippocampal sclerosis would be more common than in control patients. Furthermore, we wanted to test if there is an association between aggression, on the one hand, and hippocampal sclerosis, low IQ and poor social adjustment, on the other hand, in patients with temporal lobe epilepsy.

Patients and methods
Patients and patient assessment

Approval for this study had been obtained from the ethics committee of the National Hospital for Neurology and Neurosurgery. Patients with temporal lobe epilepsy were recruited from a tertiary referral centre (National Hospital for Neurology and Neurosurgery and the associated Chalfont Centre for Epilepsy). The clinical syndrome of interest was defined as complex partial seizures with a symptomatology, EEG and MRI findings compatible with temporal lobe epilepsy. Neurologists who were not involved in this study made the neurological diagnoses. On the basis of the discharge summaries, patients with temporal lobe epilepsy with and without a history of aggression were identified, contacted and seen by a psychiatrist (L.T.v.E.). Patients with extratemporal or generalized epilepsy were excluded, as were those with a history of mental handicap or psychoses. Informed consent was obtained from the patients prior to further investigations. Patients with temporal lobe epilepsy with and without a history of IED diagnosed according to DSM-IV criteria were included in the study. A neurological and psychiatric history and examination were obtained, as well as routine EEG investigations and neuropsychological investigations. Full, verbal and performance IQ were

measured using the well-established revised version of the Wechsler Adult Intelligence Scale (Nachson, 1991). Patients with a full IQ below 70 were excluded from the study to avoid selection bias. Frequency and severity of the three main seizure types were documented and rated according to the National Hospital Seizure Severity Scale (O'Donoghue *et al.*, 1996). All patients were asked to fill in the Beck's Depression Inventory and the State Trait Anxiety Inventory. These questionnaires are self-rating instruments for depression and anxiety, respectively (Thomson, 1989*a*, *b*). In order to assess aggression, carers were asked to fill in the Social Dysfunction and Aggression Scale (SDAS-21), a well-validated and recommended questionnaire (European Rating Aggression Group, 1992; Mak and De Koning, 1995).

Twenty healthy volunteers, matched for age and sex, were scanned and measured twice in order to assess the reliability of the volumetric measurements.

MRI assessment

The 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/TR/TE/flip = 450/15/4.2/20; 124 × 1.5 mm thick contiguous coronal slices; matrix 256 × 192, 24 cm × 18 cm FOV (field of view) (TI = inversion time; TR = repetition time; TE = echo time)]. For computation of T_2 values, conventional spin-echo sequence [TR/TE1/TE2/NEX 2000/30/120/1, 256 × 192 matrix, 24 × 18 cm FOV, 5 mm thick coronal slices with no gap; scan time 10 min (NEX = number of excitations)] 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.

Volumetric measurements

Volumetric measurements were performed using the locally developed interactive software program Mreg (available on the internet: http://www.erg.ion.ucl.ac.uk/MRreg.html) (Lemieux *et al.*, 1998; Moran *et al.*, 1999). The images were zoomed to a magnification of ×4 for outlining of the amygdala, and intensity windowing was monitored consistently. The amygdala were outlined manually following the established protocol described by Watson (Watson *et al.*, 1992). The intracranial volume was measured by manual delineation of the internal face of the cranium at every 10 slices, with a magnification of ×2. The volume of the delineated amygdala in each slice (the in-slice volume) was calculated by multiplying the number of voxels contained within each trace (corrected for magnification) by the voxel volume times 10. The total volume of each amygdala was the sum of all in-slice volumes. The amygdala volumes were corrected for total brain size by division by the intracranial volume (Cendes *et al.*, 1993). The rater (L.T.v.E) was blind

to the subject grouping. Intrarater reliability figures were calculated from repeated measurements of the subset of 20 normal controls.

Amygdala atrophy was defined as a volume <3 SD (standard deviations) below the average amygdala volume of the control group. This criterion was preferred to the less restrictive threshold of 2 SD, more commonly applied to hippocampal measurements (Cook *et al.*, 1992; Van Paesschen *et al.*, 1995) in order to account for the larger variability in the amygdala measurements due to greater difficulty of the measurements.

Amygdala T₂ (AT2) mapping

Pixel-by-pixel T_2 maps were calculated from the images obtained with the spin-echo sequence, using the expression $T_2 = (TE2 - TE1)/[ln (S1/S2)]$, where S1 and S2 are the signal intensities in the early and late echo images, with echo times TE1 and TE2, respectively. This dual-echo technique has been validated including repeated acquisitions of data and measures of intra- and inter-rater and test–retest reliability in hippocampi of controls and patients (Duncan *et al.*, 1996; Woermann *et al.*, 1998). AT2 values were measured by the same observer (F.G.W.) using DispImage image analysis software (Plummer, 1992) by placing the largest possible elliptic region of interest within the amygdala while avoiding anatomical boundaries. The coronal slice for AT2 measurements was defined as the one anterior to the slice in which the hippocampal head was seen last underlying the amygdala. Intra- and inter-rater variability of AT2 measures using this method were assessed by calculation of the limit of agreement and coefficient of repeatability (Bland and Altman, 1986). AT2 signals were defined as pathological if they were >2 SD above the mean of the control population.

Data analysis
Reliability

The intrarater reliability was assessed by three different methods to enable comparison with published figures and to provide conservative figures for further comparisons: (i) the ratio of measured standard deviations to average amygdala volumes; (ii) the coefficient of repeatability, C_r (Bland and Altman, 1986); and (iii) an intraclass correlation coefficient (Streiner and Norman, 1995).

Group comparisons

In order to test our main hypotheses of increased amygdala pathology in aggressive patients, we compared the amygdala volumes and amygdala T_2 relaxation times of patients with temporal lobe epilepsy with and without IED using two-tailed standard *t*-tests. We then compared categorical data such as laterality and nature of EEG abnormality and MRI pathology between the two groups using contingency tables.

In order to examine the influence of the different categories of the tables, we used closed test procedures (Toothaker, 1992; Horn and Vollandt, 1995). Categories of the variables that contribute significantly to the overall significance of the table are flagged in the case of $P < 0.05$ and double flagged in the case of $P < 0.01$ (Tables 2 and 3). We then compared the IQ and psychometric results between the two patient groups using standard two-tailed *t*-tests. We corrected the significance of these findings using the Bonferroni method (Norman and Steiner, 1993), and again flagged the findings in the case of $P < 0.05$ and double flagged in the case of $P < 0.01$ (Table 4). All data were analysed using SPSS for Windows (Release 7.5.1).

Results
Study group structure

Forty-three patients with epilepsy and a history of aggressive behaviour were identified; 25 fulfilled inclusion criteria and 18 were excluded for different reasons (post-surgical $n = 2$; history of mental retardation or IQ < 70 $n = 4$; psychosis $n = 2$; phenomenology of aggression, i.e. history of antisocial personality disorder, $n = 2$; classification of epilepsy $n = 8$). A quantitative MRI scan was obtained from 24 of these patients. One patient could not be scanned as he was using a vagal nerve stimulator.

Thirty-nine patients with temporal lobe epilepsy without a known history of aggressive behaviour were identified and contacted. Twenty-five of these patients were included in the study and 14 were excluded (11 because of a history of temper tantrums and four because of a history of ictal aggression on careful behavioural assessment). Quantitative MRI scans were obtained from 24 patients. One patient did not comply with the MRI procedure due to claustrophobia.

The demographic data of both groups are summarized in Table 1. The two patient groups were matched for age, sex, demographic background, duration of epilepsy and seizure severity.

There was no significant group difference regarding the history of birth complications, febrile convulsions or *status epilepticus*. However, the incidence of encephalitic brain disease (Fisher's exact test: $P = 0.05$) and left handedness (χ^2 test: $P < 0.05$) was significantly increased in aggressive patients (see Table 1).

Reference and reliability data

Amygdala volumes and intracranial volumes were measured in 20 healthy controls using the method described above. The mean right amygdala volume (1906.7 mm³; SD = 172.4 mm³; SE = 38.8) was non-significantly smaller than the mean left amygdala volume (1913.0 mm³; SD = 162 mm³; SE = 36.2). The coefficient of variation expressed as a percentage of the standard deviation of the mean volume was 8.7% which compares well with figures published in the

Table 1 *Descriptive statistics: comparison of demographical and historical data of patients with temporal lobe epilepsy with (AGG) and without (non-AGG) IED*

Variable	AGG	Non-AGG
Age [range] (years)	30.1 [18–49]	33.8 [19–56]
Sex: F/M	8/17	10/15
Work: total out of 25 unemployed	21	15
Living: total out of 25 living independently	14	10
Income: total out of 25 on social support	18	16
Social: total out of 25 living in stable relationship	8	8
Therapy: monotherapy–polytherapy	3–22	3–22
Mean duration of temporal lobe epilepsy [range] (years)	22.4 [5–45]	24.5 [7–46]
Mean seizure frequency [range] (estimated frequency per month)	13.4 [0.5–60]	21 [1.5–190]
Birth complications	9	7
Febrile convulsions	5	9
Status epilepticus	0	2
Left handed	7	1
History of encephalitis	5	0

Table 2 *Laterality of EEG abnormalities*

	AGG	Non-AGG	Group comparison
No abnormality	2	0	
R focal abnormality	2	9	*
L focal abnormality	10	10	
Bilateral focal abnormality	11	5	*

Overall significance: $P = 0.03$; closed test procedure: *$P < 0.05$. R = right; L = left; AGG = aggressive group; non-AGG = non-aggressive group.

literature (Soininen *et al.*, 1994; Kalviainen *et al.*, 1997). The coefficient of repeatability was $C_r = 295.7$ mm^3, i.e. 15% of the overall mean. The intraclass correlation coefficient calculated as described above was 0.7, which again corresponds well to what has been reported in the literature (Öngür *et al.*, 1998).

Intrarater repeatability of AT2 in the control group showed 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 $C_r = 4.7\%$.

EEG abnormalities
As shown in Table 2, there was less right-sided focal EEG abnormality and more bilateral EEG abnormality in the aggressive group compared with non-aggressive patients with temporal lobe epilepsy.

Table 3 *Radiological MRI diagnoses*

	AGG	Non-AGG	Group comparison
No pathology	10	6	
R HS	1	8	**
L HS	4	10	**
Bilateral HS	3	1	
Other left temporal pathology	7	0	**

Overall significance: $P = 0.002$; closed test procedure: * $P < 0.05$, ** $P < 0.01$. Other left temporal pathology: amygdala sclerosis = 1, amygdala glioma = 1, amygdala dysontogenetic neuroepithelial tumour = 1; multiple small temporal infarctions = 2; generalized left temporal atrophy = 2]; HS = hippocampal sclerosis; R = right; L = left; AGG = aggressive group; non-AGG = non-aggressive group.

MRI pathology
Radiological diagnosis
Table 3 summarizes the radiological diagnoses for the two patient groups. Left- as well as right-sided hippocampal sclerosis was significantly less common in patients with temporal lobe epilepsy and IED. Other left temporal pathology, including three patients with amygdala pathology (amygdala sclerosis, amygdala glioma and amygdala dysontogenetic neuroepithelial tumour), two patients with multiple small temporal infarctions and two patients with diffuse left temporal atrophy of unknown origin, was significantly more common in patients with temporal lobe epilepsy plus IED.

AT2 measurements
There was no evidence of an increased AT2 relaxation time in the aggressive group [right side: AGG (aggressive group) = 85.8 ms, SD = 4.74 m; non-AGG = 87.83 ms, SD = 6.83 ms; left side: AGG = 85.88 ms, SD = 5.23 ms; non-AGG = 87.03 ms, SD = 4.31 ms). Using the definition of amygdala T$_2$ pathology as a T$_2$ time > 2 SD above the mean of the control group, there was no significant group difference in amygdala pathology.

Amygdala volumes
A group comparison did not reveal a significant overall difference in amygdala volumes (right side: AGG = 1893 mm^3, SD = 435 mm^3; non-AGG = 1909 mm^3, SD = 231 mm^3; left side: AGG = 1840 mm^3, SD = 398 mm^3; non-AGG = 1868 mm^3, SD = 290 mm^3). However, in the aggressive patients, a subgroup of five patients (20%) showed amygdala atrophy (χ^2: $P = 0.04$). Two patients had left-sided amygdala atrophy, two had bilateral atrophy and the only patient who exhibited right-sided amygdala atrophy was left handed.

Comparing patients with and without amygdala atrophy, there was a highly significant group difference in amygdala

Table 4 *Neuropsychological and psychometric parameters*

Variable	AGG	Non-AGG	Group comparison
Mean FIQ (SD)	80.6 (8.5)	93.0 (13.9)	**
Mean VIQ (SD)	81.0 (8.6)	93.8 (14.1)	**
Mean PIQ (SD)	83.3 (11.8)	94.7 (15.1)	*
Mean BDI (SD)	8.8 (4.8)	4.2 (5.8)	*
Mean State STAI (SD)	44.1 (14.9)	32.1 (10.9)	*
Mean Trait STAI (SD)	50.1 (10.1)	34.7 (11.6)	**
Mean SDAS-9 (SD)	14.9 (7.5)	0.4 (0.7)	**
Mean SDAS-21 (SD)	30.9 (12)	3.1 (4.5)	**

*$P < 0.05$, **$P < 0.01$ after Bonferroni correction;
FIQ = full IQ; VIQ = verbal IQ; PIQ = performance IQ;
BDI = Beck's Depression Inventory; STAI = State Trait Anxiety
Inventory; SDAS = Social Dysfunction and Aggression Scores.

volumes for both sides (right side: atrophy = 1336 mm^3,
SD = 183 mm^3; no atrophy = 1982 mm^3, SD = 281 mm^3;
$P < 0.000$; left side: atrophy = 1285 mm^3, SD = 431 mm^3;
no atrophy = 1935 mm^3, SD = 244 mm^3; $P < 0.000$). Other
than this difference, an increased incidence of encephalitis
(χ^2 test: $P < 0.05$; Fisher's exact test: $P = 0.1$) was the only
clinical feature that distinguished patients with amygdala
atrophy from those with normal amygdala volumes.

Neuropsychological profile

There was a highly significant group difference in IQ figures,
with the verbal IQ, the performance IQ and hence the full
IQ all being lower in the aggressive group (Table 4). The
verbal IQ differed more than the performance IQ.

Psychometric profile

As expected, there was a highly significant group difference
in the Social Dysfunction and Aggression Scores (SDAS 9,
SDAS 21) since this was the criterion for group definition
(Table 4). There was a significant group difference in Beck's
Depression Inventory and the State Trait Anxiety Inventory
scores, with the aggressive group rating much higher in
depression ($P < 0.05$), State ($P < 0.05$) and Trait anxiety
($P < 0.01$).

Discussion

This is the first study investigating a possible link between
amygdala pathology and aggressive behaviour in temporal
lobe epilepsy using quantitative MRI. Before embarking on
the interpretation of our findings, we want to address a
number of methodological issues.

Methodological issues
Reliability of volumetric measurements

The MRI quantification methodology used has been shown
to be sensitive for the detection of mesial temporal sclerosis

including amygdala sclerosis (Van Paesschen *et al.*, 1996),
and our reliability figures are similar to those published
(Soininen *et al.*, 1994; Kalviainen *et al.*, 1997; Öngür
et al., 1998).

Patient selection

All patients suffered from chronic medically intractable
temporal lobe epilepsy and were identified at a tertiary
referral centre. Subjects with a history of major psychiatric
disorder were excluded. The two patient groups were
homogeneous in terms of demographical background and
clinical features relating to the epilepsy.

Behavioural assessment

We included only patients with a clearly defined
psychopathological syndrome according to DSM-IV criteria,
i.e. IED. Patients with other forms of aggressive behaviour
not fulfilling these criteria, such as patients with antisocial
personality disorder, were excluded. Thus our study group is
homogenous in terms of psychopathology.

Neuropsychological assessment

We have excluded patients with a history of mental handicap.
Following neuropsychological assessment, we also excluded
patients with a full IQ outside the normal range, i.e. < 70.
Thus we assert that there was no neuropsychological selection
bias and that the group differences in IQ relate to the
aggressive syndrome of interest.

Assessment of brain pathology

The main inclusion criteria were the clinical diagnoses of
temporal lobe epilepsy and IED without regard to the
underlying brain pathology. Following patient inclusion, we
obtained the MRI and neurophysiological data. Thus, no
selection bias should exist and differences in brain pathology
should be associated with the difference in psychopathology.

Intermittent explosive disorder in temporal lobe epilepsy

A subgroup of 20% of patients with IED suffered from very
severe amygdala atrophy. In this group, the mean amygdala
volumes of both sides were significantly smaller than those
of patients without amygdala atrophy, which is not surprising
since amygdala atrophy was the group-defining variable for
this comparison. However, we did not find increased T$_2$
relaxation times as an indicator of amygdala sclerosis. None
of these patients was diagnosed as suffering from amygdala
sclerosis on visual assessment. A history of encephalitis was
more common in these patients, and one might speculate,
therefore, that an encephalitic brain disease led to this severe

amygdala atrophy. However, we cannot answer the question of whether or not encephalitis renders patients more vulnerable to the development of amygdala atrophy.

Seven of the aggressive patients (28%) suffered from different pathologies affecting the left temporal lobe, including the left amygdala, compared with none in the non-aggressive group. Only one of these seven patients had amygdala atrophy. Thus in a total number of 11 of 25 patients (44%) with temporal lobe epilepsy plus IED, there was evidence of amygdala pathology. Even though the nature of this pathology is diverse, it might well be the reason for unprovoked states of arousal and anger in these patients.

The other clear difference in brain pathology between the two groups is the different prevalence of clear-cut unilateral hippocampal sclerosis. This is the most common cause of temporal lobe epilepsy, and 18 of 25 patients with temporal lobe epilepsy alone but only five of 25 patients with temporal lobe epilepsy plus IED had this condition. Thus we could not confirm the increased incidence of hippocampal sclerosis in patients with temporal lobe epilepsy and aggression reported by Falconer (Falconer, 1973).

Bilateral focal EEG abnormalities were significantly more common in patients with temporal lobe epilepsy and IED. This finding might reflect the less focal and homogeneous brain pathology in this patient group. Right-sided focal EEG abnormalities were significantly less common in the aggressive patients and may indicate a more important role for left structural brain pathology in the subsequent development of IED. IED was strongly associated with a decreased overall IQ and in particular a low verbal IQ, reflecting dominant hemisphere functions. This finding corresponds well not only with previous studies in epilepsy but also with other studies of impulsive aggression (Mungas, 1988; Foster *et al.*, 1993; Barratt *et al.*, 1997; Nelson *et al.*, 1998).

There is controversy regarding the importance of hemispheric specialization for aggressive behaviour (Bear, 1983; Nachson, 1991), with the majority of studies pointing to a more important role for the left hemisphere (Saver *et al.*, 1996). Our MRI and neuropsychological findings (i.e. particularly low verbal IQ) support this assumption. Furthermore, the increased prevalence of left handedness in our aggressive patients may indicate early brain pathology affecting the left hemisphere (i.e. lateralization of dominance to the right hemisphere).

There was a strong link between aggression and high levels of depression and anxiety, confirming reports of such an association in the non-psychiatrically ill population (Bjork *et al.*, 1997). It seems plausible that high levels of anxiety result in states of hyperarousal that might be facilitated by amygdala pathology, as suggested by other authors (Cendes *et al.*, 1994). Regarding the relationship between depression and aggression, there are only a few non-conclusive reports (Braconnier and Jeanneau, 1997). Our findings point to a clear association between depression and IED in temporal lobe epilepsy.

It is interesting to compare our data with those of Herzberg and Fenwick who did not find any specific pattern of brain pathology in a retrospective study of 31 patients with temporal lobe epilepsy with and without aggressive outbursts (Herzberg and Fenwick, 1988). However, they had to rely on CT scans for the assessment of brain pathology. In agreement with our study, they found a lower mean IQ and poorer occupational records in their aggressive patients. They also found a higher prevalence of psychiatric co-morbidity in these patients, a finding on which we cannot comment since we excluded patients with psychiatric disorders other than IED.

While from our study the amygdala emerge as a critical structure for the mediation of aggressive behaviour, the literature suggests that there are clearly other critical structures involved, such as the periaqueductal grey, the hypothalamus or the frontal lobes. In this context, it would be of particular interest to quantify frontal lobe pathology, since from a phenomenological point of view IED includes symptoms of hyperarousal and dyscontrol at the same time, and frontal lobe pathology is known to be associated with dyscontrol symptoms.

Clinical relevance of the findings

First, it is interesting to note, and reassuring for patients with this condition, that hippocampal sclerosis is not associated with the development of IED. Second, while the causal relationship between low IQ, high anxiety and high depression in those patients with temporal lobe epilepsy and IED remains unclear, our findings might indicate a possible therapeutic intervention. For example, the treatment of depression and anxiety might help these patients and their carers to cope more effectively with everyday life and to avoid hyperarousal states leading to aggressive behaviour. Finally, early treatment of possibly reactive psychiatric symptoms such as anxiety or depression in patients with temporal lobe epilepsy may have prophylactic properties for the prevention of aggressive behavioural disorders.

Conclusions

In summary, our results indicate that hippocampal sclerosis and the pathogenic process leading to it do not predispose patients with temporal lobe epilepsy to the development of interictal IED. IED is associated with more distributed and predominantly bilateral or left-sided brain pathology. There was no evidence of amygdala sclerosis in the aggressive group in terms of increased mean T_2 relaxation times. There was a significant subgroup of 20% of patients with temporal lobe epilepsy and aggression, who displayed very severe amygdala atrophy, with volumes < 3 SD below the mean. A history of encephalitis was more common in these patients and might have been the cause for this severe atrophy. Another subgroup of 28% of aggressive patients displayed different left temporal lobe lesions affecting the amygdala or periamygdaloid areas. Dominant hemisphere functions seem

to play a more important role in the genesis of IED, with right-sided EEG and MRI abnormalities being less common in patients with temporal lobe epilepsy and aggression. IED, in patients with temporal lobe epilepsy, is closely linked with a decreased intelligence, in particular verbal intelligence, and increased anxiety and depression. Treatment of anxiety and depression might help patients and carers to cope more effectively with everyday life and, by avoiding hyperarousal states, might help to improve the disturbed behaviour.

Acknowledgements

References

Aggleton JP. The contribution of the amygdala to normal and abnormal emotional states. [Review]. Trends Neurosci 1993; 16: 328–33.

Albert DJ, Walsh ML, Jonik RH. Aggression in humans: what is its biological foundation? [Review]. Neurosci Biobehav Rev 1993; 17: 405–25.

Alheid GF, de Olmos JS, Beltramino CA. Amygdala and extended amygdala. In: Paxinos G, editor.The rat nervous system. 2nd edn. San Diego: Academic Press; 1995. p. 495–578.

Amaral DG, Price JL, Pitkänen A, Carmichael ST. Anatomical organization of the primate amygdaloid complex. In: Aggleton JP, editor. The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley-Liss; 1992. p. 1–66.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders—DSM-IV. 4th ed. Washington (DC): American Psychiatric Association; 1994.

Andy OJ, Jurko MF. Hyperresponsive syndrome. In: Hitchcock E, Laitinen L, Vaernet K, editors. Psychosurgery. Springfield (IL): Charles C. Thomas; 1972. p. 117–26.

Babb TL, Brown WJ. Pathological findings in epilepsy. In: Engel J Jr, editor. Surgical treatment of the epilepsies. New York: Raven Press; 1987; p. 511–40.

Bach-Y-Rita G, Lion JR, Climent CE, Ervin FR. Episodic dyscontrol: a study of 130 violent patients. Am J Psychiatry 1971; 127: 1473–8.

Barratt ES, Stanford MS, Kent TA, Felthous A. Neuropsychological and cognitive psychophysiological substrates of impulsive aggression. Biol Psychiatry 1997; 41: 1045–61.

Bear DM. Hemispheric specialisation and the neurology of emotion. Arch Neurol 1983; 40: 195–202.

Behbehani MM. Functional characteristics of the midbrain periaqueductal gray. Prog Neurobiol 1995; 46: 575–605.

Bjork JM, Dougherty DM, Moeller FG. A positive correlation between self-ratings of depression and laboratory-measured aggression. Psychiatry Res 1997; 69: 33–8.

Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1: 307–10.

Braconnier A, Jeanneau A. Anxiety, aggression, agitation and depression: psychopathologic aspects. [Review]. [French]. Encephale 1997; 23 Spec No. 3: 43–7.

Brandao ML, Cardoso SH, Melo LL, Motta V, Coimbra NC. Neural substrate of defensive behavior in the midbrain tectum. [Review]. Neurosci Biobehav Rev 1994; 18: 339–46.

Cendes F, Andermann F, Gloor P, Evans A, Jones-Gotman M, Watson C, et al. MRI volumetric measurement of amygdala and hippocampus in temporal lobe epilepsy. Neurology 1993; 43: 719–25.

Cendes F, Andermann F, Gloor P, Gambardella A, Lopes-Cendes I, Watson C, et al. Relationship between atrophy of the amygdala and ictal fear in temporal lobe epilepsy. Brain 1994; 117: 739–46.

Chapman WP, Schroeder HR, Geyer G, Brazier MA, Fager C, Poppen JL, et al. Physiological evidence concerning importance of amygdaloid nuclear region in the integration of circulatory function and emotion in man. Science 1954; 120: 949–50.

Charney DS, Deutch A. A functional neuroanatomy of anxiety and fear: implications for the pathophysiology and treatment of anxiety disorders. [Review]. Crit Rev Neurobiol 1996; 10: 419–46.

Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. Brain 1992; 115: 1001–15.

Currie S, Heathfield KW, Henson RA, Scott DF. Clinical course and prognosis of temporal lobe epilepsy: a survey of 666 patients. Brain 1971; 94: 173–90.

Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behav Brain Res 1990; 41: 81–94.

Davis M, Rainnie D, Cassell M. Neurotransmission in the rat amygdala related to fear and anxiety. Trends Neurosci 1994; 17: 208–14.

Dicks P, Myers RE, Kling A. Uncus and amygdala lesions: effects on social behavior in the free-ranging rhesus monkey. Science 1969; 165: 69–71.

Duncan JS, Bartlett P, Barker GJ. Technique for measuring hippocampal T2 relaxation time. AJNR Am J Neuroradiol 1996; 17: 1805–10.

Elliott FA. Neurological findings in adult minimal brain dysfunction and the dyscontrol syndrome. J Nerv Ment Dis 1982; 170: 680–7.

Elliott FA. The episodic dyscontrol syndrome and aggression. [Review]. Neurol Clin 1984; 2: 113–25.

Elliott FA. Violence. The neurologic contribution: an overview. [Review]. Arch Neurol 1992; 49: 595–603.

European Rating Aggression Group. Social dysfunction and aggression scale (SDAS-21) in generalised aggression and in aggressive attacks: a validity and reliability study. Int J Methods Psychiatric Res 1992; 2: 15–29.

Falconer MA. Reversibility by temporal-lobe resection of the behavioral abnormalities of temporal-lobe epilepsy. N Engl J Med 1973; 289: 451–5.

Fenwick PB. Aggression and epilepsy. In: Trimble MR, Bolwig T, editors. Epilepsy and psychiatry. Chichester: John Wiley; 1986. p. 31–60.

Foster HG, Hillbrand M, Silverstein M. Neuropsychological deficit and aggressive behavior: a prospective study. Prog Neuropsychopharmacol Biol Psychiatry 1993; 17: 939–46.

Gallagher M, Chiba AA. The amygdala and emotion. [Review]. Curr Opin Neurobiol 1996; 6: 221–7.

Gastaut H, Morrin G, Lesevre N. Etudes du compartment des epileptiques psychomoteur dans l'interval de leurs crises. Ann Med Psychol 1955; 113: 1–29.

Geschwind N. The clinical setting of aggression in temporal lobe epilepsy. In: Fields WS, Sweet WH, editors. Neural basis of violence and aggression. St. Louis (MO): Warren H. Green; 1975. p. 273–81.

Gloor P, Olivier A, Quesney LF, Andermann F, Horowitz S. The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 1982; 12: 129–44.

Gloor P. Mesial temporal sclerosis: historical background and an overview from a modern perspective. In: Luders HO, editor. Epilepsy surgery. New York: Raven Press; 1991. p. 689–703.

Goldstein M. Brain research and violent behavior: a summary and evaluation of the status of biomedical research on brain and aggressive violent behavior. [Review]. Arch Neurol 1974; 30: 1–35.

Halgren E. Emotional neurophysiology of the amygdala within the context of human cognition. In: Aggleton JP, editor. The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley-Liss; 1992. p. 191–228.

Herzberg JL, Fenwick PB. The aetiology of aggression in temporal-lobe epilepsy. Br J Psychiatry 1988; 153: 50–5.

Horn M; Vollandt R. Multiple Tests und Auswahlverfahren. Stuttgart: Gustav Fischer; 1995.

Hudson LP, Munoz DG, Miller L, McLachlan RS, Girvin JP, Blume WT. Amygdaloid sclerosis in temporal lobe epilepsy. Ann Neurol 1993; 33: 622–31.

Jackson GD, Berkovic SF, Tress BM, Kalnins RM, Fabinyi GC, Bladin PF. Hippocampal sclerosis can be reliably detected by magnetic resonance imaging. Neurology 1990; 40: 1869–75.

Kalviainen R, Salmenpera T, Partanen K, Vainio P, Riekkinen P Sr, Pitkanen A. MRI volumetry and T2 relaxometry of the amygdala in newly diagnosed and chronic temporal lobe epilepsy. Epilepsy Res 1997; 28: 39–50.

Kim JH, Tien RD, Felsberg GJ, Osumi AK, Lee N, Friedman AH. Fast spin-echo MR in hippocampal sclerosis: correlation with pathology and surgery. AJNR Am J Neuroradiol 1995; 16: 627–36.

Kligman D, Goldberg DA. Temporal lobe epilepsy and aggression. J Nerv Ment Dis 1975; 160: 324–41.

Kling AS, Brothers LA. The amygdala and social behavior. In: Aggleton JP, editor. The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley-Liss; 1992. p. 353–77.

LaBar KS, LeDoux JE, Spencer DD, Phelps EA. Impaired fear conditioning following unilateral temporal lobectomy in humans. J Neurosci 1995; 15: 6846–55.

LeDoux JE. Emotions: clues from the brain. [Review]. Annu Rev Psychol 1995; 46: 209–35.

Leicester J. Temper tantrums, epilepsy and episodic dyscontrol. Br J Psychiatry 1982; 141: 262–6.

Lemieux L, Wieshmann UC, Moran NF, Fish DR, Shorvon SD. The detection and significance of subtle changes in mixed-signal brain lesions by serial MRI scan matching and spatial normalization. Med Image Anal 1998; 2: 227–42.

Lishman WA. Organic psychiatry—the psychological consequences of cerebral disorder. 3rd ed. Oxford: Blackwell Science; 1998.

Mak M, De Koning P. Clinical research in aggressive patients: pitfalls in study design and measurement of aggression. [Review]. Prog Neuropsychopharmacol Biol Psychiatry 1995; 19: 993–1017.

Maletzky BM. The episodic dyscontrol syndrome. Dis Nerv Syst 1973; 34: 178–85.

Margerison JH, Corsellis JA. Epilepsy and the temporal lobe: a clinical, electroencephalographic and neuropathological study of the brain in epilepsy, with particular reference to the temporal lobes. Brain 1966; 89: 499–530.

Miller LA, McLachlan RS, Bouwer MS, Hudson LP, Munoz DG. Amygdalar sclerosis: preoperative indicators and outcome after temporal lobectomy. J Neurol Neurosurg Psychiatry 1994; 57: 1099–105.

Miller BL, Darby A, Benson DF, Cummings JL, Miller MH. Aggressive, and socially disruptive and antisocial behaviour associated with fronto-temporal dementia. Br J Psychiatry 1997; 170: 150–4.

Moran NF, Lemieux L, Maudgil DD, Kitchen ND, Fish DR, Shorvon SD. Analysis of temporal lobe resections in MR images. Epilepsia. In press 1999.

Moyer KE. Violence and aggression—a physiological perspective. New York: Paragon House; 1987.

Mungas D. An empirical analysis of specific syndromes of violent behavior. J Nerv Ment Dis 1983; 171: 354–61.

Mungas D. Psychometric correlates of episodic violent behaviour. A multidimensional neuropsychological approach. Br J Psychiatry 1988; 152: 180–7.

Nachson I. Neuropsychology of violent behavior: controversial issues and new developments in the study of hemisphere function. In: Milner JS, editor. Neuropsychology of aggression. Boston: Kluwer Academic; 1991. p. 93–116.

Nelson MD, Saykin AJ, Flashman LA, Riordan HJ. Hippocampal volume reduction in schizophrenia as assessed by magnetic

resonance imaging: a meta-analytic study. Arch Gen Psychiatry 1998; 55: 433–40.

Norman GR; Streiner DL. Biostatistics—the bare essentials. St. Louis: Mosby; 1993.

O'Donoghue MF, Duncan JS, Sander JW. The National Hospital Seizure Severity Scale: a further development of the Chalfont Seizure Severity Scale. Epilepsia 1996; 37: 563–71.

Öngür D, Drevets WC, Price JL. Volumetric studies of the amygdala in mood disorders [abstract]. Neuroimage 1998; 7 (4 Pt 2): S507

Plummer DL. DispImage, a display and analysis tool for medical images. Riv Neuroradiol 1992; 5: 489–95.

Raine A, Stoddard J, Bihrle S, Buchsbaum M. Prefrontal glucose deficits in murderers lacking psychosocial deprivation. Neuropsychiatry Neuropsychol Behav Neurol 1998; 11: 1–7.

Ramamurthi B. Stereotactic operation in behaviour disorders. Amygdalotomy and hypothalamotomy. Acta Neurochir Suppl (Wien) 1988; 44: 152–7.

Ratner RA, Shapiro D. The episodic dyscontrol syndrome and criminal responsibility. Bull Am Acad Psychiatry Law 1979; 7: 422–31.

Rodin EA. Psychomotor epilepsy and aggressive behavior. Arch Gen Psychiatry 1973; 28: 210–3.

Rolls ET. Neurophysiology and functions of the primate amygdala. In: Aggleton JP, editor. The amygdala: neurobiological aspects of emotion, memory, and mental dysfunction. New York: Wiley-Liss; 1992. p. 143–65.

Saver JL, Salloway SP, Devinsky O. Neuropsychiatry of aggression. In: Fogel BS, Schiffer RB, Rao SM, editors. Neuropsychiatry. Baltimore: Williams & Wilkins; 1996. p. 523–48.

Soininen HS, Partanen K, Pitkanen A, Vainio P, Hanninen T, Hallikainen M, et al. Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: correlation to visual and verbal memory. Neurology 1994; 44: 1660–8.

Stone JL, McDaniel KD, Hughes JR, Hermann BP. Episodic dyscontrol disorder and paroxysmal EEG abnormalities: successful treatment with carbamazepine. Biol Psychiatry 1986; 21: 208–12.

Streiner DL, Norman GR. From health measurements scales. A practical guide to their development and use. London: Oxford Medical; 1995.

Swartz MS, Swanson JW, Hiday VA, Borum R, Wagner HR, Burns BJ. Violence and severe mental illness: the effects of substance abuse and nonadherence to medication. Am J Psychiatry 1998; 155: 226–31.

Thomson C. Affective disorders. In: Thomson C, editor. The instruments of psychiatric research. New York: John Wiley; 1989a. p. 34–46.

Thomson C. Anxiety. In: Thomson C, editor. The instruments of psychiatric research. New York: John Wiley; 1989b. p. 47–54.

Toothaker LE. Multiple comparison procedures. Blackwell; 1992.

Treiman DM. Psychobiology of ictal aggression. [Review]. Adv Neurol 1991; 55: 341–56.

Trimble MR. Biological psychiatry. Chichester: John Wiley; 1996.

Trimble MR, Ring HA, Schmitz B. Neuropsychiatric aspects of epilepsy. In: Fogel BS, Schiffer RB, Rao SM, editors. Neuropsychiatry. Baltimore: Williams & Wilkins; 1996. p. 771–803.

Valzelli L. Psychobiology of aggression and violence. New York: Raven Press; 1981.

Van Paesschen W, Sisodiya S, Connelly A, Duncan JS, Free SL, Raymond AA, et al. Quantitative hippocampal MRI and intractable temporal lobe epilepsy. Neurology 1995; 45: 2233–40.

Van Paesschen W, Connelly A, Johnson CL, Duncan JS. The amygdala and intractable temporal lobe epilepsy: a quantitative magnetic resonance imaging study. Neurology 1996; 47: 1021–31.

Vitiello B, Stoff DM. Subtypes of aggression and their relevance to child psychiatry. [Review]. J Am Acad Child Adolesc Psychiatry 1997; 36: 307–15.

Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A, et al. Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 1992; 42: 1743–50.

Wieser HG. Electroclinical features of the psychomotor seizures. Stuttgart: Fisher Butterworths; 1983.

Woermann FG, Barker GJ, Birnie KD, Meencke HJ, Duncan JS. Regional changes in hippocampal T2 relaxation and volume: a quantitative magnetic resonance imaging study of hippocampal sclerosis. J Neurol Neurosurg Psychiatry 1998; 65: 656–64.