Left-sided EEG focus and positive psychiatric family history are independent risk factors for affective disorders in temporal lobe epilepsy

José Augusto Bragatti a,∗, Carolina Machado Torres a, Juliana Bohn Assmann a, Vivian Fontana a, Clarice Pereira Rigotti a, Maria Paz Loayza Hidalgo b, Márcia Lorena Fagundes Chaves a, Marino Muxfeldt Bianchina

a Division of Neurology, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil
b Division of Psychiatry, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

Received 13 June 2009; received in revised form 27 July 2009; accepted 23 August 2009
Available online 16 September 2009

SUMMARY

Objective: To identify independent risk factors for affective disorders in temporal lobe epilepsy.
Methods: We studied 97 patients with temporal lobe epilepsy (TLE) exploring variables like age, gender, family history of epilepsy and psychiatric disorders, duration of epilepsy, control of seizures, presence of aura and initial precipitant insult, abuse of substances, neuroimaging and EEG features.
Results: Forty-one patients (42.3% of the total population) had affective disorders. A positive family history of psychiatric disorders (O.R. = 3.8; p = 0.003) and interictal EEG epileptiform discharges involving the left temporal lobe (O.R. = 2.9; p = 0.041) were significantly associated with an increased risk for an affective disorder. These associations remained significant after logistic regression, confirming the independent effects of the risk factors observed. Moreover, a binary logistic regression model obtained was able to correctly predict presence or absence of a life-time affective disorder in 71.1% of patients.
Conclusion: This study points out that a positive family history of psychiatric disorders and interictal EEG epileptiform discharges involving the left temporal lobe are isolated risk factors for affective disorders in TLE. Our results suggest that biological factors are crucial for affective disorders development in TLE. Further studies are necessary to better specify the genetic and

© 2009 Elsevier B.V. All rights reserved.

∗ Corresponding author. Tel.: +55 51 3359 8520; fax: +55 51 32224690.
E-mail address: jbragatti@hcpa.ufrgs.br (J.A. Bragatti).

0920-1211/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.eplepsyres.2009.08.010
Introduction

Epilepsy, like all chronic diseases, is associated with several cognitive, behavioral and psychiatric comorbidities (Devinsky, 2003; B.P. Hermann et al., 2008; B. Hermann et al., 2008). There is much evidence that the presence of a psychiatric disorder in epileptic patients exerts a stronger impact over quality of life than other clinical variables, including seizure frequency and severity (Lehrner et al., 1999; Boylan et al., 2004). For this reason, proper diagnosis and treatment of psychiatric comorbidities in epilepsy are essential issues in the modern treatment of epilepsy.

Depression is the most frequent psychiatric disorder in epileptic patients. It is more prevalent in temporal or frontal lobe epilepsies, and in patients with poor seizure control (Edenh and Toone, 1987; Mendez et al., 1993; Jacoby et al., 1996). Patients with active epilepsy have a five-fold higher risk for depression compared with epileptic patients in seizure remission (Tellez-Zenteno et al., 2007). The risk for depression in epilepsy was estimated to be 1.5 times higher in epilepsy than in other chronic diseases, like asthma and diabetes (Ettinger et al., 2004). This evidence supports a role for biological mechanisms that could explain the development of epilepsy and affective disorders in the same patient. Among these mechanisms are possible genetic factors and limbic system dysfunction.

Despite the general consensus that depression is more often observed in epileptic patients than in the general population, studies looking for independent risk factors for such association are still lacking. This is particularly true for patients in the developing world, where about 75% of epileptics are currently living (Sander, 2003) but, paradoxically, studies of this type are scarce. These studies are important for an earlier identification of epileptic patients at risk to develop affective disorders and may also help to clarify the mechanisms involved in the development of psychiatric symptoms in epileptic patients.

Thus, the objective of the present study was to identify independent risk factors for affective disorders in epilepsy. Moreover, we believe that our research has additional importance because we are studying a population living in the developing world, where studies of this type are very necessary.

Methods

Patients

We studied a cohort of 97 consecutive patients (59 women and 39 men) with temporal lobe epilepsy (TLE) selected from the Epilepsy Outpatient Clinic of Hospital de Clínicas de Porto Alegre, a tertiary hospital located in Rio Grande do Sul, the southern region of Brazil. The clinical variables studied were age, gender, family history of epilepsy, family history of psychiatric disorders, duration of epilepsy, control of seizures, presence of aura, history of initial precipitant insult, use of recreational or illicit drugs, neuroimaging abnormalities, and lateralization of seizure focus. Family history was obtained from the patients using a comprehensive check-list that included first-degree relatives (i.e., parent, sibling, offspring) and second-degree relatives (i.e., grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling). Inclusion criteria were patients with semiological and electroencephalographic (EEG) features of TLE (Commission, 1989; Maillard et al., 2004; Pascual, 2007) and compatible neuroimaging. Exclusion criteria were patients with generalized or focal extratemporal epilepsies, mental retardation, systemic diseases, and penetrating head trauma. All patients signed an informed consent term. This study was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre.

EEG and neuroimaging variables

We included patients using the electroclinical international classification of the epilepsies by ILAE (Commission, 1989). Anterior temporal discharges (localized in electrodes F7/F8) were classified as lateralized if they had a predominance of more than 70% over the opposite hemisphere. A 60:40% relation was classified as non-lateralized. Interictal spikes were independently reviewed by two board-certified electroencephalographers (J.A.B. and C.M.T.) that were blind to psychiatric evaluation. Whenever the results were discordant, EEGs were reviewed by the two examiners together to reach a consensus. When available, all MRI exams were reviewed to improve etiological diagnostic.

Psychiatric evaluation

The patients were submitted to a structured clinical interview (SCID; First et al., 2001) divided into six modules, with a search for a life-time diagnosis using the Axis I Diagnostic and Statistical Manual Fourth Edition (DSM-IV; American Psychiatric Association, 2000).

Statistical analysis

Categorical variables were compared by the two-tailed Fisher exact test and numerical variables by the independent Student t-test, with the Levene’s test for equality of analysis of variance. In order to examine the independent effect of each factor on affective disorders we used a binary logistic regression model. To determine the number of independent variables to be included in our logistic regression model we used the parameters suggested by Stevens (1996). Results are reported as odds ratio (95% confidence interval) and were considered significant if p was lower than 0.05. Logistic regression was also used to calculate the predictive value of each independent variable as a predictor of affective disorders in temporal lobe epilepsy by using the
following equation:

\[ \text{Prob (event)} = \frac{1}{1 + e^{-Z}} \]

Prob (event) is the estimated probability of having affective disorder according with risk predictors (Z):

\[ Z = B_0 + (B_1 \times \text{PPFH}) + (B_2 \times \text{LTLS}), \]

where: \( B_0 = 1.0; B_1 = -0.45; B_2 = -0.83. \)

Based on the binary logistic regression results, positive psychiatric family history (PPFH) and left temporal lobe involvement (LTLS) were used as the independent variables (see Table 1). The regression parameters \( B_0, B_1 \) and \( B_2 \) were estimated by logistic regression procedure. All statistical analyses were carried out with the SPSS statistical package for Windows (SPSS Inc., Chicago, IL, USA).

### Results

A total of 97 patients, 58 (60%) women and 39 (40%) men, were studied. Mean age was 43.4 (±12.3) years, mean age at the onset of seizures was 18.3 (±14.3) years, and mean duration of epilepsy was 25.3 (±13.0) years. Demographic data are presented in Table 2.

Fifty-two (53.6%) patients had a life-time Axis I DSM-IV psychiatric disorder. Forty-one (42.3% of the total population, 78.9% of patients with psychiatric disorders) had affective disorders; 20 patients (20.6% of the total, 38.5% of patients with psychiatric disorders) had an anxiety disorder; 6 patients (6.2% of the total, 11.5% of patients with psychiatric disorders) had a psychotic disorder, and 6 patients had alcohol or drug abuse (see Table 3). The most frequent psychiatric comorbidity encountered was an association between affective and anxiety disorders, which was observed in 22 patients (42% of patients with psychiatric disorders).

The association between the variables studied and risk for affective disorders in TLE are shown in Table 4. A positive family history of psychiatric disorders was significantly associated with an increased chance of a life-time history of affective disorder (O.R. = 3.8; CI\(_{95}\% = 1.6–9.1; \ p = 0.003\)). Types of psychiatric family history found are listed in Table 5. Also, patients with interictal EEG epileptiform discharges involving the left temporal lobe presented a significantly higher prevalence of life-time affective disorder (O.R. = 2.9; CI\(_{95}\% = 1.1–7.8; \ p = 0.041\)). These associations remained significant after logistic regression, confirming the independent effects of the risk factors observed.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Crude O.R.</th>
<th>CI(_{95}%)</th>
<th>(p)</th>
<th>Adjusted O.R.</th>
<th>CI(_{95}%)</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive family psychiatric history</td>
<td>3.8</td>
<td>1.6–9.1</td>
<td>0.003</td>
<td>4.0</td>
<td>1.6–9.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Left temporal focus</td>
<td>2.9</td>
<td>1.1–7.8</td>
<td>0.041</td>
<td>3.1</td>
<td>1.1–8.8</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Based on the presence of positive family history of psychiatric disorders and EEG interictal evidence of left hemisphere involvement, the regression model obtained was able to correctly predict the presence or absence of a life-time affective disorder in 71.1% of patients. These results are shown in Fig. 1.
Table 3  Axis I DSM-IV diagnoses of TLE patients.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>Percentage of AD</th>
<th>Percentage of +SCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td>24</td>
<td>58.5</td>
<td>46.1</td>
</tr>
<tr>
<td>Dysthmic disorder</td>
<td>8</td>
<td>19.5</td>
<td>15.4</td>
</tr>
<tr>
<td>Past depressive episode</td>
<td>6</td>
<td>14.6</td>
<td>11.5</td>
</tr>
<tr>
<td>Cyclothymic disorder</td>
<td>1</td>
<td>2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Past manic episode</td>
<td>1</td>
<td>2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>1</td>
<td>2.4</td>
<td>1.9</td>
</tr>
</tbody>
</table>

AD: Affective disorders; +SCID: patients with psychiatric disorders.

Table 4  Risk factors for life-time affective disorders (N=97).

<table>
<thead>
<tr>
<th>Factor</th>
<th>AD+ (n=41) N (%)</th>
<th>AD− (n=56) N (%)</th>
<th>O.R.</th>
<th>CI95%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28 (68.3)</td>
<td>30 (53.6)</td>
<td>0.5</td>
<td>(0.2—1.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Male</td>
<td>13 (31.7)</td>
<td>26 (46.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH of epilepsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (56.1)</td>
<td>22 (39.3)</td>
<td>2.0</td>
<td>(0.9—4.5)</td>
<td>0.15</td>
</tr>
<tr>
<td>No</td>
<td>18 (43.9)</td>
<td>34 (60.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FH of psychiatric disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (56.1)</td>
<td>14 (25)</td>
<td>3.8</td>
<td>(1.6—9.1)</td>
<td>0.003*</td>
</tr>
<tr>
<td>No</td>
<td>18 (43.9)</td>
<td>42 (75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (34.2)</td>
<td>26 (46.4)</td>
<td>1.7</td>
<td>(0.7—3.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>No</td>
<td>27 (65.8)</td>
<td>30 (53.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aura</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (73.2)</td>
<td>34 (60.7)</td>
<td>1.6</td>
<td>(0.6—2.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>No</td>
<td>11 (26.8)</td>
<td>22 (39.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus lateralization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>7 (17.1)</td>
<td>21 (37.5)</td>
<td>2.9</td>
<td>(1.1—7.8)</td>
<td>0.041*</td>
</tr>
<tr>
<td>Left</td>
<td>34 (82.9)</td>
<td>35 (62.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesional</td>
<td>12 (29.3)</td>
<td>16 (28.6)</td>
<td>0.5</td>
<td>(0.2—1.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (14.6)</td>
<td>6 (10.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS depressor drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (39)</td>
<td>4 (7.1)</td>
<td>0.9</td>
<td>(0.4—2.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>25 (61)</td>
<td>52 (92.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (24.4)</td>
<td>14 (25)</td>
<td>0.4</td>
<td>(0.2—1.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>31 (75.6)</td>
<td>42 (75)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AD+: Patients with life-time affective disorder; AD−: without affective disorder; FH: family history; IPI: initial precipitant insult.
* statistically significant data.

Table 5  Types of psychiatric family history found in the population studied. Some patients had more than one relative affected, or one relative affected by more than one disorder.

<table>
<thead>
<tr>
<th>Affective disorders</th>
<th>27a (60%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
<td>22 (48.9%)</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>5 (11.1%)</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>4 (8.9%)</td>
</tr>
</tbody>
</table>

a Major depression: 25; bipolar disorder: 2; 1 suicide and 1 suicide attempt.

Discussion

Our results agree with previous studies showing that affective disorders are the most frequent psychiatric disorders observed in epileptic patients (Kanner, 2005; Schmitz, 2005). The highest prevalence (Ring et al., 1998; Victoroff et al., 1994; Wrench et al., 2004; Grabowska-Grzyb et al., 2006; Briellmann et al., 2007) is observed in patients from tertiary health care centers (40—60%), while a lower prevalence (Altshuler et al., 1990; Mendez et al., 1993; De Boer et al., 2008) is observed in general populations (about 20%).
Left-sided EEG focus and positive psychiatric in temporal lobe epilepsy

The prediction was correct for having affective disorders if the predicted probability (pp) was >0.5. The closer the pp value of each patient approaches the value 1, the higher the estimated probability of having life-time affective disorder in temporal lobe epilepsy (TLE). The prediction was correct for patients that do not develop affective disorders if the pp was ≤0.5. The closer pp value approaches the value 0, the higher the estimated probability of not having life-time affective disorder in TLE. In the figure, ''A'' means absence and ''P'' means presence of life-time affective disorders. Each symbol (A or P) represents 5 patients. Overall the model correctly predicted the life-time probability of having an affective disorder in 71.1% of the patients.

Moreover, in our study a positive family history of psychiatric disorders and EEG interictal activity involving the left temporal lobe were independently associated with affective disorders in TLE. These two independent factors might offer some insight about the possible mechanisms involved in the development of affective disorders in TLE. Finally, in this study we used the two independent risk factors to develop a model that could predict affective disorders in TLE. In our patients this model was effective in correctly predict affective disorders in 71% of the sample.

In our study, patients with a positive family history of psychiatric disorders had a four-fold increased risk for a diagnosis of a life-time affective disorder as also reported in a previous study. Robertson et al. (1987), studying 66 consecutive patients with a combined clinical diagnosis of depression and epilepsy seen over a 2-year period at the Institute of Neurology of London, found a family history of psychiatric illness in 34 of them (52%). Depression was the most common reported condition. Because of this familial association, genetic disorders may be important for the development of affective disorders in epilepsy. We believe that the identification of these genetic factors should be a matter of intense research in the near future.

In our study, patients with interictal EEG epileptiform discharges on the left-side (dominant) hemisphere had a three-fold increased risk for the diagnosis of a life-time affective disorder. Lateralization of the irritative zone as a neurobiological factor involved in the genesis of affective disorders in epilepsy has been studied before, but this issue remains unsolved (Altshuler et al., 1990; Bromfield et al., 1992; Septien et al., 1992; Kanner and Palac, 2000). Bromfield et al. (1992) showed that patients with a left temporal focus had more depressive symptoms. Victoroff et al. (1994) studied 53 candidates for epilepsy surgery and observed that an epileptogenic zone in the left temporal lobe was associated with a higher frequency of depression. Hermann et al. (1991) found a direct association between frontal dysfunction (assessed by the Wisconsin Card Sort Test) and dysphoria severity in patients with a left temporal seizure focus. Although many studies have correlated depressive affect with an epileptogenic zone located in the left hemisphere (Bear and Fedio, 1977; Hurwitz et al., 1985; Robertson et al., 1987; Altshuler et al., 1990; Victoroff et al., 1994; Perini et al., 1996), others have failed to confirm this association (Helmstaedter et al., 2004). Thus, this issue remains unsolved. As Hurwitz et al. hypothesized, the dominant hemisphere could be related to positive emotional states (Hurwitz et al., 1985). Seizure activity in one hemisphere might "release" the opposite side. Alternatively, as stated by Lambert and Robertson, seizure activity in the non-dominant hemisphere could result in neglect of negative emotions (Lambert and Robertson, 1999). Our study is important to clarify this matter because we studied only TLE patients, ensuring the involvement of the limbic system in their epileptic disorder.

Other authors (Kogeorgos et al., 1982; Perini and Mendius, 1984; Robertson, 1985) have reported that gender, seizure frequency, age at the onset of epilepsy, and duration of epilepsy are risk factor for affective disorders in TLE. We, as well as several other authors, were unable to confirm these associations. Thus, these variables remain to be better studied before final conclusions can be made. However, there is strong biological plausibility supporting our positive findings. Common physiopathological mechanisms such as limbic system dysfunction or genetic predispositions present in both disorders seem to be important for the association between TLE and affective disorders (Kanner, 2005, 2008).

Regarding limbic system dysfunction, there are several clinical studies showing common pathogenic mechanisms for both conditions. Among many, there are abnormalities of several neurotransmitter systems, particularly serotonergic, noradrenergic, dopaminergic, GABAergic and glutamatergic (Jobe et al., 1999; Tockez et al., 2003; Hasler et al., 2007; Theodore et al., 2007). Moreover, in both conditions, there are evidence for atrophy of temporal and frontal lobes (Bremner et al., 2002; Sheline et al., 2003; Gilliam et al., 2007), as well as abnormalities in hypothalamic–pituitary–adrenal axis (Holboer, 2001).

More recently, there are compelling evidence for a bidirectional relationship between depression and TLE. Population-based, controlled studies performed over the last decade demonstrated that adult patients with newly diagnosed epilepsy are more likely to have a history of depression than matched controls (Hesdorffer et al., 2000, 2006, 2007). Moreover, as Kanner pointed out in his recent review, a history of depression might have a negative impact on pharmacological and surgical control of seizures in patients with epilepsy (Kanner, 2008). Nevertheless, our results are in line with this bidirectional hypothesis, once
possible genetic predispositions seem to antedate both conditions.

In the present study, about 40% of the patients with a lifetime psychiatric diagnosis had more than one psychiatric disorder, and the most frequent comorbidity was an association between an affective and an anxiety disorder. This not yet clarified association has been known since ancient times (Temkin, 1971). More recently, studies on adults and children with epilepsy showed a high prevalence of these comorbidities in association with epilepsy, with prevalences as high as 70% (Caplan et al., 2005; Jones et al., 2005; Kobau et al., 2006). It is interesting to observe that not only affective disorders and epilepsy are associated each other, but that anxiety is also related to both. In fact, affective disorders, anxiety disorders, and epilepsy seem to share common neurobiological and neuroanatomic mechanisms that only recently started to be better understood.

Limitations of our study exist and we recognize them. One of these limitations concerns the incapacity to diagnose affective disorders not yet defined in the DSM-IV (Krishnamoorthy et al., 2007). There is a consensus that affective disorders have special presentations in epileptic patients compared to the general population. For example, there is an increasing recognition of an association between epilepsy and an affective-somatiform disorder named Interictal Dysphoric Disorder (IDD), characterized by angry and dysphoric affective outbursts associated with less specific affective symptoms such as depression, anergy, pain, insomnia, fear, and anxiety (Blumer et al., 2004). Moreover, due to its cross-sectional design, this study was unable to discriminate psychiatric conditions temporally related to the occurrence of seizures such as peri-ictal or interictal disorders. It is a relatively common observation that affective changes precede the beginning of the epileptic event (Blanchet and Frommer, 1986), and also occur as a post-ictal phenomenon (Taylor and Lochery, 1987). Peri-ictal depression (Barczak et al., 1988; Robertson, 1992) and mania (Barczak et al., 1988; Humphries and Dickinson, 1988) are less frequent situations but are also possible. Additionally, not all patients were submitted to a brain MRI to confirm the diagnosis of TLE and to rule out extratemporal lesions. However, we adopted an electroclinic criterion for classification and included only the patients with epileptiform discharges stringently limited to one or both anterior temporal regions. Indeed, with this procedure we excluded the majority of patients with extrahippocampal temporal lesions, who tend to have more diffuse temporal EEG discharges (Hamer et al., 1999), and patients with the so-called “pseudoepileptiform epilepsy”, who normally show clinical signs of a seizure of extratemporal origin (Andermann, 2003). Finally, in spite of an overall accuracy of 71% of our algorithm in predicting life-time affective disorders, we recognize that it has a limited sensitivity. Thus this algorithm might not be adequate for screening patients in large populations. Nevertheless, it might be a useful tool for referring selected patients earlier to a more careful psychiatric evaluation.

The present study points out genetic and anatomically related substrates as important and independent factors involved with affective disorders in temporal lobe epilepsy, suggesting the direction for future research. Studies assessing the role of different genetic mechanisms and of complex limbic neural networks in the genesis of psychiatric comorbidities in temporal lobe epilepsy seem to be necessary for a better understanding of the association between temporal lobe epilepsy and affective disorders.

Conflict of interest

The authors declare that there are no actual or potential financial and other conflict of interest related to the submitted manuscript.

Acknowledgements

This study was supported by Brazilian governmental funds (MS/CNPq/FAPERGS-06/2006-1528.6 and CNPq 305501/2007-0, 504430/2008-4 and 481222/2008-1).

References


