Amygdala Enlargement in Dysthymia—A Volumetric Study of Patients with Temporal Lobe Epilepsy

Ludger Tebartz van Elst, Friedrich G. Woermann, Louis Lemieux, and Michael R. Trimble

Background: *Previous studies indicated an important role of the amygdala for emotional information processing. We investigated a possible relationship between amygdala volumes, aggressive behavior, and dysthymia, in patients with temporal lobe epilepsy (TLE).*

Methods: *Patients with TLE with and without aggression or dysthymia and healthy volunteers were assessed using quantitative MRI. Amygdala volumes were measured in a blinded fashion and corrected for total brain volumes.*

Results: *There was a highly significant enlargement of left and right amygdala volumes in patients with dysthymia (right side,* $p < .000$*; left side,* $p = .001$*). We found a significant positive correlation between left amygdala volumes (*$p = .02$*) and a trend towards positive correlation between right amygdala volumes and depression (*$p = .06$*), as measured with the Beck Depression Inventory. Amygdala volumes of females were significantly larger than those of males (left side:* $p = .005$*; right side:* $p = .06$*).*

Conclusions: *This is the second report of a relationship between amygdala volumes and depressed mood, confirming an earlier finding in patients with bipolar disease, and the first study reporting a correlation between amygdala volumes and depression. Increased processing of emotional information might increase amygdala blood flow and subsequently, result in amygdala enlargement.* Biol Psychiatry 1999;46:1614–1623 © *1999 Society of Biological Psychiatry*

Key Words: Amygdala, depression, dysthymia, temporal lobe epilepsy, MRI, volumetry

Introduction

The amygdala form an ovoid shaped conglomerate of subnuclei in the medial temporal lobe of humans and monkeys, which receive extensive input from many different sensory areas. They project, among others, to the hippocampus, hypothalamus, thalamus, and frontal lobe (Amaral et al 1992; Pitkänen et al 1997) thus, influencing neuroendocrine, cognitive, and emotional aspects of biologic information processing. They are known to play an important role in the mediation of affective behavior in primates and humans (Aggleton 1993; Kling and Brothers 1992). Fear conditioning experiments show that intact amygdala are crucial for the acquisition and extinction of conditioned fear responses in animals (Davis 1997; LeDoux 1995). Recent studies implicated a role of these nuclei in complex emotional phenomena like fear, depression, and aggression in humans (Amen et al 1996; Drevets et al 1992; Ho et al 1996; LeDoux 1995; Morris et al 1996, 1998).

From functional imaging studies, there is an increasing body of evidence indicating that emotional information processing, for example the presentation of angry or happy faces, results in activation of the amygdaloid complex (Morris et al 1996, 1998; Schneider et al 1997). In patients with major depression, there is increased metabolism in limbic areas, and an overactivation of the amygdala might be a trait marker of depression (Drevets et al 1992; Ho et al 1996).

Recently, two volumetric studies of the amygdala in patients with affective disorders came to conflicting results. Altshuler et al reported an amygdala enlargement in patients with major depression (Altshuler et al 1998). Sheline et al did not find a difference in the overall amygdala volumes of patients with a history of depression, and reported a reduction of amygdala core volumes in these patients (Sheline et al 1998). Amygdala atrophy as an indicator of amygdala sclerosis has been reported in a subgroup of patients with temporal lobe epilepsy (TLE) (Van Paesschen et al 1996). An association between ictal fear and amygdala atrophy has been demonstrated earlier (Cendes et al 1994).

Finally, there is a well-established association between amygdala function and aggression (Adolphs et al 1998). Kluver and Bucy, in their classical experiments, demonstrated that bilateral amygdalectomy led to complete loss of aggressive behavior of previously aggressive animals (Kluver and Bucy 1939). In humans, it is known from many case reports and some open label studies, that

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destruction of the amygdala results in a clear reduction of aggressive behavior (Balasubramaniam et al 1972; Breggin 1975; Kiloh and Smith 1978; Siegfried and Ben-Shmuel 1972).

These findings are in agreement with the assumption that the amygdala are critical brain structures for the emotional evaluation of specific sensory input on the background of individual experience (Saver et al 1996).

There are but a few methods to assess the functional integrity of the amygdala in vivo in humans, like magnetic resonance imaging (MRI), functional MRI (f-MRI), or positron emission tomography (PET). MRI-based volumetry is one method of quantitative MRI assessment of the amygdala. Amygdala atrophy has been associated with mesial temporal lobe sclerosis in epilepsy (Van Paesschen et al 1996). Varying volumes of brain substructures have been reported in different neuropsychiatric diseases, but the mechanisms leading to the volume change are yet poorly understood (Altshuler et al 1998; Keshavan et al 1994).

Emotional disturbances and psychiatric problems are frequently encountered in patients with temporal lobe epilepsy (Trimble 1988; Trimble et al 1996). Ictal fear; depressed mood; and ictal, postictal, or interictal syndromes of affective aggression can pose a serious problem in the management of these patients (Lishman 1998). An interictal syndrome of episodic affective aggression independent of 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; Elliott 1984; Leicester 1982; Maletzky 1973; Ratner and Shapiro 1979; Stone et al 1986). Episodic dyscontrol is characterized by several discrete episodes of failure to resist aggressive impulses, which result in serious assaultive acts or destruction of property. The behavior is out of proportion to any precipitation psychosocial stressor and is not due to substance abuse; another mental disorder like personality disorder, ADHD, any other first axis disorder; or a general medical condition like head trauma or neurodegenerative diseases. The phenomenological criteria are those of intermittent explosive disorder (IED) according to DSM-IV (American Psychiatric Association 1994; Elliott 1984).

In the background of the information presented, the question arises as to whether pathology of the amygdala might contribute to the emotional disturbances seen in patients with TLE with and without IED. It was the intention of our study to establish whether there might be a relationship between amygdala volumes and interictal intermittent explosive disorder. To obtain homogenous study groups, we excluded patients with any other psychopathology apart from IED and dysthymia according to DSM-IV. We included patients with dysthymia since this condition was very common in our patients with TLE.

Methods and Materials

Patients and Patient Assessment

Approval for this study was obtained from the Ethics Committee of the National Hospital for Neurology and Neurosurgery. Patients with TLE were recruited from a tertiary referral center (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 semiology, EEG, and MRI findings compatible with TLE. Neurologic diagnoses were made by neurologists who were not involved in this study. Patients with TLE with and without a history of IED diagnosed according to DSM-IV criteria were included into the study. Patients with extratemporal or generalized epilepsy were excluded, as were those with a history of mental handicap or psychoses. Patients with TLE plus dysthymia (DSM-IV: 300.4) were included into the study since dysthymia is very common in patients with chronic TLE and depression was one of the affective states of interest. Patients with TLE plus major depressive disorder or bipolar disorders (DSM-IV: 296.xx) were excluded to obtain a more homogeneous study group.

On the basis of the discharge summaries of the center, patients with epilepsy with and without a history of aggression were identified, contacted, and seen by a psychiatrist (LTvE).

A neurologic and psychiatric history and examination were obtained, as well as routine EEG investigations and neuropsychological investigations. Psychiatric diagnosis was made by a psychiatrist on the basis of DSM-IV criteria. Informed consent was obtained from the patients before going ahead with further investigations. All patients were asked to fill out the Beck Depression inventory (BDI-13) and the State Trait Anxiety Inventory (STAI). Both questionnaires are self-rating instruments for depression and anxiety, respectively. They are well validated for the assessment of depression and anxiety (Thomson 1989a; 1989b). Having excluded patients with major affective disorders, we only employed self-rating instruments for depression and anxiety to control our volumetric results for minor affective symptoms. To assess aggression, carers were asked to fill out the Social Dysfunction and Aggression Scale (SDAS-21). This instrument has been developed and validated by the European Rating Aggression Group (European Aggression Rating Group 1992). It includes a subscale for outward aggression (SDAS-9) and is recommended in the literature for the assessment of aggressive behavior (Mak and de Konning 1995).

Imaging and Measurements

The MRI images were obtained at the Chalfont Centre for Epilepsy on a 1.5 T GE Signa Horizon scanner (GE Medical Systems, Milwaukee, USA) using a T1-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). The images were transferred to a Sun workstation via a network (Sun

Microsystems, Mountain View, California, USA). Volumetric measurements were performed using the locally developed interactive software program MReg (Lemieux et al 1998). Using this software, the images were zoomed to a magnification of ×4 for outlining of the amygdala and intensity windowing was set to: level = 80; width = 140. The amygdala were outlined manually using a mouse driven cursor following the established protocol described by Watson et al (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 each structure in each slice (the in-slice volume) was calculated by multiplying the number of voxels contained within each trace by the voxel volume, 0.937 × 0.937 × 1.5 mm^3, and dividing by the magnification factor. The total volume of each structure was the sum of all in-slice volumes. The amygdala volumes were corrected for total brain size by division by the intracranial volume, following Cendes et al (Cendes et al 1993). The images of 48 patients and 20 healthy control subjects were mixed and rated by one blinded scientist (LTvE). Intrarater reliability figures were calculated from repeated measurements of the subset of 20 normal control subjects.

Data Analysis

RELIABILITY. The intrarater reliability was assessed with three different methods to enable comparison with published figures and to provide conservative figures for further comparisons. Apart from giving the ratio of measured standard deviations to average amygdala volumes, we also calculated the coefficient of repeatability, C_r, according to the method suggested by Bland and Altman (Bland and Altman 1986). Furthermore, an intraclass correlation coefficient was calculated as suggested by Streiner and Norman (p 111) (Streiner and Norman 1995).

GROUP COMPARISONS. According to our hypotheses, we performed two major group comparisons. First, we compared the amygdala volumes of patients with TLE plus IED to those of patients with TLE without IED and healthy controls. Then, we compared the amygdala volumes of patients with TLE with dysthymia to those of patients with TLE without dysthymia and healthy controls. These group comparisons were done using factorial ANOVA with the variables aggression (non-IED/IED/CON) and depression (dysthymia/non-dysthymia/control) as main factors. Post hoc pairwise group comparisons were done using Tukey's honestly significant difference procedure (HSD) (Norman and Streiner 1994). We analyzed a possible gender difference in amygdala volumes using an independent sample *t* test including all 68 patients and control subjects and, in a second step, excluding those patients with dysthymia, to analyze a possible gender difference without the intervening variable of depression. We used factorial ANOVA to test if there was a significant interaction between the factors gender, depression, and aggression. Categorical data were compared using Chi-square tests.

CORRELATION ANALYSIS. As mentioned previously, psychopathology was quantified using different questionnaires. Amygdala volumes were analyzed for possible correlations with BDI, STAI, and SDAS scores, using the Pearson correlation analysis. All data were analyzed using SPSS for Windows (release 7.5.1).

Table 1. Illustration of Selection Process of the Study

Patients identified and contacted	Patients included	MRI scans obtained	Diagnosis of dysthymia
43 patients with TLE and aggressive behavior	25 patients with TLE and IED	24 patients with TLE and IED	7 of 25 patients
39 patients with TLE without any history of aggression	25 patients with TLE without IED	24 patients with TLE without IED	5 of 25 patients
20 healthy control subjects	20 healthy control subjects	20 healthy control subjects	None

IED, intermittent explosive disorder; TLE, temporal lobe epilepsy.

Results

Study Group Structure

Table 1 illustrates the selection process in this study. Forty-three patients with epilepsy and a history of aggressive behavior were identified; 25 fulfilled inclusion criteria and 18 were excluded for different reasons (postsurgical $n = 2$, mental retardation $n = 4$, psychosis $n = 2$, phenomenology of aggression $n = 2$, classification of epilepsy $n = 8$). A quantitative MRI scan could be obtained of 24 of these patients. One patient could not be scanned since he was using a vagal nerve stimulator.

Thirty-nine patients with TLE without a known history of aggressive behavior were identified and contacted. Twenty-five of these patients were included into the study and 14 were excluded (11 because of a history of temper tantrums and 3 because of a history of ictal aggression on careful behavioral assessment). Quantitative MRI scans could be obtained from 24 patients. One patient did not comply with the MRI procedure due to claustrophobia.

The demographic data of patient groups with and without IED are summarized in Table 2. The comparison of the clinical data like EEG, MRI and neuropsychological and psychometric results of these two groups have been reported and discussed elsewhere (Tebartz van Elst et al 1998, in press).

Twelve of the 50 patients (24%) included in the study suffered from dysthymia, 7 in the aggressive group and 5 in the nonaggressive group. Since we were not able to obtain a quantitative MRI scan of one of the 7 patients with TLE with IED plus dysthymia (due to a vagal nerve stimulator), a total number of 11 patients with TLE plus dysthymia (6 with and 5 without IED) were compared to

Table 2. Descriptive Statistics: Comparison of Demographic and Clinical Data Between Patients With TLE With (IED) and Without (non-IED) Intermittent Explosive Disorder

Variable (total: $n = 50$ patients)	IED ($n = 25/50$)	Non-IED ($n = 25/50$)	Significance
Age [range] (in years)	30.1 [18–49]	33.8 [19–56]	$p = .18$
Sex: f–m	8–17	10–15	$p = .78$
Duration of TLE [range] (in years)	22.4 [5–45]	24.5 [7–46]	$p = .49$
Frequency habitual seizure (estimated frequency per month) [range]	13.4 [0.5–60]	21 [1.5–90]	$p = .36$
Housing: *n* living independently	14	10	$p = .4$
Income: *n* on social support	18	16	$p = .13$
Social: *n* living in stable relationship	8	8	$p = 1$
Therapy: monotherapy–polytherapy	3–22	3–22	$p = 1$
Left-handed	7	1	$p = .05$
Hippocampal sclerosis	8	19	$p = .01$
Other brain pathology	7	0	$p = .005$
No brain pathology	16	19	$p = .24$
Amygdala atrophy	5	1	$p = .08$

IED, intermittent explosive disorder; TLE, temporal lobe epilepsy.

37 patients with TLE without dysthymia (Table 1). The demographic and clinical data of these two patient groups are summarized in Table 3. Apart from female gender being significantly more common in the dysthymic group (8 of the 12 patients with dysthymia were female: Chi-square = 6,4; $p = .04$), there was no significant difference in the structure of the two subgroups.

Clinically, it was remarkable that, following quantitative assessment, none of the dysthymic patients suffered from amygdala atrophy as compared to 6 of the 37 patients without dysthymia. This finding did not reach statistical significance (Chi-square = 2.039, $p = .153$), and neither did any other of the clinical findings like nature and laterality of EEG or MRI pathology or the neuropsychological results. The 20 healthy volunteers (mean age: 36.5 years; SD = 9.7 years; range: 22 to 58 yrs; 40% female, $n = 8$) were matched for age and gender for both group comparisons. Since they were scanned to obtain reliability and reference figures, they did not fill out any of the psychometric questionnaires.

Reference Data and Intrarater Reliability

For the 20 healthy control subjects, the mean right amygdala volume (1906.7 mm^3; SD 172.4 mm^3; standard error (SE) 38.8; range: 1580.1–2203.0 mm^3) was nonsignificantly smaller than the mean left amygdala volume (1913.0 mm^3; SD 162 mm^3; SE: 36.2; range: 1533.7–2154.9 mm^3). The mean intracranial volume was 1314.5 cm^3 (SD: 114.8 cm^3; range: 1051.5–1487.0 cm^3). For the repeated measurements, the coefficient of variation (standard deviation expressed in percent of the mean volume) was 9.0% for the right amygdala and 8.4% for the left amygdala. These figures compare well to those published in the literature (Kalviainen et al 1997; Soininen et al 1994) (each 8.7%). As required to calculate C_r, the mean of the differences of the two measurements in this study tended towards zero. Ninety percent of the measurements of the right amygdala and 92.5% of the measurements of the left amygdala were found within the mean of all measurements ± 2 SD of the mean difference. The coefficient of repeatability was $C_{rR} = 277.5$ mm^3 for the right amygdala and $C_{rL} = 313.8$ mm^3 for the left amygdala. The intraclass correlation coefficient (ICC) calculated as described was 0.7, which again corresponds well

Table 3. Descriptive Statistics: Comparison of Demographic and Clinical Data Between Patients With (DEP) and Without (non-DEP) Dysthymia

Variable (total: $n = 50$ patients)	DEP ($n = 12/50$)	Non-DEP ($n = 38/50$)	Significance
Age [range] (in years)	30 [18–51]	32 [19–56]	$p = .51$
Sex: f–m	8–4	10–28	$p = .02$
Duration of TLE [range] (in years)	22 [7–45]	24 [5–46]	$p = .56$
Frequency habitual seizure (estimated frequency per month) [range]	12 [2–20]	19 [1–90]	$p = .53$
Housing: *n* patients living independently	7	19	$p = .75$
Income: *n* patients on social support	7	27	$p = .14$
Social: *n* patients living in stable relationship	6	10	$p = .17$
Therapy: monotherapy–polytherapy	1–11	5–33	$p = 1$
Left-handed	2	6	$p = .85$
Hippocampal sclerosis	5	22	$p = .33$
Other brain pathology	2	5	$p = .79$
No brain pathology	5	10	$p = .72$
Amygdala atrophy	0	6	$p = .31$

to what has been reported in the literature (Öngür et al 1998) (ICC = 0.7).

Amygdala Volumes and Intermittent Explosive Disorder

There was no significant difference in amygdala volumes of either side between patients with TLE with (left side: V = 1840 mm^3; right side: V = 1893 mm^3) or without IED (left side: V = 1868 mm^3; right side: V = 1910 mm^3) and normal control subjects (left side: V = 1922 mm^3; right side: V = 1915 mm^3; right side: $F = .088$, $p = .767$; left side: $F = .134$, $p = .716$). The comparison of clinical and electrophysiologic data between these two patient groups are published elsewhere (Tebartz van Elst et al 1998, in press).

Amygdala Volumes and Dysthymia

There was a significant enlargement of amygdala volumes in patients with TLE and dysthymia, as compared to patients with TLE without dysthymia and normal control subjects, for both the right ($F = 14{,}379$, $p < .000$) and the left side ($F = 13{,}361$, $p = .001$) (Table 4). Post hoc group analysis comparing the different subgroups to each other proved that the highly significant difference in overall variance was due to amygdala enlargement in the group with TLE plus dysthymia. The mean volume of the right amygdala of patients with TLE plus dysthymia was 2185 mm^3, as compared to 1817 mm^3 in patients with TLE without dysthymia ($p = .001$) and 1915 mm^3 in normal control subjects ($p = .03$). The mean volume of the left amygdala of patients with TLE plus dysthymia was 2125 mm^3, as compared to 1773 mm^3 in patients with TLE without dysthymia ($p = .002$) and 1922 mm^3 in normal control subjects ($p = .13$).

To test if these significant findings were due to the 6 patients with amygdala atrophy in the patient group with TLE without dysthymia, we repeated this analysis after exclusion of these six patients (Figure 1). There was no major change in the significance of the findings, with both amygdala still being significantly larger in the dysthymic patients as compared to patients without dysthymia (left amygdala: $p = .002$; right amygdala: $p = .004$) and healthy control subjects (left amygdala: $p = .02$; right amygdala: $p = .01$) (Figure 1).

Table 4. Amygdala Volumes in Patients with Temporal Lobe Epilepsy (TLE) with and without Dysthymia and Healthy Control Subjects

	Left amygdala volume	Right amygdala volume
Patients with TLE and dysthymia ($n = 11$)	2125 mm^3 SE: 82.5 mm^3	2185 mm^3 SD: 66.3 mm^3
Patients with TLE and euthymic mood ($n = 37$)	1773 mm^3 SE: 53.3 mm^3	1817 mm^3 SE: 54.5 mm^3
Healthy control subjects ($n = 20$)	1922 mm^3 SE: 40.1 mm^3	1915 mm^3 SE: 42.4 mm^3
Factorial ANOVA	$F = 13, 316$ $p = .001$	$F = 14, 379$ $p < .000$

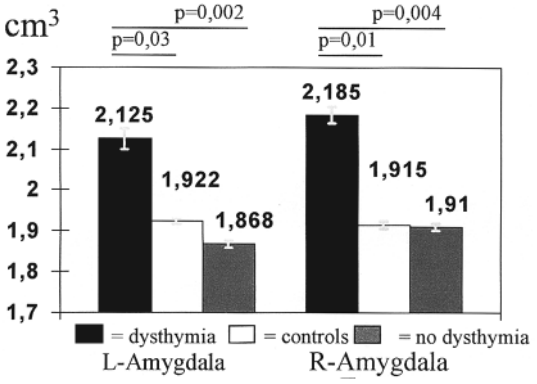

Figure 1. Mean amygdala volumes and 95% confidence intervals in patients with temporal lobe epilepsy with and without dysthymia and healthy controls after exclusion of patients with amygdala atrophy.

To test the influence of IED on the finding of enlarged amygdala in dysthymia, we repeated the analysis after exclusion of those 24 patients with TLE and IED. By reducing the total number of included patients, we obviously reduced the power of this statistical test. But there was still a significant group difference in amygdala volumes between patients with dysthymia and those without (left side: $F = 3{,}235$, $p = .05$; right side: $F = 6{,}371$, $p = .004$).

Amygdala Volumes and Gender

In the total of 68 patients and control subjects measured (Table 1), there was a significant gender difference in amygdala volumes. In the female group ($n = 25$), the mean left amygdala volume was 2006 mm^3, as compared to 1797 mm^3 in the male group ($t = 2.872$, $p = .005$) and the mean right amygdala volume was 1995 mm^3 as compared to 1853 in the male group ($t = 1.87$, $p = .06$). Since dysthymia was more common in female patients, we repeated this analysis after exclusion of all patients with dysthymia. There was still an amygdala enlargement in the female group (left side: 1934 mm^3 versus 1779 mm^3, $t = 2.444$, $p = .01$; right side: 1915 mm^3 versus 1825 mm^3, $t = 1.069$, $p = .3$). To test if there was a significant interaction between the factors gender, dysthymia, and aggression, we repeated the factorial ANOVA described, adding gender as a further factor to the two factors depression and aggression. There was no significant interaction between the three factors on either

side and the significance of the main finding of amygdala enlargement in dysthymia was still present on both sides (right side: $F = 11{,}577$, $p = .001$; left side: $F = 5{,}179$, $p = .02$).

Correlation Analyses

AMYGDALA VOLUMES AND SDAS SCORES. The SDAS-21 and the subscale SDAS-9 for outward aggression were completed for 41 (85%) of the patients with TLE. The mean score of the SDAS-9 was 6.78 (SD 8.8; range: 0–30). The mean score of the SDAS-21 was 15.29 (SD 16.34; range: 0–51). There was no correlation between the different aggression scores and the amygdala volumes of either side.

AMYGDALA VOLUMES AND STAI SCORES. The STAI was completed by 42 patients (87.5%). The mean score of the state anxiety scale was 37.55 (SD: 14.06; range: 20–70). The mean score of the trait anxiety scale was 41.69 (SD: 13.29; range: 20–68). There was no significant correlation between these scores and amygdala volume of either side.

AMYGDALA VOLUMES AND BDI SCORES. The BDI-13 was completed by 43 patients (89.6%). The mean score was 6.33 (SD = 5.78). Data analysis revealed a positive correlation between left amygdala volumes and BDI scores ($r = .346$, $p = .02$). There was also a trend toward positive correlation between the right amygdala volumes and BDI scores ($r = .296$, $p = .06$). To test the influence of IED on this correlation, we repeated the analysis after exclusion of those 25 patients with TLE and IED. In this group, the correlation was even stronger (left: $r = .51$, $p = .01$; right: $r = .412$, $p = .05$). Analysis of the correlation between mean amygdala volumes and BDI scores revealed an even more significant finding in the overall group of 43 patients ($r = .36$, $p = .02$), as well as in the subgroup of patients without IED ($r = .57$, $p = .005$).

Discussion

This is the second report of an association between increased amygdala volumes and depressed mood. Recently, Altshuler et al (Altshuler et al 1998) reported increased amygdala volumes in patients with bipolar disease. In our study, we obtained a similar finding in patients with TLE and dysthymia. Apart from a highly significant group difference, we could also demonstrate a significant positive correlation between amygdala volumes and BDI scores. However Sheline et al did not find any difference in amygdala volumes in patients with a history of recurrent major depression (Sheline et al 1998) and, thus, this finding obviously needs replication. Furthermore, we found larger amygdala in female patients and control subjects, an observation that was more pronounced on the left-hand side.

Before embarking on the interpretation of these interesting findings, we want to make some methodologic considerations.

Study Design

The study was designed to examine a possible association between amygdala volumes and intermittent explosive disorder in patients with TLE. Patients with any other major affective disorder were excluded from the very beginning. Since dysthymia is very common in patients with chronic TLE, we included patients with dysthymia and controlled for minor affective symptoms using the self-rating instruments BDI and STAI. We did not employ a large battery of questionnaires, however, since we did not expect a significant interaction between these factors when we designed the study.

It would have been interesting to assess other brain regions simultaneously, but since amygdala volumetry is very difficult and time consuming and our primary focus of interest was aggression rather than depression, we choose to focus on this important limbic substructure. Other cerebral substructures of particular interest in the context of aggression, like hypothalamic areas or the periaquaeductal gray, are even more difficult to assess and to our knowledge, there are no generally accepted algorithms that allow reliable volumetry of these structures. On the other hand, we are working on methods to assess the frontal lobe volumes in these patient groups to analyze if changes in frontal lobe volumes might be associated with aggressive behavior or not. Finally, it would have been desirable to include a disease control group (i.e., a patient group with dysthymia without TLE). But since we performed our study at a neurologic center for practical reasons, we were not able to assess such patients with the same imaging technology.

Reliability

MRI volumetry of the amygdala is difficult due to the many subjective decisions required when delineating it from its surrounding cortical and white matter structures. Thus, it is important to assess the reliability of the measurements. Unfortunately, in many publications there are no or only very vague reliability figures. Using a very conservative method of assessing reliability, we found that the intra-class correlation coefficient of our measurements was satisfactory. Overall reliability was in general agreement with figures published in some

previous studies (Kalviainen et al 1997; Öngür et al 1998; Soininen et al 1994).

Patient Selection

All patients suffered from chronic and medically intractable TLE and were identified at a tertial referral center for epilepsy. Thus, our patient group is not representative of patients with epilepsy in general. However, the patient group should be representative for patients at similar referral centers for epilepsy. The history of any major psychiatric disorder, including major depression apart from dysthymia, served as exclusion criterion. Thus, the two major subgroups turned out to be very homogenous. Twelve of 50 patients (24%) with TLE suffered from dysthymia according to DSM-IV criteria. This is not surprising, since all patients selected suffered from a chronic and treatment-resistant condition and dysthymia is known to be more common in chronic disorders. Seven of these 12 patients also suffered from IED, and 5 did not suffer from any other psychopathology. Obviously, dysthymia is not more common in patients with IED, which might be surprising since patients with IED often are socially less adjusted because of their aggressive behavior. Comparing aggressive patients with dysthymia to those without, there was no significant difference whatsoever, neither in amygdala volumes nor in clinical, neuropsychological, electrophysiologic or radiologic variables. Thus, dysthymia and IED seem to be independent phenomena in patients with TLE.

Amygdala Volume and IED

Our failure to find an association between aggression and amygdala volume is of relevance on account of the considerable experimental evidence that this structure is involved in aggressive behaviors. One explanation might be that our aggressive group is too heterogeneous in terms of underlying brain pathology, in that atrophy in one subgroup might be compensated for by increased amygdala volumes in another subgroup. Even following exclusion of those patients with amygdala atrophy, we did not find significant group differences in amygdala volumes of either side. It might be that the aggressive syndrome of interest (i.e., intermittent explosive disorder) is a disorder of dyscontrol representing frontal lobe functions, rather than a problem of emotional information processing for which the amygdala are known to be crucial. Furthermore, considerations should be given to the fact that the modulation of behavior is thought to be organized in functional circuitry, rather than in a single critical region (Alexander et al 1990). Thus, pathology in one component of the circuitry might be compensated for by other functional elements, and distant pathology might affect amygdala function without changing its morphology. In this context, it would be of particular interest to simultaneously assess amygdala and frontal lobe parameters since the frontal lobe is most likely involved in controlling affective impulses.

MRI Pathology and Dysthymia

It was noted that on quantitative assessment, amygdala atrophy was present only in patients with TLE without dysthymia. Thus, one might argue that the nondysthymic group of patients had artificially small amygdala, leaving the dysthymic group with enlarged amygdala. Even after exclusion of all patients with amygdala atrophy, however, the finding of amygdala enlargement in dysthymic patients was unchanged (Figure 1). Furthermore, the amygdala volumes of patients without dysthymia were similar to those of 20 healthy control subjects, whereas amygdala volumes of patients with dysthymia were significantly larger.

Correlation Analysis

We found a positive correlation between amygdala volumes and the BDI scores. This finding, obviously, is independent of a possible selection bias in the process of a priori group assignment. Furthermore, exclusion from analysis of those patients with TLE plus IED left this correlation even more significant. These findings indicate that the association between depression and amygdala enlargement is independent of an additional aggressive psychopathology and a gradual, rather than categorical, phenomenon. Since the BDI is an instrument that focuses on the cognitive symptoms of depression, we conclude that there is a gradual correlation between amygdala volumes on the one hand and the processing of negative cognition on the other hand.

Other Studies

As mentioned earlier, Altshuler et al reported an amygdala enlargement in patients with bipolar disorder. Our finding is in agreement with that report even though we investigated patients with epilepsy and dysthymia. One study by Sheline et al reported decreased volumes of the core nuclei of the amygdala in the context of unchanged overall amygdala volumes in patients with a history of recurrent major depression and control subjects. Amygdala volumes were not corrected for total brain volume. From our experience, it is very difficult to delineate amygdala subnuclei from each other. Thus, we are not able to comment on that finding.

Amygdala Volumes and Gender

We were surprised by our finding of amygdala enlargement in female patients and control subjects, particularly on the left hand side. To our knowledge, there are no similar findings reported in the literature and we do not see a plausible explanation for this finding. Further research is needed to replicate this finding, and for the time being, we prefer to just report the observation without speculating about possible explanations.

Etiopathogenetic Implications

The causal relation between amygdala enlargement and dysthymia is open to discussion. It might be that increased processing of negative emotional information in the process of depression subsequently leads to an enlargement of the amygdala. On the other hand, an existing enlargement of the amygdala might render individuals more sensitive to the development of depression. There is no known mechanism leading to varying volumes of brain substructures in humans with changing mental states, however, there are reports of changing volumes of the caudate nuclei in patients with schizophrenia, which seem to be treatment related (Chakos et al 1994; Frazier et al 1996; Keshavan et al 1994). In our study, none of the patients received antidepressive medication, but one might speculate that the antiepileptic medication led to an enlargement of the amygdala. There was no significant difference in antiepileptic medication between patients with dysthymia and those without, with the majority in both groups receiving polytherapy. Our finding corresponds well to functional imaging studies in patients with major depression where Ho et al (Ho et al 1996) reported an increased glucose metabolism in limbic structures including the amygdala; and Drevets et al (Drevets et al 1992) found an increased amygdala blood flow to be a trait marker of depression in patients with pure familial major depression. It may be, therefore, that amygdala enlargement is a consequence of chronically increased amygdala blood flow and associated increase in cell size. Alternatively, one might speculate that increased emotional information processing result in cell proliferation of the amygdaloid complex. Recently, there are several reports on experience dependent cell proliferation of cerebral subregions in rodents as well as primates (Greenough et al 1999; Gould et al 1998, 1999; van Praag et al 1999). It has to be stressed, however, that these interpretations of our findings are very speculative and until now, there are no generally accepted models that explain the mechanisms leading to the widely reported phenomena of varying volumes of cerebral substructures (Altshuler et al 1998; Chakos et al 1995; Keshavan et al 1994, 1998).

Independent of the underlying pathogenesis, amygdala enlargement might turn out to be a trait marker of different depressive subsyndromes. In keeping with that assumption, our findings indicate that in epilepsy, atrophy of the amygdala does not predispose to the development of dysthymia and might, in fact, be protective since none of the patients with dysthymia displayed amygdala atrophy.

In conclusion, we demonstrated an association between amygdala enlargement and depression (i.e., dysthymia) in patients with TLE and a correlation between depressed cognition, as measured with the BDI and amygdala volumes. These findings were very robust in that they were independent of whether or not patients with amygdala atrophy or patients with IED were included into the analysis. Our finding fits well with reports of previous functional imaging studies, which indicate that increased limbic metabolism might be a trait marker of depression, and is in agreement with a similar finding in patients with bipolar disorder.

These findings do have implications for the way we think about the functioning of the brain since they challenge the notion that there is no macroscopic morphologic change as a consequence of altered function in the brain. We speculate that an increased processing of negative emotional information, associated with dysthymia, subsequently results in amygdala enlargement. The mechanism through which this change in volume of the cerebral substructure is realized, however, remains unclear and open to discussion.

Further research is needed to replicate this observation, to establish whether amygdala enlargement might be found in all depressive subsyndromes, and whether it might be reversible after treatment response. A promising approach might be to combine functional and structural imaging to establish whether there is an association between amygdala volumes and functional variables such as amygdala blood flow or glucose metabolism.

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References

Adolphs R, Tranel D, Damasio AR (1998): The human amygdala in social judgment. *Nature* 393:470–474.

Aggleton JP (1993): The contribution of the amygdala to normal and abnormal emotional states. *Trends Neurosci* 16:328–333.

Alexander GE, Crutcher MD, DeLong MR (1990): Basal gan-

glia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog Brain Res* 85:119–146.

Altshuler LL, Bartzokis G, Grieder T, Curran J, Mintz J (1998): Amygdala enlargement in bipolar disorder and hippocampal reduction in schizophrenia: An MRI study demonstrating neuroanatomic specificity. *Arch Gen Psychiatry* 55:663–664.

Amaral DG, Price JL, Pitkänen A, Carmichael ST (1992): 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, Inc., pp 1–66.

Amen DG, Stubblefield M, Carmichael B, Thisted R (1996): Brain SPECT findings and aggressiveness. *Ann Clin Psychiatry* 8:129–137.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association.

Bach-Y-Rita G, Lion JR, Climent CE, Ervin FR (1971): Episodic dyscontrol: A study of 130 violent patients. *Am J Psychiatry* 127:1473–1478.

Balasubramaniam V, Ramanujam PB, Kanaka TS, Ramamurthi B (1972): Stereotaxic surgery for behavior disorders. In: Hitchcock E, Laitinen L, Vaernet K, editors. Psychosurgery. Springfield, Il: Charles C. Thomas, pp 156–163.

Bland JM, Altman DG (1986): Statistical methods for assessing agreement between two methods of clinical measurements. *Lancet* 8:307–312.

Breggin PR (1975): Psychosurgery for the control of violence: a critical review. In: Fields WS, Sweet WH, editors. *Neural Basis of Violence and Aggression.* St. Louis, Missouri: Warren H. Green, Inc., pp 350–378.

Cendes F, Andermann F, Gloor P, Evans A, Jones-Gotman M, Watson C, et al (1993): MRI volumetric measurement of the amygdala and hippocampus in temporal lobe epilepsy. *Neurology* 43:719–725.

Cendes F, Andermann F, Gloor P, Gambardella A, Lopes-Cendes I, Watson C, et al (1994): Relationship between atrophy of the amygdala and ictal fear in temporal lobe epilepsy. *Brain* 117:739–746.

Chakos MH, Lieberman JA, Bilder RM, Borenstein M, Lerner G, Bogerts B, et al (1995): Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *Am J Psychiatry* 151:1430–1436.

Davis MD (1997): Neurobiology of fear responses: The role of the amygdala. *J Neuropsychiatry Clin Neurosci* 9:382–402.

Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME (1992): A functional anatomical study of unipolar depression. *J Neurosci* 12:3628–3641.

Elliott FA (1984): The episodic dyscontrol syndrome and aggression. *Neurol Clin* 2:113–125.

European Aggression Rating Group (1992): Social dysfunction and aggression scale (SDAS-21) in generalised aggression and in aggressive attacks: A validity and reliability study. *Int J Meth Psychiat Res* 2:15–29.

Frazier JA, Giedd JN, Kaysen D, Albus K, Hamburger S, Alaghband-Rad J, et al (1996): Childhood onset schizophrenia: Brain MRI rescan after 2 years of clozapine maintenance treatment. *Am J Psychiatry* 153:564–566.

Gould E, Beylin A, Tanapat E, Reeves A, Shors TJ (1999): Learning enhances adult neurogenesis in hippocampal formation. *Nat Neurosci* 2:260–265.

Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E (1998): Proliferation of granule cell precursors in the dentate gyrus of adult monkeys is diminished by stress. *Proc Natl Acad Sci U S A* 95:3168–3171.

Greenough WT, Cohen NJ, Juraska JM (1999): New neurons in old brains: Learning to survive? *Nat Neurosci* 2:203–204.

Ho AP, Gillin JC, Buchsbaum MS, Wu JC, Abel L, Bunney WE (1996): Brain glucose metabolism during non-rapid eye movement sleep in major depression. *Arch Gen Psychiatry* 53:645–652.

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

Keshavan MS, Bagwell WW, Haas GL, Sweeney JA, Schooler NR, Pettegrew JW (1994): Changes in caudate volume with neuroleptic treatment. *Lancet* 344:1434–1434.

Keshavan MS, Rosenberg D, Sweeney JA, Pettegrew JW (1998): Decreased caudate volume in neuroleptic-naive psychotic patients. *Am J Psychiatry* 155:774–778.

Kiloh LG, Smith JS (1978): The neural basis of aggression and its treatment by psychosurgery. *Aust N Z J Psychiatry* 12:21–28.

Kling AS, Brothers LA (1992): The amygdala and social behavior. In: Aggleton JP, editor. *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction.* New York: Wiley-Liss, Inc., pp 353–377.

Kluver H, Bucy PC (1939): Preliminary analysis of functions of the temporal lobes in monkeys. *Arch Neur Psychiatry* 42: 979–1000.

LeDoux JE (1995): Emotions: Clues from the brain. *Annu Rev Psychol* 46:209–235.

Leicester J (1982): Temper tantrums, epilepsy and episodic dyscontrol. Br J Psychiatry 141:262–266.

Lemieux L, Wieshmann UC, Moran NF, Fish DR, Shorvon SD (1998): The detection and significance of subtle changes in mixed-signal brain lesions by serial MRI scan matching and spatial normalisation. *Med Image Analysis* 2:227–242.

Lishman WA (1998): *Organic Psychiatry—the Psychological Consequences of Cerebral Disorder*, 3rd ed. London: Blackwell Science.

Mak M, de Konning P (1995): Clinical research in aggressive patients: Pitfalls in study design and measurements of aggression. *Prog Neuropsychopharmacol Biol Psychiatry* 19:993–1017.

Maletzky BM (1973): The episodic dyscontrol syndrome. *Dis Nerv Sys* 34:178–185.

Morris JS, Friston KJ, Büchel C, Frith CD, Young AW, Calder AJ, et al (1998): A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain* 121:47–57.

Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, et al (1996): A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* 383:812–815.

Norman GR, Streiner DL (1994): Biostatistics—The Bare Essentials. St. Louis: Mosby.

Öngür D, Drevets WC, Price JL (1998): Volumetric studies of the amygdala in mood disorders. *Neuroimage* 7:507.

Pitkänen A, Savander V, LeDoux JE (1997): Organisation of intraamygdaloid circuitries in the rat: An emerging framework for understanding functions of the amygdala. *Trends Neurosci* 20:517–523.

Ratner RA, Shapiro D (1979): The episodic dyscontrol syndrome and criminal responsibility. *Bull Am Acad Psychiatry Law* 7:422–431.

Saver JL, Salloway SP, Devinsky O, Bear DM (1996): Neuropsychiatry of aggression. In: Fogel BS, Schiffer RB, Rao SM, editors. *Neuropsychiatry.* Baltimore: William & Wilkins, pp 523–548.

Schneider F, Grodd W, Weiss U, Klose U, Mayer KR, Nagele T, et al (1997): Functional MRI reveals left amygdala activation during emotion. *Psychiatry Res* 76:75–82.

Sheline YI, Gado MH, Price JL (1998): Amygdala core nuclei volumes are decreased in recurrent major depression. *Neuroreport* 9:2023–2028.

Siegfried J, Ben-Shmuel A (1972): Neurosurgical treatment of aggressivity: Stereotaxic amygdalotomy versus leukotomy. In: Hitchcock E, Laitinen L, Vaernet K, editors. *Psychosurgery.* Springfield, Il: Charles C. Thomas, pp 214–218.

Soininen HS, Partanen K, Pitkanen A, Vainio P, Haninen T, Hallikainen M, et al (1994): Volumetric MRI analysis of the amygdala and the hippocampus in subjects with age-associated memory impairment: Correlation to visual and verbal memory. *Neurology* 44:1660–1668.

Stone JL, McDaniel KD, Hughes JR, Hermann BP (1986): Episodic dyscontrol disorder and paroxysmal EEG abnormalities: Successful treatment with carbamazepine. *Biol Psychiatry* 21:208–212.

Streiner DL, Norman GR (1995): From Health Measurements Scales. *A Practical Guide to Their Development and Use*, 2nd ed. London: Oxford Medical Publications.

Tebartz van Elst L, Woermann F, Lemieux L, Thompson PJ, Trimble MR (in press): Affective aggression in patients with temporal lobe epilepsy—a quantitative magnetic resonance study of the amygdala. *Brain*.

Tebartz van Elst L, Woermann F, Trimble MR (1998): An MRI study of affective aggression in temporal lobe epilepsy. *Epilepsia* 39:69.

Thomson C (1989a): Affective disorders. In: Thomson C, editor. *The Instruments of Psychiatric Research.* New York: John Wiley and Sons, 34–46.

Thomson C (1989b): Anxiety. In: Thomson C, editor. *The Instruments of Psychiatric Research.* New York: John Wiley and Sons, 47–54.

Trimble MR (1988): Personality disorder and epilepsy. *Acta Neurochir Suppl* (Wien) 44:98–101.

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

van Praag H, Kempermann G, Gage FH (1999): Running increases cell proliferation and neurogenesis in adult mouse dentate gyrus. *Nat Neurosci* 2:266–270.

Van Paesschen W, Connelly A, Johnson CL, Duncan JS (1996): The amygdala and intractable temporal lobe epilepsy: A quantitative magnetic resonance imaging study [published erratum appears in Neurology 1997 Jun;48(6):1751]. *Neurology* 47:1021–1031.

Watson C, Andermann F, Gloor P, Jones-Gotman M, Peters T, Evans A, et al (1992): Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology* 42:1743–1750.