acquisition, quantification, and analysis were performed by one investigator (KL) and reviewed by an experienced neuroradiologist/spectroscopist (HJC).

**Statistics**

All results were presented as mean ± standard deviation (SD) to define dispersion. Statistical analysis was performed with the following packages SPSS for Windows 10.01 Standard Version (SPSS Inc., Chicago, IL, U.S.A.) Statistica for Windows 4.2 (StatSoft Inc., Tulsa, OK, U.S.A.) and STATA Statistics Data Analysis 5 (Stata Corporation, College Station, TX, U.S.A.). Difference between patients and controls with respect to age was assessed using Student’s t-test. Comparison of age at seizure onset and duration of epilepsy between patients with and without PD was performed with Student’s t-test. The gender distribution, manual dominance, and treatment of epilepsies were examined by the Fisher’s exact test. Association between the number of positive scores in SCID-II and clinical variables were examined by Pearson coefficient of correlation (r). Furthermore, a multiple correlation analysis with stepwise method was performed to evaluate a possible relation between the number of positive scores in SCID-II and values of NAA/Cr and GLX/Cr ratios among JME patients. Group differences for each spectroscopic ratio between JME and healthy controls were compared using one-way analysis of variance (ANOVA) and post hoc analysis with least significant difference (LSD) test (two-tailed). Given that concentrations of measured metabolites vary among different regions (Helms, 1999; Savic et al., 2000) and between different sides assessed by paired ANOVA paired, only values from the same record and from the same side were compared among groups. With the aim of providing a normal distribution of data, we excluded individuals with abnormal regional concentrations of the metabolites from statistical analysis. Abnormality of the regional concentration of a given metabolite in individual patients was defined as a value outside the 2 SD of the mean of normal controls. This procedure, however, did not compromise statistical analysis, once the data loss was <5% of our sample. The results were also corrected for multiple comparisons using a false discovery rate (FDR) analysis [q = 0.15; c(V) = 1]. Once there are no data describing adequate parameters of FDR in spectroscopy, the q value of 0.15 would be reasonable to use in most situations regarding neuroimagi studies according to literature (Genovese et al., 2002).

**Results**

**Demographic and clinical data**

In the JME group, 16 patients fulfilled criteria for only cluster B PDs, whereas 41 did not have any PD. The MRS of these 57 patients and of 30 healthy controls was analyzed. Groups were homogeneous according to age (p = 0.20), gender distribution (p = 0.74), and manual dominance (p = 0.67). Table 1 shows the demographic data for the three groups.

When the clinical variables of the two JME groups were compared, there were no differences in duration of disease, age at epilepsy onset, photosensitivity, and the proportion of patients with adequate treatment, which was defined by the use of therapeutic doses of a first-line drug for generalized epilepsies, in monotherapy or in association, such as valproate (VPA), topiramate (TPM), lamotrigine (LTG), and clonazepam (CNZ). Inadequate treatment was defined by the use of non-recommended drugs for this type of epileptic syndrome, such as pentytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), clobazam (CLB), and phenobarbital (PB). The number and types of seizures, like myoclonia, absences, and GTCS were also compared to investigate seizure control in the two groups. According to seizure control, patients who presented more than four GTCS per year or more than 15 myoclonia or absences, either isolated or in clusters, per month were considered to have inadequate control of seizures (Prasad et al., 2003). The JME group with PD presented significantly more patients with inadequate control of both myoclonic (p = 0.007) and absence (p = 0.04) seizures. There was no difference regarding the control of GTCS between the groups (p = 0.28). There was a positive correlation between the number of positive scores in SCID-II, an indicator of PD severity, and worse control of myoclonia (r = 0.69, p < 0.0001), absences (r = 0.52, p < 0.0001), and GTCS (r = 0.63, p < 0.0001). This was made comparing the number of positive scores and the degree of control of

<p>| Table 1. Demographic data of patients with juvenile myoclonic epilepsy and a control group |
|-----------------------------------------------|------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Demographic data</th>
<th>JME without PDs</th>
<th>JME with PDs</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>41 (47.1)</td>
<td>16 (18.4)</td>
<td>30 (34.5)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>26.1 ± 9.4</td>
<td>28.3 ± 8.2</td>
<td>30.1 ± 9.0</td>
<td>0.201</td>
</tr>
<tr>
<td>Gender (females)</td>
<td>19 (46.3)</td>
<td>9 (56.3)</td>
<td>14 (46.7)</td>
<td>0.748</td>
</tr>
<tr>
<td>Number of right-handed (%)</td>
<td>34 (82.9)</td>
<td>15 (93.8)</td>
<td>28 (93.3)</td>
<td>0.679</td>
</tr>
</tbody>
</table>

Values within parenthesis represent percentages.

JME, juvenile myoclonic epilepsy; PD, personality disorder; SD, standard deviation.
each type of seizure. Table 2 shows the differences in clinical data.

**MRS values**

A synopsis of metabolite concentrations (mean and SD) in different groups and regions is given in Tables 3 and 4, showing the amplitude values of NAA/Cr and GLX/Cr ratios. A general tendency of lower values of NAA/Cr and higher values of GLX/Cr in the group of JME with PDs was observed, mainly in frontal regions. The results were described according to the differences found in regions of interest between JME versus controls and JME with PDs versus JME patients without any psychiatric disorder, as follows:

**JME patients versus controls**

The comparison of NAA/Cr values showed a significant reduction in JME patients when compared with controls in right medial primary motor region (p = 0.01). There was also an increase of GLX/Cr in the JME group when compared with controls in left insula (p = 0.02) and in left striatum (p = 0.03). There were no significant differences between JME patients and controls in other regions.

**JME with PDs versus JME without PDs**

Patients with JME and PDs had significantly lower concentrations of NAA/Cr in the right thalamus (p = 0.03), in the left medial primary motor region (p = 0.003), and in the left parietal region (p = 0.007) when compared with JME patients without PDs. An increase of the GLX/Cr in the right medial primary motor (p = 0.03) and in the left lateral primary motor (p = 0.02) regions in the JME group with PDs was also observed. The same analysis showed an important reduction of NAA/Cr in the right medial supplementary motor region (p = 0.05) in JME with PDs.

A multiple regression analysis with stepwise method was performed to evaluate a possible relation between

<table>
<thead>
<tr>
<th>Areas</th>
<th>Controls (mean ± SD)</th>
<th>JME with PDs (mean ± SD)</th>
<th>JME without PDs (mean ± SD)</th>
<th>p-value</th>
<th>Controls (mean ± SD)</th>
<th>JME with PD (mean ± SD)</th>
<th>JME without PD (mean ± SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>1.6 ± 0.14</td>
<td>1.59 ± 0.20</td>
<td>1.75 ± 0.29</td>
<td>0.031**</td>
<td>1.64 ± 0.19</td>
<td>1.79 ± 0.58</td>
<td>1.97 ± 0.68</td>
<td>0.053</td>
</tr>
<tr>
<td>Striatum</td>
<td>1.38 ± 0.31</td>
<td>1.32 ± 0.15</td>
<td>1.41 ± 0.33</td>
<td>0.659</td>
<td>1.24 ± 0.20</td>
<td>1.36 ± 0.25</td>
<td>1.32 ± 0.21</td>
<td>0.178</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
<td>1.62 ± 0.54</td>
<td>1.66 ± 0.42</td>
<td>1.69 ± 0.49</td>
<td>0.869</td>
<td>1.67 ± 0.58</td>
<td>1.74 ± 0.46</td>
<td>1.57 ± 0.38</td>
<td>0.497</td>
</tr>
<tr>
<td>Insula</td>
<td>1.59 ± 0.20</td>
<td>1.47 ± 0.19</td>
<td>1.58 ± 0.22</td>
<td>0.141</td>
<td>1.33 ± 0.13</td>
<td>1.30 ± 0.24</td>
<td>1.33 ± 0.23</td>
<td>0.873</td>
</tr>
<tr>
<td>Medial primary motor</td>
<td>2.11 ± 0.19</td>
<td>1.91 ± 0.25</td>
<td>1.98 ± 0.22</td>
<td>0.010**</td>
<td>2.07 ± 0.16</td>
<td>1.87 ± 0.19</td>
<td>2.02 ± 0.18</td>
<td>0.003**</td>
</tr>
<tr>
<td>Lateral primary motor</td>
<td>2.17 ± 0.23</td>
<td>1.99 ± 0.24</td>
<td>2.12 ± 0.26</td>
<td>0.073</td>
<td>1.89 ± 0.15</td>
<td>1.78 ± 0.19</td>
<td>1.84 ± 0.21</td>
<td>0.199</td>
</tr>
<tr>
<td>Medial supplementary motor</td>
<td>1.74 ± 0.18</td>
<td>1.81 ± 0.20</td>
<td>1.79 ± 0.21</td>
<td>0.051</td>
<td>1.69 ± 0.14</td>
<td>1.66 ± 0.22</td>
<td>1.75 ± 0.21</td>
<td>0.346</td>
</tr>
<tr>
<td>Lateral supplementary motor</td>
<td>2.00 ± 0.17</td>
<td>1.84 ± 0.29</td>
<td>1.93 ± 0.33</td>
<td>0.199</td>
<td>1.92 ± 0.16</td>
<td>1.81 ± 0.17</td>
<td>1.85 ± 0.28</td>
<td>0.242</td>
</tr>
<tr>
<td>Parietal</td>
<td>1.95 ± 0.26</td>
<td>1.82 ± 0.53</td>
<td>1.96 ± 0.40</td>
<td>0.519</td>
<td>1.95 ± 0.16</td>
<td>1.87 ± 0.29</td>
<td>2.11 ± 0.30</td>
<td>0.007**</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.83 ± 0.41</td>
<td>1.82 ± 0.65</td>
<td>2.14 ± 0.61</td>
<td>0.054</td>
<td>1.80 ± 0.38</td>
<td>1.89 ± 0.56</td>
<td>2.08 ± 0.55</td>
<td>0.094</td>
</tr>
</tbody>
</table>

Cr, creatine; JME, juvenile myoclonic epilepsy; NAA, N-acetyl-aspartate; PD, personality disorder; SD, standard deviation. **Significant; corrected for multiple comparisons using false discovery rate [q = 0.15; c(V) = 1].
positive scores in SCID-II and values of NAA/Cr and GLX/Cr ratios among JME patients. The strongest correlations based on beta % value occurred in left medial primary motor region (r = 0.28, p = 0.03) and right thalamus (r = 0.22, p = 0.08) for NAA/Cr. For GLX/Cr, the strongest correlations occurred in the right medial primary motor (r = 0.35, p = 0.01) and in the left lateral primary motor (r = 0.25, p = 0.08) regions. A synopsis of multiple regression data is given in Table 5.

**DISCUSSION**

The aim of this study was to perform a functional controlled correlation of possible neuronal dysfunctions between a group of patients with JME and cluster B PDs and JME patients without any psychiatric diagnosis treated in a tertiary center through the use of the technique of quantitative multivoxel MRS. We also aimed to find specific network-region associated dysfunction in relation to specific personality traits and to correlate the findings with a number of clinical variables, such as seizure type and frequency, number and types of AED, and duration of epilepsy. To the best of our knowledge this is the first study using a combined analysis of MRS and psychiatric evaluation to investigate such personality traits in JME.

Although it is generally accepted that there is no neuroimaging abnormality in patients with IGE, quantitative MRI studies suggest that subtle structural abnormalities may in fact exist among them (Woermann et al., 1998, 1999; Duncan, 2005; Betting et al., 2006). Proton quantitative MRS is a technique that provides MR signals from a number of cerebral metabolites, such as NAA, GLX, and Cr. Previous studies have suggested that these metabolite signals may be valuable in the assessment of certain brain disorders (Bottomley, 1992; Prichard & Brass, 1992).

NAA is found exclusively in neurons and neuronal processes and is considered an indicator of neuronal function. Its reduction is thought to represent neuronal and axonal loss, injury, or metabolic dysfunction (Duncan, 2005; Betting et al., 2006). Glutamate is another neurotransmitter for which higher levels indicate increased neuronal excitability, whereas Cr is relatively homogeneously distributed throughout the brain and is not significantly influenced by the epileptic state (Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005).

Because metabolites are measured in voxels, units of volume, their increase or reduction could be related to a large variety of confounding factors, such as neuronal shrinkage or increase/decrease in water content (Bernasconi et al.,

<table>
<thead>
<tr>
<th>Table 4. Values of GLX/Cr ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areas</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
</tr>
<tr>
<td>Striatum</td>
</tr>
<tr>
<td>Cingulate gyrus</td>
</tr>
<tr>
<td>Insula</td>
</tr>
<tr>
<td>Medial primary motor</td>
</tr>
<tr>
<td>Lateral primary motor</td>
</tr>
<tr>
<td>Medial supplementary</td>
</tr>
<tr>
<td>Lateral supplementary</td>
</tr>
<tr>
<td>Parietal</td>
</tr>
<tr>
<td>Occipital</td>
</tr>
</tbody>
</table>

Cr, creatine; JME, juvenile myoclonic epilepsy; GLX, glutamate–glutamine; PD, personality disorder; standard deviation. *Significant; corrected for multiple comparisons using false discovery rate [q = 0.15; c(V) = 1].

**Table 5. Correlations between NAA/Cr and GLX/Cr ratios and number of SCID-II scores**

<table>
<thead>
<tr>
<th>Areas</th>
<th>Beta %</th>
<th>Correlation coef.</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left medial primary motor</td>
<td>-0.28</td>
<td>-0.28</td>
<td>0.03*</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>-0.22</td>
<td>-0.22</td>
<td>0.08</td>
</tr>
<tr>
<td>GLX/Cr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right medial primary motor</td>
<td>0.35</td>
<td>0.35</td>
<td>0.01</td>
</tr>
<tr>
<td>Left lateral primary motor</td>
<td>0.25</td>
<td>0.25</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Beta %, regression coefficient percentage; CI, confidence interval; Correlation coef, partial correlation coefficient; Cr, creatine; GLX, glutamate–glutamine; NAA, N-acetyl-aspartate; SCID, Scheduled Clinical Interview for DSM-IV. *Table presents final models obtained from stepwise multiple regressions.

*Significant at p < 0.05.
of frontal lobe injury (Doval et al., 2001; Koepp, 2005). To prevent possible mistakes in their measuring that could lead to incorrect interpretations of the results, we performed an analysis of the NAA/Cr and GLX/Cr ratios, providing more reliability to all the comparisons performed. The method used to calculate the values of metabolites is another matter of controversy, and different studies have discussed what would be the more sensitive and specific to apply (Savic et al., 2000; Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Haki et al., 2007). However, the majority of recent studies in epilepsy have used the amplitude NAA/Cr and GLX/Cr values as a valid method to compare the differences found in their respective analyses (Simister et al., 2003; Haki et al., 2007; Hetherington et al., 2007). Therefore, we preferred to use the same methodology, aiming to unify our results with the current literature, making future comparisons possible.

Different types of anxiety and mood disorders, such as generalized anxiety disorder (GAD), phobias, major depression, dysthymia, and somatization disorders have been described as psychiatric comorbidities in JME (Gelisse et al., 2001; de Araújo Filho et al., 2006; Trínka et al., 2006; de Araújo Filho et al., 2007). We previously found a general prevalence of 49% of PDs among 100 JME patients and also diagnosed in 17% of them mild to moderate cluster B PD, particularly histrionic, borderline, and passive-aggressive, which share most psychopathological characteristics and are clinically described by a marked impulsivity, humor reactivity, emotional instability, unsteadiness, and difficulty in accepting social rules (American Psychiatric Association, 2000; Gelisse et al., 2001; de Araújo Filho et al., 2007).

As mentioned before, the association between JME and some personality traits has already been suggested in the pivotal description of Janz and Christian (1957). These traits were characterized by emotional instability and immaturity, unsteadiness, lack of discipline, hedonism, frequent and rapid mood changes, and indifference toward the disease (Simonsen et al., 1976; Janz, 1985; Janz & Christian, 1994; Trimble, 2000; Trimble et al., 2000; Swinkels et al., 2003). Clinical and electroencephalographic studies have referred to these as “typical” traits and “psychiatric symptoms” (Leder, 1967; Lund et al., 1976; Tsuboi, 1977). Therefore, the description of symptoms and clinical manifestations provided by authors in the past among JME patients could correspond to the cluster B PD cited earlier and described in the DSM-IV-TR (American Psychiatric Association, 2000), since these patients share almost the behavioral characteristics already mentioned for JME.

These manifestations may correspond to frontal lobe impairment, once there have been descriptions of similar behavioral abnormalities in patients with different types of frontal lobe injury (Doval et al., 2001; Koepp, 2005). There is evidence in that literature that such regions involved in those PDs could correspond to the frontal lobes and thalamus, which already have been involved in the pathophysiology of JME (Devinsky et al., 1997; Woermann et al., 1998, 1999; Gelisse et al., 2001; Koepp, 2005; Betting et al., 2006; Pascalicchio et al., 2007). However, we performed a study of other regions over thalamus and frontal lobes aiming to verify possible dysfunctions in cerebral cortex also related to PDs, once JME is generalized epilepsy syndrome and there are no data in literature of MRS findings in PD related to JME.

Studies utilizing the technique of MRS have demonstrated a significant decrease of thalamic and frontal lobe NAA in JME (Savic et al., 2000) and to other types of IGE (Savic et al., 2004) when compared with normal controls. Although the neurochemical abnormality underlying JME is not fully determined, evidence exists to support that a hypersynchrony within the thalamocortical circuitry maintained through γ-aminobutyric acid (GABA) and GLX-mediated mechanisms may play an important role in this epileptic syndrome (Savic et al., 2000; Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005; Haki et al., 2007). Therefore, current evidence of frontal lobe involvement provided by neuroimaging techniques suggests that JME could be a frontal lobe variant of a multiregional, thalamocortical “network” epilepsy, rather than simply a generalized epilepsy syndrome (Duncan, 2005; Koepp, 2005).

The amplitude analysis of the values of metabolite showed significant alterations of the NAA/Cr and GLX/Cr values in JME patients with cluster B PDs, predominantly in the thalamus and frontal lobes. Such differences particularly present on the left side could be explained by differences in gray matter volumes between both cerebral hemispheres. Frontal gray matter volumes have been shown to be higher in the right hemisphere in human brain, which would generally be associated with higher metabolite concentrations. MRI studies have already suggested lower concentrations of all metabolites in the left side when right–left comparisons are made (Amunts et al., 1996; Watkins et al., 2001). Another explanation could be the hemispheric dominance, once manual dominance of almost the totality of patients (85.9%) and controls (93.3%) of this study was located on right side. However, these findings could demonstrate a dysfunction in those cited areas, since NAA reduction may indicate neuronal damage (Savic et al., 2000; Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005; Haki et al., 2007). We also found an increase of GLX/Cr ratio in the same areas that could correspond to increased neuronal excitability and/or increased number of glutamatergic neurons (Duncan, 2005). These findings possibly confirm a more intense thalamic and frontal lobe dysfunction among JME patients with cluster B PDs. In addition, quantitative MRI studies in patients with cluster B PDs without
epilepsy demonstrated significant reductions in frontal lobe structures when compared to normal controls (Lyoo et al., 1998; Raine et al., 2000; Rüscher et al., 2003). Other MRS studies that measured frontal lobe NAA in borderline personality have also described a significant decrease of this metabolite among these patients (Tebartz von Elst et al., 2001). These behavioral characteristics could be, therefore, a consequence of frontal lobe damage, being a constituent of JME or at least be present in more severe forms of this syndrome (Devinsky et al., 1997; Gelisse et al., 2001; Koepp, 2005; de Araújo Filho et al., 2007).

Recent studies have demonstrated that JME patients with PDs have more difficulty in seizure control and worse functional performance when compared to those without these behavioral traits (de Araújo Filho et al., 2007). The importance of seizure control for the mental health of these patients is already defined, and previous studies have associated a higher seizure frequency and the appearance of psychiatric symptoms in generalized epilepsies and consequent worsening in quality of life (Trimble, 2000; Kanner & Weisbrot, 2001; Mula & Trimble, 2003). On the other hand, treatment with VPA for more than 2 years appears to be a protective factor against psychiatric disorders in JME (de Araújo Filho et al., 2007). In the present study, the JME patients with PDs showed worse control of myoclonias and absences in the presence of adequate treatment when compared to those with JME without psychiatric disorders, confirming previous data (de Araújo Filho et al., 2007).

In conclusion, data from MRS might aid support of the hypothesis that PD in JME could represent a more severe form of thalamic and frontal lobe dysfunction as an underlying mechanism of epilepsy generation, consequently producing neuronal damage and PDs (Savic et al., 2000; B�rnasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005; Haki et al., 2007). More studies involving neuroimaging and psychiatric evaluation in JME are, therefore, highly encouraged.

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We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Personality traits related to juvenile myoclonic epilepsy: MRI reveals prefrontal abnormalities through a voxel-based morphometry study

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Psychiatric disorders
Cluster B personality disorders

A B S T R A C T
Studies involving juvenile myoclonic epilepsy (JME) patients have demonstrated an elevated prevalence of cluster B personality disorders (PD) characterized as emotional instability, immaturity, unsteadiness, lack of discipline, and rapid mood changes. We aimed to verify a possible correlation between structural brain abnormalities in magnetic resonance image (MRI) and the PD in JME using voxel-based morphometry (VBM). Sixteen JME patients with cluster B PD, 38 JME patients without psychiatric disorders, and 30 healthy controls were submitted to a psychiatric evaluation through SCID I and II and to a MRI scan. Significant reduction in thalami and increase in mesiofrontal and frontobasal regions’ volumes were observed mainly in JME patients with PD. Structural alterations of the orbitofrontal cortex (OFC), involved in regulation of mood reactivity, impulsivity, and social behavior, were also observed. This study supports the hypothesis of frontobasal involvement in the pathophysiology of cluster B PD related to JME.

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1. Introduction

Juvenile myoclonic epilepsy (JME) is a well-defined type of idiopathic generalized epilepsy (IGE) that comprises 5–11% of patients with epilepsy, characterized by myoclonic jerks, generalized tonic-clonic seizures (GTCS), and typical findings of generalized 4–6 Hz spike and wave or poly-spike and wave discharges in the electroencephalogram (EEG) [1,2]. Studies involving JME patients have highlighted difficulties in their treatment, which have been attributed to some specific psychological and personality traits, described as emotional instability and immaturity, unsteadiness, lack of discipline, hedonism, frequent and rapid mood changes, and indifference toward their disease [3–9]. These observations have been confirmed by studies utilizing modern psychiatric criteria, which have disclosed a high frequency of psychiatric disorders among JME patients, particularly anxiety, mood, and mild to moderate cluster B personality disorders (PD) (histrionic, passive-aggressive, and borderline) [10–13]. They have also shown that patients with these personality characteristics present a worse seizure control and more psychosocial dysfunctions [14].

In the last decades there has been an increased interest in characterizing these manifestations that could correspond to frontal lobe impairment, once these behavioral abnormalities have been described among patients with different types of frontal lobe lesions [15,16].

Neuroimaging studies in JME, such as magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), have suggested the presence of structural and functional brain abnormalities among these patients, particularly in the thalamus and frontal lobes [16–25]. While studies using morphometric MRI techniques have demonstrated reduction of gray matter concentration (GMC) in thalamus [16,17] and increase in mesiofrontal and frontobasal areas [18–20], MRS studies have highlighted the thalamocortical circuitry dysfunctions [21–25]. Neuropsychological evaluation has confirmed these frontal lobe dysfunctions in patients with JME [26,27], which could be related to pathophysiological mechanisms involved in the generation of epileptic activity [21–25].

The voxel-based morphometry (VBM) is an MRI technique that measures brain tissue concentrations and volume and makes inferences about the brain on the basis of differences in tissue classifications [18–20,28]. It is a postprocessing method of morphological images which can provide detailed information relating to changes in gray-white matter composition within the brain, which has been reliably used in psychiatric and neurological studies for many...
years [28]. Based on the previous neuroimaging studies in JME, the VBM was performed aiming to investigate thalamic and frontal lobe gray matter abnormalities related to PD in JME patients. We hypothesized that JME would be associated with smaller thalamus and increased frontobasal and mesiofrontal gray matter and greater alterations in these areas would be observed in JME patients with PD. An exploratory VBM analysis was also performed to investigate possible additional differences in white matter volume (WMV) between controls and JME patients with and without PD.

2. Methods

2.1. Subjects

All patients included in this study were followed up in the outpatient clinic of a tertiary center (Epilepsy Section of the Universidade Federal de São Paulo, São Paulo, Brazil), from July 2005 to July 2007. After the Ethical Committee approval, advantages and risks for participation were explained and informed consent was obtained. The inclusion criteria for the patients' group were the presence of electroclinical diagnosis of JME based on ILAE classification [2] and having been treated in our unit for at least 6 months. JME patients had typical EEG showing generalized 3–6 Hz spike and wave or poly-spike and wave activity maximum in frontocentral regions. We excluded patients with clinical illnesses besides epilepsy. Caffeine or nicotine use on the day of psychiatric interview, differently from that usually taken, were also considered exclusion criteria.

2.2. Psychiatric evaluation

A clinical and socio-demographic questionnaire including age, gender, schooling, duration of epilepsy, neurological and psychiatric family antecedents, previous psychiatric treatment, type and frequency of seizures, occurrence of status epilepticus, and drug treatment was applied before imaging acquisition. The psychiatric evaluation was performed through two structured questionnaires—Schedule Clinical Interview for DSM, axis I and II (SCID I and SCID II, respectively) [29,30]. These are psychiatric scales designed for the evaluation of most psychiatric diseases (e.g., mood, anxiety, and affective disorders) and on DSM-IV, respectively, and have been internationally used to evaluate psychiatric disorders. The axis I refers to the evaluation of most psychiatric diseases (e.g., mood, anxiety, and psychotic disorders), while the axis II refers to the evaluation of all types of PD. Each patient could have had more than one psychiatric diagnosis in each axis (I and II).

2.3. Procedures

The MRIs of 16 patients that fulfilled criteria for the diagnosis of cluster B PD only (histrionic, borderline, and passive-aggressive) were compared to 38 patients without any psychiatric diagnosis. The control group consisted of 30 age- and sex-matched healthy volunteers who were also evaluated by the same psychiatrist (GMAF). None of them presented any seizures, antihistamine administration, or alcohol consumption within 72 hours prior to the psychiatric evaluation.

2.4. MRI data acquisition

The MRI examination of the brain was obtained from all subjects using a 1.5 T Magnetom Sonata [Maestro (class) – Siemens AG, Medical Solutions, Erlangen, Germany] using an eight-channel head coil. To minimize variation, the subjects were positioned by the same investigator using the orbito-meatal line as landmark. Two conventional sequences were performed in order to exclude structural lesions: (a) Axial T2-weighted FLAIR (fluid-attenuated inversion recovery) in a plane parallel to the anterior commissure-posterior commissure (AC-PC) line [TR (repetition time) = 8500 ms, TE (echo time) = 107 ms, IT (inversion time) = 2500 ms, slice thickness = 5.0 mm, slice interval = 1.5 mm, FOV (field of view) = 240 mm, matrix size = 256 × 256, NEX = 1]; (b) Sagittal T1-gradient echo volumetric acquisition for multiplanar reconstruction [TR = 2000 ms, TE = 3.42 ms, flip angle = 15°, FOV = 245 mm, 1.0-mm slice thickness with no gaps, totaling 160 slices per slab, matrix size = 256 × 256, NEX = 1]. All patients and controls had normal images on visual inspection.

2.5. MRI data preprocessing and analysis

The present study employed the VBM5 toolbox (http://dbm.neuro.uni-jena.de/), which utilizes and extends the new unified segmentation approach implemented in SPM 5 (Ashburner and Friston, 2005; Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm), executed in Matlab 7.0. (Mathworks, Sherborn, MA). Unified segmentation provides a generative model of VBM preprocessing that integrates tissue classification, image registration, and MRI inhomogeneity bias correction. The DICOM files (TI images) were converted to NIFTI-1 (http://nifti.nimh.nih.gov) format. The converted files were then segmented into gray and white matter and normalized using the unified model cited above. Voxel values were modulated by the Jacobian determinants derived from the spatial normalization, thus allowing brain structures that had their volumes decreased after spatial normalization to have their total counts decreased by an amount proportional to the degree of volume discounted. The final tissue maps of gray and white matter were modulated with the Jacobian determinants of the deformation parameters obtained by normalization to the Montreal Neurological Institute (MNI) standard space. The final voxel resolution after normalization was 1×1×1 mm. The obtained gray and white matter images were finally smoothed with a Gaussian filter at full width at height maximum equal to 8 and 12 mm, respectively, and entered in statistical analysis. Additionally, intracranial volume was computed from the sum of gray, white, and cerebrospinal fluid volume and entered as a covariate in the statistical analysis.

2.6. Statistics

Clinical and demographic results were presented as mean ± standard deviation (SD) to define dispersion. Statistical analysis was performed with the following packages: SPSS for Windows 10.01 Standard Version, SPSS Inc., Statistica for Windows 4.2, StatSoft Inc., and STATA Statistics Data Analysis 5, Stata Corporation. Difference between patients and controls with respect to age was assessed using Student’s t test. Comparison of age at seizure onset and duration of epilepsy between patients with and without PD was performed with Student’s t test. The gender distribution, manual dominance, and treatment of epilepsies were examined by Fisher’s exact test. Group differences between JME and healthy controls were compared using one-way analysis of variance (ANOVA) and post hoc analysis with LSD test. Association between the number of positive scores in SCID-II and clinical variables were examined by Pearson coefficient of correlation (r). The level of statistical significance was set at P < 0.05.

By employing the general linear model an analysis of covariance (AnCova) was designed in order to investigate focal GM and WM volume differences between the JME with PD and without PD and healthy controls groups. Total brain volume was entered as a covariate. Statistical significance was set at P < 0.001, uncorrected for multiple comparisons. Small-volume correction (SVC) for...
multiple comparisons, using a sphere radius of 3 mm, corresponding to a volume of 100 mm³, was used for regions that had been predicted in advance regions (thalamus, frontobasal, and mesiofrontal regions) and false discovery rate (FDR) correction was used to correct for multiple comparisons in the exploratory gray and white matter analyses. A voxel-level FDR-corrected $P < 0.05$ was used as a criterion for significance.

3. Results

3.1. Demographic and clinical data

In the JME group, 16 patients fulfilled criteria for only cluster B PD, while 38 did not have any psychiatric diagnosis. The MRIs of these 54 patients and of 30 healthy controls were analyzed. Groups were homogeneous according to age ($P = 0.24$), gender ($P = 0.75$), and hand dominance ($P = 0.68$). Table 1 shows the demographic data in the three groups.

Comparing the clinical variables of the two JME groups, there were no differences in duration of the disease, age at epilepsy onset, photosensitivity, and the proportion of patients with adequate treatment. However, the number of positive scores in SCID-II, an indicator of PD severity, was significantly more patients with inadequate control of both myoclonic ($P = 0.007$) and absence ($P = 0.04$) seizures. No differences, however, were observed regarding the control of GTCS between the groups ($P = 0.28$). There was a positive correlation between the number of positive scores in SCID-II, an indicator of PD severity, and an inadequate control of myoclonia ($r = 0.69$, $P < 0.0001$), absences ($r = 0.52$, $P < 0.0001$), and GTCS ($r = 0.63$, $P < 0.0001$). This was made comparing the number of positive scores and the degree of control of each type of seizure. Table 2 shows the differences in clinical data.

3.2. VBM analysis

A synopsis of all regions in which significant differences were found is seen in Tables 3 and 4. The differences were represented by two types of comparisons, which were JME patients versus controls and JME patients with PD versus JME patients without PD, as follows.

3.2.1. JME patients versus controls

There were gray matter volume (GMV) reductions in left ($P = 0.01$) and right ($P < 0.001$) thalamus in JME patients when compared with controls. A significant GMV reduction was also observed in left ($P = 0.006$) and right ($P = 0.006$) insula and in left ($P = 0.006$) and right ($P = 0.006$) cerebellar hemispheres in JME patients. In addition, GMV increases in right superior ($P < 0.001$) and in right medial ($P = 0.001$) frontal gyri were observed in the JME patient group when compared with controls. The exploratory

### Table 1

Demographic data of both juvenile myoclonic epilepsy groups and controls.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>JME without PD</th>
<th>JME with PD</th>
<th>Control</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>38 (45.2%)</td>
<td>16 (19.0%)</td>
<td>30 (35.8%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>27.1 ± 9.5</td>
<td>28.3 ± 8.2</td>
<td>30.1 ± 9.0</td>
<td>0.241</td>
</tr>
<tr>
<td>Gender (females)</td>
<td>18 (47.3%)</td>
<td>9 (56.3%)</td>
<td>14 (46.7%)</td>
<td>0.756</td>
</tr>
<tr>
<td>Number of right-handed (%)</td>
<td>32 (84.2%)</td>
<td>15 (93.8%)</td>
<td>28 (93.3%)</td>
<td>0.685</td>
</tr>
</tbody>
</table>

JME, juvenile myoclonic epilepsy; PD, personality disorder.

### Table 3

Voxel-based morphometry evaluation of gray matter regions; $P$ and $Z$ scores corresponding to significant group effects.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI coordinates</th>
<th>$P_{uncorrected}$</th>
<th>$P_{corrected}$</th>
<th>$Z$ score</th>
<th>Ke</th>
</tr>
</thead>
<tbody>
<tr>
<td>JME patients &lt; controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right insula</td>
<td>42; 9; 6</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td>4.14</td>
<td>981</td>
</tr>
<tr>
<td>Left insula</td>
<td>−39; 21; 9</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td>4.04</td>
<td>476</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>12; 28; 9</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>3.86</td>
<td>61</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>−12; 29; 10</td>
<td>&lt;0.0001</td>
<td>0.001”</td>
<td>3.52</td>
<td>42</td>
</tr>
<tr>
<td>Right cerebellar hemisphere</td>
<td>28; −82; −32</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td>4.35</td>
<td>38209</td>
</tr>
<tr>
<td>Left cerebellar hemisphere</td>
<td>−29; −70; −50</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td>3.95</td>
<td>38209</td>
</tr>
<tr>
<td>JME patients &gt; controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right superior frontal gyrus</td>
<td>21; 62; 15</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
<td>3.86</td>
<td>183</td>
</tr>
<tr>
<td>Right medial frontal gyrus</td>
<td>8; 37; −16</td>
<td>&lt;0.0001</td>
<td>0.001“</td>
<td>3.34</td>
<td>17</td>
</tr>
</tbody>
</table>

JME, juvenile myoclonic epilepsy; PD, personality disorder; $Z$ score, difference in number of standard deviations; Ke, voxel extent threshold.

*pVcorr < 0.05.

*pFDR < 0.05.
white matter analysis showed a significant reduction of left ($P = 0.03$) and right ($P = 0.03$) cerebellar hemispheres in the group of JME patients.

### 3.2.2. JME patients with PD versus JME patients without PD

There was a significant reduction of GMV in right thalamus ($P < 0.001$) when JME patients with PD were compared with JME without PD (Fig. 1). In addition, there were GMV increases in left ($P = 0.002$) and right ($P < 0.001$) middle frontal gyrus in the JME with PD group. There was also a GMV increase in the right orbitofrontal cortex (OFC) of JME patients with PD compared to JME without PD ($P = 0.004$) (Fig. 2). A significant reduction of the posterior corpus callosum (CC) region in the JME with PD group when compared with JME without PD was also observed ($P = 0.04$) in the white matter analysis.

### 4. Discussion

The aim of this study was to perform a controlled investigation of possible structural abnormalities between a group of patients with JME and cluster B PD and JME patients without any psychiatric diagnosis treated in a tertiary center using the VBM approach. The healthy control group from the general population was performed observing specific pairing criteria in order to make all the comparisons reliable. We also aimed to correlate the data to a number of clinical variables, such as seizure type and frequency.
number and types of AED, and duration of epilepsy. To the best of our knowledge this is the first study using a combined analysis of VBM and psychiatric evaluation to investigate personality traits in JME.

Contrary to the concept that there are no neuroimaging abnormalities in IGE patients, investigations using MRI and MRS have demonstrated the presence of structural and functional alterations among JME patients, particularly in thalamus and frontal lobes [18–20,32–34]. Controlled structural MRI studies in JME using the techniques of volumetry and VBM have suggested frontal GMV increase in the superior mesiofrontal and frontotobasal regions, as well as GMV reduction in thalamus [18–20,33,34]. These abnormal regions, as the literature has already emphasized, correspond to the thalamocortical circuitry related to the pathophysiology of JME, which involves the thalamus and the cortical mesiofrontal regions [16]. To support this hypothesis, neuropathological studies involving IGE patients have shown the presence of minimal malformations of cortical development called microdysgenesis, with varying regional distribution in gray and white matter and have attributed its participation in the pathophysiology of this type of epilepsy [35,36]. In the present study we have observed such thalamic and frontal structural alterations in patients with JME when compared with controls. In addition, we also observed more accentuated thalamic and frontal abnormalities in the JME with PD group in comparison to JME patients without PD. Such differences particularly present on the right side could be explained by differences in gray matter volumes between both cerebral hemispheres. Frontal gray matter volumes have been shown to be higher in the right hemisphere in human brain, which would generally be associated with higher metabolite concentrations. Functional MRI studies have already suggested lower concentrations of all metabolites in the left side when right-left comparisons are made [37,38].

Different types of anxiety and mood disorders, like generalized anxiety disorder (GAD), phobias, major depression, dysthymia, and somatization disorders have been described as psychiatric comorbidities in JME [11–14]. We previously found a general prevalence of 49% of PD among 100 JME patients [14], including 17% of mild to moderate cluster B PD (histrionic, borderline, and passive-aggressive), clinically characterized by a marked impulsivity, mood reactivity, emotional instability, and difficulty to accept social rules [14,39]. The association between JME and some personality traits had previously been suggested in the pivotal description of Janz and Christian in 1957 being characterized by emotional instability and immaturity, unsteadiness, lack of discipline, hedonism, frequent and rapid mood changes, and indifference toward the disease [3–9]. Clinical and electroencephalographical studies have referred to these characteristics as “typical” traits and “psychiatric symptoms” [40–42]. Thus, the description of symptoms and clinical manifestations provided by authors in the past in JME [6–9,40–42] could correspond to the cluster B PD described in modern psychiatric nosography [39], since these patients share almost the same behavioral characteristics noted above. These manifestations may possibly be related to some degree of frontal lobe impairment, considering the descriptions of similar behavioral abnormalities in patients with different types of frontal lobe injuries [15,16] and evidence of frontal lobe involvement in the pathophysiology of JME [18–22].

The critical role of frontotobasal structures and prefrontal regions in several psychiatric disorders such as schizophrenia, depression, and cluster B PD is already known [43]. The OFC, an important subdivision of the prefrontal cortex, is connected with structures directly involved in emotional processing, such as the hippocampal formation and amygdala. Functional neuroimaging studies have suggested that OFC is related to the formation of associations between emotions and cognition [43]. This region also plays a critical role in the regulation of mood reactivity and impulsivity, possibly exercising a modulating effect in other frontal regions related to motor functions [43]. Structural MRI studies have already demonstrated abnormalities of OFC volume in patients with cluster B PD, suggesting a possible role of this region, added to other fronto-limbic structures such as cingulum, amygdale, and hippocampus in the pathophysiology of cluster B PD [44–47]. In this study we observed structural abnormalities in OFC in the JME with PD group when compared with JME patients without PD. Psychiatric effects of AEDs are recognized to be of importance in predisposing to or protecting against psychiatric disorders, which may be predictable based on the patient’s preexisting mental status [48]. The mechanisms that are possibly involved in the pathogenesis of these adverse events are pharmacodynamic problems associated with polytherapy, dosage-related toxic effects, dosage- and type-related idiosyncratic effects in predisposed patients, and effects related to efficacy of treatment, like forced normalization and drug withdrawal [48]. While emotional liability, depression, and psychosis have been associated with TPM and PB, few psychiatric side effects have been seen with VPA or LTG in the treatment of patients with epilepsy [3,49,50]. Already known are the positive psychiatric effects of VPA and LTG, which have been successfully used in treating psychiatric syndromes, such as mood and anxiety disorders [3,48–50]. In our study there were no differences in the proportion of patients with adequate AED treatment in both JME groups. We also found no differences regarding the number or type of AED used; however, there was a high number of patients taking VPA in both groups, which made this comparison less reliable.

The GMV in the insula was reduced in JME patients when compared to controls, without any differences when both JME groups were compared. Literature data have already shown the connection of insula to several cortical areas, and a possible insular involvement in focal and generalized epilepsies [51]. Exploratory VBM analysis also showed significant structural alterations of WM in the CC and cerebellum in the group of JME patients. The CC is a major interhemispheric connection pathway and the primary white matter tract in the brain [33]. Reductions in callosal area, an indicator of the degree of white matter lesion and/or the number of crossing axons, could be a structural marker of disruptions in connectivity already impaired among cluster B PD [46,47]. Impaired structural interhemispheric connectivity could possibly lead to poor integration of neural networks that, in turn, is linked to impulsivity and emotional instability [44–47]. Cerebellum involvement in epilepsy has already been emphasized in the literature, since this structure has connections with a large number of afferent and efferent neurological tracts [52,53].

In conclusion, the present study observed GMV alterations in JME patients, particularly in thalami, mesiofrontal, and frontotobasal regions. Such findings, which were more intense in the JME with PD group, are concordant with previous structural and functional JME neuroimaging studies [18–25]. In patients with JME and PD, we also found significant structural abnormalities of the OFC, highlighting the involvement of this structure in the regulation of mood reactivity, impulsivity, and social behavior [43], which has been considered dysfunctional in patients with cluster B PD [44–47]. These data support the hypothesis that those “typical personality traits” found in JME, which correspond to cluster B PD in the modern psychiatric nosography, might represent a more severe form of thalamic and frontal lobe dysfunction as an underlying mechanism of epilepsy generation [16,23–27], consequently producing neuronal dysfunction and PD [14,17,26]. More studies involving neuroimaging and psychiatric evaluation in JME are therefore highly encouraged.

Acknowledgments

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Provocative and inhibitory effects of a video-EEG neuropsychologic protocol in juvenile myoclonic epilepsy

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Department of Neurology and Neurosurgery, Universidade Federal de São Paulo, Escola Paulista de Medicina, São Paulo, Brazil

SUMMARY

Purpose: Studies suggest that higher cognitive functions could precipitate seizures in juvenile myoclonic epilepsy (JME). The present study aimed to analyze the effects of higher mental activity on epileptiform discharges and seizures in patients with JME and compare them to those of habitual methods of activation.

Methods: Seventy-six patients with JME (41 female) underwent a video-EEG (electroencephalography) neuropsychologic protocol (VNPP) and habitual methods of activation for 4–6 h.

Results: Twenty-nine of the 76 (38.2%) presented provocative effect, and inhibition was seen in 28 of 31 (90.3%). A mixed effect was observed in 11 (35.5%), and 30 patients (39.5%) suffered no effect of VNPP. Action-programming tasks were more effective than thinking in provoking epileptiform discharges (23.7% and 11.0% of patients, respectively, p = 0.03). Inhibitory effect was observed equally in the various categories of tasks, except in mental calculation, which had a higher inhibitory rate. Habitual methods of activation were more effective than VNPP in provoking discharges. Anxiety disorders were diagnosed in 24 of 58 patients (41.4%); anxious patients had greater discharge indexes and no significant inhibitory effect on VNPP.

Discussion: Praxis exerted the most remarkable provocative effect, in accordance with the motor circuitry hyperexcitability hypothesis in JME. Inhibitory effect, which had no such task specificity, might be mediated by a widespread cortical–thalamic pathway, possibly involving the parietal cortex. The frequent inhibitory effect found under cortical activation conditions, influenced by the presence of anxiety, supports nonpharmacologic therapeutic interventions in JME.

KEY WORDS: Idiopathic generalized epilepsy, Reflex epilepsy, Precipitant factors, Activation methods.

Juvenile myoclonic epilepsy (JME) is the most common age-related idiopathic generalized epilepsy (IGE), corresponding to 5–11% of all epilepsies (Panayiotopoulos et al., 1991). It is characterized by myoclonic jerks, generalized tonic–clonic seizures (GTCS), and absences (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Bilateral spike or polyspike-wave complexes of 4–6 Hz, more often asymmetric, on a normal background, are the typical electroencephalography (EEG) findings (Panayiotopoulos et al., 1991).

Patients with JME frequently recognize that sleep deprivation, fatigue, alcohol intake, stress, and flashing lights may act as precipitant factors for their seizures (Clement & Wallace, 1988; Panayiotopoulos et al., 1991; Oguni et al., 1994; Pedersen & Petersen, 1998; Waltz, 2000; Da Silva Sousa et al., 2005a). Beyond these general factors, some patients report other precipitant factors: being sensitive to situations in which they are obliged to consider complicated spatial tasks in a sequential fashion, specifically with the intention of decision making; and responding practically by using a part of their bodies under stressful circumstances. These were conceptualized as
praxis induction (Inoue et al., 1994) and include ideation and execution of elaborated movements involving a sequential spatial process such as arithmetic, playing cards and sequential games, drawing, writing, and finger manipulation in more elaborated tasks or those of constructive character. In addition, reflex seizures have been identified during reading and speaking as perioral myoclonia, especially in patients with JME (Mayer et al., 2006).

Neuropsychological methods of EEG activation have been used by groups from Japan (Matsuoka et al., 2000), Germany (Mayer et al., 2006), Italy (Chifari et al., 2004), and Greece (Karachristianou et al., 2004) as an auxiliary method to identify specific seizure patterns in various epileptic syndromes. Some studies suggest that JME would be the most sensitive epileptic syndrome to this form of cognitive activation (Matsuoka et al., 1988, 2000; Senanayake, 1992; Chifari et al., 2004; Karachristianou et al., 2004; Da Silva Sousa et al., 2005b; Mayer et al., 2006).

The aim of this study was to assess the effect of a video-EEG neuropsychological protocol (VNPP), whether precipitant or inhibitory, on epileptiform discharges and seizures in patients with JME, and to compare the effect of this protocol with those of habitual methods of activation.

## Methods

Seventy-six patients (41 female) with JME underwent VNPP at the Epilepsy Unit of the Hospital São Paulo, Universidade Federal de São Paulo, São Paulo, Brazil. After ethical committee approval, advantages and risks for participation were explained and written informed consent was obtained. Inclusion criteria were age over 12 years, clinical and electroencephalographic features of JME, and a minimum of 4 years of formal education. Clinical signs of antiepileptic drug (AED) intoxication, occurrence of a GTCS, and use of intravenous AED within the last 72 h were exclusion criteria.

Fifty-eight of the 76 patients were submitted to psychiatric evaluation. To assess patients older than 18 years, Schedule Clinical Interview for DSM-IV, Axes I and II (SCID-I and SCID-II) were performed, and the Brazilian version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS-PL) was used to assess those 18 years old or younger. Because of its high prevalence and the potential role of stress as a trigger of seizures in JME, only anxiety disorders were investigated, and patients were divided into anxious and nonanxious groups. This division was based upon current anxiety disorders, as opposed to lifetime history of anxiety disorders. All patients presented normal physical and neurologic examinations, as well as normal routine blood tests. Forty patients had a 1.5T magnetic resonance imaging (MRI) of the brain, and all had normal results.

Video-EEG was recorded on a 32-channel digital equipment (Ceegraph software, Bio-Logic Systems Corp., Mundelein, IL, U.S.A.) using the 10–20 International Electrode System, in addition to perioral and deltoid electrodes.

Our protocol was based on those reported by Matsuoka et al. (2000) and Mayer and Wolf (2004) and will be referred to as VNPP. After having slept for at least 6 h, all patients were submitted to 30-min awake video-EEG recording starting at 7 a.m. Medications were maintained in all treated patients. Sixty-seven were treated with AED at the time of the examination and nine were not. Among the treated patients, therapeutic scheme was considered appropriate in 49 (73.1%) and inappropriate in 18 (26.9%). As appropriate treatment we included valproate, phenobarbital, benzodiazepines, lamotrigine, and topiramate, in monotherapy or in different combinations. Treatment with carbamazepine, oxcarbazepine, or phenytoin was considered inappropriate.

The VNPP and habitual methods of activation were performed as described in Table 1 and lasted 4–6 h. Video-EEG was registered during lunchtime and postprandial sleep. Upon awakening, patients were submitted to 5-min hyperventilation (HV) and intermittent photic stimulation (IPS).

<table>
<thead>
<tr>
<th>Table 1. Video-EEG protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recording of background activity, awake, for 30 min</td>
</tr>
<tr>
<td>Eyes opened/closed (5 min)</td>
</tr>
<tr>
<td>Reading a Portuguese text (patients read the same sentences aloud that they had read silently); this was a medical text describing seizures</td>
</tr>
<tr>
<td>10 min silently</td>
</tr>
<tr>
<td>10 min aloud</td>
</tr>
<tr>
<td>Writing for 5 min (patients were asked to write about their seizures)</td>
</tr>
<tr>
<td>Mental calculation: subjects responded aloud with answers to four arithmetic problems (18 – 7, 23 + 46, 11 × 11, 125 + 5); when calculation was difficult, an easier problem was presented</td>
</tr>
<tr>
<td>Written calculation: patients responded in writing to one arithmetic problem (15 × 67 × 23 × 48)</td>
</tr>
<tr>
<td>Drawing: patients were instructed to draw a family, a house, and a clock showing quarter to four</td>
</tr>
<tr>
<td>Spatial construction: Patients performed a sequence of tasks, for 10 min each: Rubik’s cube, Jenga tower, Conundrum’s cube, Pyramid puzzle, Hanoi tower</td>
</tr>
<tr>
<td>For 5 min they reproduced a figure with matchstick pattern and for 1 min, plastic models</td>
</tr>
<tr>
<td>Photic stimulation for 5 min (flashes 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 33, 50, and recovered)</td>
</tr>
<tr>
<td>Hyperventilation for 5 min</td>
</tr>
</tbody>
</table>

When a task induced epileptiform discharges or seizures, reproducibility was confirmed by retrial of the same or a modified task. According to the effect of induction or inhibition of discharges, four groups were identified: (1) provocative effect, when there was induction of
discharges; (2) inhibitory effect, when there was reduction; (3) mixed effect, when there was provocative effect in a determined category of task and inhibitory effect in another; and (4) no effect.

The same criteria defined by Matsuoka et al. (2000) were used in the EEG analysis: When no discharge was found on the awake EEG, “a provocative effect” meant that one or more tasks induced paroxysmal discharges and its reproducibility was confirmed by retrial. No discharges either in the awake or in the task EEG was judged as “no effect.” When epileptiform discharges were found on the awake EEG, the discharge index was calculated for each task as follows: The number of discharges per recording time (number/minute) during each task condition was divided by the frequency (number/minute) during awake recording. Discharge indexes greater than 2.0 were considered as “provocative effect”; below 0.5 as “inhibitory effect”; and between 0.5 and 2.0 as “no effect” (Matsuoka et al., 2000). Reproducibility was always mandatory to exclude contamination of incidental seizures or discharges.

In VNPP, the different modalities of tasks were categorized according to Matsuoka et al. (2005) in two groups: action-programming (reading aloud, speaking, writing, written calculation, drawing, and spatial construction) and thinking (reading silently and mental calculation). In each of these groups, we considered tasks to be related to spatial (mental and written calculation, drawing, and spatial construction) or linguistic (reading aloud and silently, speaking, and writing) functions.

When both inhibitory and provocative effects were observed in different tasks within the same group, a mean of the discharge indexes was calculated. The same methodology was used for habitual methods of activation. The provocative effect of eyes opening and closure and IPS provocation was always mandatory to exclude contamination of incidental seizures or discharges.

Influence of Cognitive Activity in JME

RESULTS

At the time of VNPP the mean age was 24.3 ± 8.33 years (range 12–53 years) and duration of epilepsy 11.3 ± 8.85 (range 1–38); 54 patients (71.0%) had a positive family history of epilepsy, being JME in 9 (11.8%). Demographic and clinical data are in Table 2.

**Table 2.** Demographic and clinical data of 76 patients with juvenile myoclonic epilepsy

<table>
<thead>
<tr>
<th>Data</th>
<th>Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>35 (46.1)</td>
</tr>
<tr>
<td>Schooling</td>
<td>Elementary</td>
<td>27 (35.5)</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>40 (52.6)</td>
</tr>
<tr>
<td></td>
<td>University level</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Antiepileptic therapy</td>
<td>Without antiepileptic drugs</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td></td>
<td>Appropriate treatment</td>
<td>49 (64.5)</td>
</tr>
<tr>
<td></td>
<td>Inappropriate treatment</td>
<td>18 (23.7)</td>
</tr>
<tr>
<td>Type of seizures</td>
<td>Only myoclonia</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td></td>
<td>Myoclonia + generalized tonic–clonic</td>
<td>41 (54.0)</td>
</tr>
<tr>
<td></td>
<td>Myoclonia + generalized tonic–clonic + absences</td>
<td>32 (42.1)</td>
</tr>
<tr>
<td></td>
<td>Myoclonia + absences</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Seizure control</td>
<td>Controlled</td>
<td>23 (30.3)</td>
</tr>
<tr>
<td></td>
<td>Noncontrolled</td>
<td>53 (69.7)</td>
</tr>
</tbody>
</table>

**Video-EEG neuropsychological protocol effect**

Awake EEG was normal in 45 (59.2%) and showed epileptiform discharges in 31 (40.8%), consisting of spike and polyspike-wave complexes. Seizures were observed in 31 patients (40.8%): myoclonia in 23 (74.2%), absences in 16 (51.6%), and GTCS in 4 (12.9%). Myoclonia were observed during VNPP in 13 patients, HV in 7, and IPS in 5. Among those patients with myoclonic seizures, four presented perioral reflex myoclonia during speaking or reading aloud, in two of them accompanied by reflex limb myoclonia during action-programming tasks. Absences were observed in 16, during HV in 12, VNPP in 3, and IPS in one. GTCS were observed in four patients: one during resting, two during habitual methods of activation (somnolence and HV), and the last during spatial construction tasks of the VNPP.

Twenty-nine of the 76 patients (38.2%) presented provocative VNPP effect in at least one task. The rate of provocative effect was similar in patients with paroxysms in the awake EEG (14 of 31, 45.2%) and in those without (15 of 45, 33.3%; p = 0.34). Among the former, 11 (35.5%) also had inhibitory effect in another task, thus considered as having a mixed effect. Inhibitory effect was seen in 28 of 31 (90.3%) patients with epileptiform discharges on awake EEG. Thirty of the 76 patients (39.5%) had no effect (Table 3).

Regarding treatment there was no difference among appropriately, inappropriately, and nontreated patients in VNPP effects, both in those with discharges in awake EEG and in the group without (Table 4). The mean discharge rate in awake EEG was similar in the three treatment groups: 0.21 ± 0.25, 0.17 ± 0.25, and 0.23 ± 0.33 discharges/min, respectively (p = 0.91).

As for seizure control, VNPP effects were similar for groups with and without persistent seizures (Table 4). There was no difference in discharge rate in awake EEG for these two groups: 0.10 ± 0.42 and 0.25 ± 0.37 discharges/min, respectively (p = 0.13).
Video-EEG neuropsychologic protocol effect according to categories of tasks

The effects obtained in the two categories of tasks (action-programming and thinking), subdivided into four subcategories (action-programming linguistic, action-programming spatial, thinking linguistic, and thinking spatial) are depicted in Fig. 1.

Action-programming tasks were more effective than thinking tasks in provoking discharges (23.7% and 11.0% of patients, respectively, p = 0.03). No difference was observed between linguistic and spatial tasks in both categories (18.7% and 21.1% of patients, respectively, p = 0.43).

Inhibitory effect was more frequently observed than provocative effect. However, no difference was observed either between action-programming and thinking (p = 1.00) or between spatial and linguistic categories (p = 0.31). When comparing the four subcategories, thinking spatial (represented by mental calculation task) more often exerted inhibitory effect than the other three subcategories (p = 0.02). This subcategory showed inhibitory effect in 18 of 27 (66.7%) of the patients (mean discharge index 0.57 ± 1.07).

Video-EEG neuropsychologic protocol effect according to individual tasks

In Fig. 2, individual tasks are shown in decreasing order of inhibitory effects. Mental and written calculations were the most inhibitory tasks (66.7% and 64.0%, respectively). Among all tasks, those involving manual praxis, such as spatial construction 15 of 75 (20.0%), written calculation 12 of 60 (20.0%), and writing 9 of 62 (14.5%) were the most provocative ones. They were followed by reading aloud (Portuguese 7 of 70, 10.0%; and English 10 of 69, 14.5%), speaking 6 of 65 (9.2%), drawing 5 of 65 (7.7%), reading silently (Portuguese 4 of 63, 6.7%), and in reading English 1 of 69 (1.5%).

<table>
<thead>
<tr>
<th>Table 3. Video-EEG neuropsychological protocol effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNPP effect</td>
</tr>
<tr>
<td>DA absent</td>
</tr>
<tr>
<td>DA present</td>
</tr>
<tr>
<td>MDI</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Values expressed in parentheses are %.

DA, discharges in awake EEG; MDI, mean of discharge indexes (mean ± SD).

*Z-test for single means = 1 (one-tailed), representing comparison between the mean and a preestablished value (μ0), in this case μ0 = 1.

<table>
<thead>
<tr>
<th>Table 4. Effects of Video-EEG neuropsychological protocol according to treatment and seizure control. The mean of discharge indexes in each subgroup is compared to the awake value equal to 1 and to each other</th>
</tr>
</thead>
<tbody>
<tr>
<td>VNPP effect</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>DA absent</td>
</tr>
<tr>
<td>Without antiepileptic drugs</td>
</tr>
<tr>
<td>Appropriate treatment</td>
</tr>
<tr>
<td>Inappropriate treatment</td>
</tr>
<tr>
<td>DA present</td>
</tr>
<tr>
<td>Without antiepileptic drugs</td>
</tr>
<tr>
<td>MDI</td>
</tr>
<tr>
<td>Appropriate treatment</td>
</tr>
<tr>
<td>MDR</td>
</tr>
<tr>
<td>Inappropriate treatment</td>
</tr>
<tr>
<td>MDI</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>DA absent</td>
</tr>
<tr>
<td>Controlled</td>
</tr>
<tr>
<td>Uncontrolled</td>
</tr>
<tr>
<td>DA present</td>
</tr>
<tr>
<td>Controlled</td>
</tr>
<tr>
<td>MDI</td>
</tr>
<tr>
<td>Uncontrolled</td>
</tr>
<tr>
<td>MDI</td>
</tr>
</tbody>
</table>

Values expressed in parentheses are %.

DA, discharges in awake EEG; MDI, mean of discharge indexes (mean ± SD); MDR, mean discharge rate *Z-test for single means = 1 (one-tailed).
6.3%; and English 5 of 64 (7.8%), and mental calculation 5 of 66 (7.6%).

**Habitual methods of activation**

The mean discharge rate during sleep (0.73 ± 1.43) was higher than that during awake EEG (0.20 ± 0.39; p = 0.001). Sleep activated discharges in 36 of 62 (58.0%) and inhibited in 2 patients.

HV was effective in activating discharges in 27 of 70 (38.6%; discharge rate mean 0.58 ± 1.14; p = 0.001) and in inhibiting in 2 patients. Photosensitivity was present in 19 of 64 patients (29.7%). Eye closure sensitivity was observed in 13 patients (21.3%), 8 of whom (14.6%) were also photosensitive (Table 5).

**Comparison between video-EEG neuropsychological protocol and habitual methods of activation effects**

Discharge indexes were higher in habitual methods of activation than in VNPP tasks (sleep p = 0.018, HV p < 0.001), as shown in Table 5 and Fig. 3. No difference was observed in VNPP effect between photosensitive and nonphotosensitive patients (Table 6).

Photosensitive patients were younger than nonphotosensitive. The mean age for each group was 20.4 ± 6.32
and 26.4 ± 8.98 years, respectively (p = 0.01). On the other hand, a correlation between VNPP effects and age was not observed. Patients who had provocative effect of VNPP (22.4 ± 6.92 years) were of a similar age when compared to those without VNPP effect (23.1 ± 7.04) and to patients with inhibitory effects (28.1 ± 11.36, p = 0.09).

**Psychiatric evaluation and discharge indexes**

Anxiety disorders were diagnosed in 24 of 58 patients (41.4%). Twenty-three had generalized anxiety disorder and one had obsessive-compulsive disorder. Regarding the presence of discharges in the awake EEG, there was no difference between anxious (11 of 24, 45.8%) and nonanxious patients (11 of 34, 32.4%; p = 0.41). In addition, there were no differences between these two groups in the mean of discharge indexes in VNPP. However, in all tasks except writing, there was a tendency to greater discharge indexes in anxious patients (Fig. 3).

Although the anxious group had no significant inhibitory VNPP effect in any task, the nonanxious group had inhibition in mental calculation, a thinking spatial task (0.19 ± 0.56; p = 0.001), and in action-programming spatial tasks (0.62 ± 0.64; p = 0.04). Considering individual tasks, the nonanxious group had significant inhibitory effect when doing mental calculation (0.19 ± 0.56; p = 0.001), speaking (0.28 ± 0.56; p = 0.003), spatial construction (0.31 ± 0.65; p = 0.003), and reading English silently (0.63 ± 0.60; p = 0.035). Mental calculation was the only VNPP task exerting inhibitory effect when both groups of JME patients were analyzed together (0.57 ± 1.07; p = 0.02).

**DISCUSSION**

Reflex seizures and epileptiform discharges induced by higher mental function in JME patients have been reported in a few studies (Matsuoka et al., 1988; Senanayake, 1992; Matsuoka et al., 2000; Karachristianou et al., 2004; Mayer & Wolf, 2004; Matsuoka et al., 2005; Mayer et al., 2006). As photosensitivity and eye closure sensitivity, they suggest the presence of regional hyperexcitability and raise questions about the strict concept of JME as an IGE (Wolf & Mayer, 2000; Inoue & Zifkin, 2004; Inoue, 2007).

Among cognitive tasks, linguistic operations and decision-making associated with visuospatial manipulation are the best-characterized triggers (Ritaccio et al., 2002). Matsuoka et al. (2000) reported induction of discharges by cognitive activities almost exclusively in IGE (36 of 38 patients), particularly JME (22 of 36).

We found a VNPP provocative effect in at least one task in 29 of 76 patients (38.2%), a rate much inferior to that described in smaller series such as 21 of 25 (84%) of treated (Matsuoka et al., 1988) and 23 of 30 (76.6%) of nontreated (Karachristianou et al., 2004) JME patients. However, it was closer to 22 of 45 (48.8%) of JME patients reported by Matsuoka et al. (2000).

The rate we found was neither dependent on treatment nor on seizure control. The lack of influence of these factors over the provocative effect might indicate that it is a true reflex trait. According to this idea, two JME patients were reported to remain sensitive to neuropsychological provocative tasks for more than 20 years, indicating that this feature was not transitory (Matsuoka et al., 2002). Indeed, we found no correlation between sensitivity to VNPP provocative effect and age. This did not hold true in relation to photosensitivity, as the mean age was lower in the photosensitive group.

In our series, action-programming tasks were more effective than thinking in exerting provocative effect. This is in accordance with previous reports of Matsuoka et al. (2000, 2005) who also found action-programming as the most crucial provocative task category. In their series, among 38 patients who had EEG discharges activation by neuropsychological tasks, 32 (84.2%), had this effect by action-programming and only 4 (10.5%) by thinking.

On the other hand, in our series, the provocative effect of linguistic and spatial tasks was similar (p = 0.84). Eighteen patients had activation of discharges by action-programming tasks, linguistic in 14 (77.8%), and spatial in 15 (83.3%). These numbers also equal those of Matsuoka et al. (2005), who, within the action-programming category, found 33 of 36 activations (91.7%) by linguistic subtype and 30 of 36 (83.3%) by spatial tasks.

**Table 5. Discharge indexes in habitual methods of activation.** The mean of discharge indexes in sleep and hyperventilation was compared to the awake value; photosensitivity and eye closure sensitivity were considered present or absent

<table>
<thead>
<tr>
<th>Habitual methods effects</th>
<th>Provocative</th>
<th>Inhibitory</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence/sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA absent</td>
<td>25 (64.1)</td>
<td>–</td>
<td>14 (35.9)</td>
<td>39</td>
</tr>
<tr>
<td>DA present</td>
<td>11 (47.8)</td>
<td>2 (8.7)</td>
<td>10 (43.5)</td>
<td>23</td>
</tr>
<tr>
<td>MDI</td>
<td>7.78 ± 14.881 (p = 0.018)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA absent</td>
<td>9 (22.5)</td>
<td>–</td>
<td>39 (77.5)</td>
<td>40</td>
</tr>
<tr>
<td>DA present</td>
<td>18 (60.0)</td>
<td>2 (6.7)</td>
<td>10 (33.3)</td>
<td>30</td>
</tr>
<tr>
<td>MDI</td>
<td>4.08 ± 4.353 (p &lt; 0.001)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>19 (29.7)</td>
<td>–</td>
<td>45 (70.3)</td>
<td>64</td>
</tr>
<tr>
<td>Eye closure sensitivity</td>
<td>13 (21.3)</td>
<td>–</td>
<td>48 (78.7)</td>
<td>61</td>
</tr>
<tr>
<td>Photo and eye</td>
<td>8 (14.6)</td>
<td>–</td>
<td>35 (64.8)</td>
<td>54</td>
</tr>
</tbody>
</table>

Values expressed in parentheses are %. DA, discharges in awake EEG; MDI, mean of discharge indexes (mean ± SD). *Z-test for single means = 1 (one tailed).
Among individual tasks, those related to manual praxis were the most provocative. Although in a much higher rate, Matsuoka et al. (2000) also identified as significant triggers tasks involving praxis, such as writing in 26 of 38 (68.4%), spatial construction in 24 (63.2%), and written calculation in 21 (55.3%). In contrast, mental calculation exerted provocative effect in only three (7.9%) and reading in two of their patients (5.3%). In a smaller series of 25 patients with JME, Mayer et al. (2006) did not consider the role of praxis as pivotal in inducing discharges, since in their series reading exerted provocative effect in 20% and praxis and speaking in 16% each.

Considering calculation, in our series, the provocative effect of written was twice that of mental calculation. This has also been a matter of discussion: whereas in the series of Matsuoka et al. (2000), written calculation exerted provocative effect in 55.3% versus only 7.9% in mental calculation, in the report of Mayer et al. (2006) the effect of calculation was irrelevant (1 of 25 JME patients). In the present series, mental calculation was a powerful inhibitor of discharges (18 of 27, 66.7%). The same was seen in written calculation that exerted inhibition in 16 of 25 (64%) of the patients. However, the last also elicited discharges in 12 of 60 (20%) of patients. Wolf (2005) stated that the same function could sometimes be provocative or inhibitory depending on the state of cortical activation; when resting, a task could precipitate discharges and seizures, whereas when already firing, the activation of a nearby network could inhibit its activity. The parietal cortex would be the structure involved in this process from Matsuoka et al. (2000), written calculation exerted provocative effect in 55.3% versus only 7.9% in mental calculation, in the report of Mayer et al. (2006) the effect of calculation was irrelevant (1 of 25 JME patients). In the present series, mental calculation was a powerful inhibitor of discharges (18 of 27, 66.7%). The same was seen in written calculation that exerted inhibition in 16 of 25 (64%) of the patients. However, the last also elicited discharges in 12 of 60 (20%) of patients. Wolf (2005) stated that the same function could sometimes be provocative or inhibitory depending on the state of cortical activation; when resting, a task could precipitate discharges and seizures, whereas when already firing, the activation of a nearby network could inhibit its activity. The parietal cortex would be the structure involved in this process from

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where the spatial thinking processes would or would not be transformed into voluntary movements (Goossens et al., 1990; Senanayake, 1992; Striano et al., 1993; Inoue et al., 1994). When parietal cortex processes involve the frontal region, for example, in written calculation, it could activate discharges; when there is no recruitment of the motor network, as in mental calculation, the parietal cortex might act as the nearby region, inhibiting the hyperexcitable motor cortex, or on the contrary, promoting discharges on it in the dependency of the state of the network at that moment.

In this series, although tasks involving motor networks exerted excitation, those restricted to thinking had the opposite effect, regardless of spatial or linguistic character. Praxis induction would be the preponderant trigger in JME, implying the role of the motor network in the epileptogenic process (Inoue & Zifkin, 2004). Its hyperexcitability determines the clinical hallmark of this syndrome, the motor manifestations and the great amount of evidence of frontal dysfunction by EEG (Janz, 1985), neuropsychological studies (Devinsky et al., 1997; Pascalicchio et al., 2007; Piazzini et al., 2008), quantitative MRI (Woermann et al., 1998), functional imaging such as positron emission tomography (PET) (Koepp, 2005), and MR spectroscopy (Savic et al., 2000) and, finally, anatomopathologic findings (Meencke & Janz, 1984; Meencke, 1985). Therefore, current evidence suggests that JME is a frontal lobe variant of a multiregional, thalamocortical epilepsy “network” (Koepp, 2005). However, the participation of other cortical areas in this network, in particular the parietal, needs to be clarified.

In addition to specificity, the complexity of a function should be considered. Action-programming might recruit a more extensive amount of hyperexcitable cortex than thinking activities. The sum of tissue involved in a network would explain the fact that the more complex the task, the greater the probability of exerting a provocative effect (Wilkins et al., 1982; Ferlazzo et al., 2005). In our series, comparing drawing and spatial construction, both related to visuospatial functions, similar proportions of provocative and inhibitory effects were observed; however, spatial construction, a task involving a more complex, three-dimensional manipulation was more effective when compared to drawing, a two-dimensional task. Different to what was reported in reading epilepsy, in which the provocative effect is enhanced by increasing the difficulties of the reading material (Wolf & Inoue, 2002), we failed to demonstrate this effect in reading different languages.

As a diagnostic tool, the comparison between habitual methods of activation and VNPP favored the first. The awake EEG recordings in our JME patients resulted in 59.2% of normal tracings. This percentage was higher than previously described, at between 19% and 56% (Canevini et al., 1992; Panayiotopoulos et al., 1994; Murthy et al., 1998; Pedersen & Petersen, 1998), probably due to the fact that 64.5% of the patients in our series were appropriately treated. In our sample, sleep was the most effective activation method, followed by HV and IPS. In JME patients, Matsuoka et al. (1988) considered the neuropsychological tasks as the most effective provocative method, being observed in 21 of 25 (84%), followed by light drowsiness in 17 (68%), HV in 10 (40%), and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks as the most effective provocative method, being observed in 9 of 25 (36%) followed by HV in 7 (28%) and IPS in 5 (20%). In our unselected series, only four (5%) patients presented perioral reflex myoclonia.

Inoue and Kubota (2000) observed that no patient in the praxis-sensitive group showed EEG photosensitivity and stated that “photosensitivity and praxis sensitivity seem to stand in clear contrast.” Mayer et al. (2006) found photosensitivity in both groups—three of their six patients with praxis-induced discharges also showed photosensitivity. We also found praxis sensitivity in photosensitive (4 of 19, 21%) and nonphotosensitive patients (9 of 45, 20%). This indicates that these two traits may coexist in the same patient.
Another interesting application of VNPP is related to the possibility of inhibition of epileptiform discharges through cognitive activity, a fact that beyond helping to clarify physiopathologic aspects may be explored as a therapeutic tool. Unexpectedly, inhibitory (28 of 31, 90.3%) was more prevalent than provocative effect (29 of 76, 38.2%). In a population of 480 patients with epilepsy, Matsuoka et al. (2000) reported 63.9% of inhibitory versus 7.9% of provocative effect. However, the authors decided not to deal with inhibitory effect, since the discharge index under this circumstance did not show a peak clearly separated from that under “no effect” condition. Because inhibitory effect was defined in a very strict manner (between 0 and 0.5), in order to provide a better demonstration of this effect, we decided to consider the inverse of each index.

The stronger inhibitory effect exerted by the subcategory of spatial mental task could be biased, given that this subcategory was composed of only one task—mental calculation—of short duration. Alternatively, the activation of parietal cortex without motor involvement could explain the inhibitory effect by a cortical mechanism as already mentioned. However, considering the great categories of tasks, inhibitory effect was not related to any one of them. This may suggest that the inhibitory cognitive effect might be mediated by a more widespread inhibitory pathway, such as the cortical-thalamic. Normally cortical-thalamic feedback loops regulate the flow of sensory information to the cortex through activation of inhibitory neurons in the reticular nucleus, gating thalamic output to the cortex (Kostopoulos, 2001; Zikopoulos & Barbas, 2006).

In addition to influence of subcortical structures, many authors have emphasized the role of stress in precipitating reflex seizures independent of the epileptic syndrome (Matsuoka et al., 1988; Goossens et al., 1990; Inoue & Kubota, 2000; Inoue, 2007). Furthermore, it was found in JME patients a correlation between the presence of anxiety, lack of seizure control, and antecedent of more than 20 lifetime GTCS (De Araújo Filho et al., 2006). We confirmed this suggestion, once the presence of anxiety determined a less expressive inhibitory effect and a tendency to higher discharge indexes. In addition, a high prevalence of anxiety in JME patients might indicate a common physiopathology of the two morbidities. Recent neuroimaging studies in animal models of anxiety have indicated the participation of the amygdala-prefrontal circuitry in the manifestation of this symptom (Bishop, 2007).

In conclusion, we advise habitual methods of activation for EEG diagnoses in JME. However cognitive tasks, mainly those involving hand praxis, may be useful on an individual basis and for research purposes. The understanding of all these dynamic interactions, including the stress contribution, would help to clarify the physiopathologic mechanisms of this prototype of IGE. At last, it could facilitate the design and development of successful nonpharmacologic therapeutic interventions for the treatment of JME patients as cognitive therapy or antistress programs, as already done in an empirical form (Dahl et al., 1985, 1987; Martinovic, 2001; Wolf, 2002).

**Acknowledgments**

We would like to thank Prof. Peter Wolf and Dr. Thomas Mayer for having kindly forwarded their valuable expertise, including handing us their protocol. We would also like to thank Patricia Guilhem de Almeida Ramos for her valuable help with statistics.

CAPES and FAPESP from Brazil and DAAD from Germany supported this study.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure: The authors have no conflicts of interest to declare.

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Epilepsia, **(8)**:1–10, 2009


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Abstract

**Purpose:** The neuroanatomical basis and the neurochemical abnormalities that underlie juvenile myoclonic epilepsy (JME) are not fully understood. While the thalamus plays a central role in synchronization of widespread regions of the cerebral cortex during a seizure, emerging evidence suggests that all cortical neurons may not be homogeneously involved. The purpose of this study was to investigate the cerebral metabolic and structural differences between JME patients and normal controls.

**Methods:** All patients had a JME diagnosis based on seizure history and semiology, EEG recording, normal magnetic resonance neuroimaging (MRI) and video-EEG according to the Commission on Classification and Terminology of the International League Against Epilepsy, 1989. Sixty JME patients (JME-P) were submitted to 1.5 T MRI multi-voxel proton spectroscopy and voxel-based morphometry (VBM). The control group consisted of 30 age and sex-matched healthy volunteers. The Institutional Ethics Committee approved the study, and informed consent was obtained from all participants.

**Results:** Group analysis demonstrated lower N-acetyl-aspartate/Creatine (NAA/Cr) ratio among patients compared to controls on prefrontal, frontal cortices and thalamus. Patients had a statistically significant difference in glutamate-glutamine complex (GLX)/Cr on prefrontal and frontal cortices, insula, striatum and posterior cingulate gyrus. When evaluating the relationship among the various components of this epileptic network among JME-P, the strongest correlation occurred between thalamus and prefrontal cortex and a significant negative correlation between NAA/Cr and duration of epilepsy was found. Also, VBM demonstrated significantly reduced gray matter volume (GMV) in thalami, insula cortices and cerebellar hemispheres bilaterally; while significantly increased GMV was observed in right superior frontal, orbitofrontal and medial frontal gyri among JME-P when compared to controls.

**Conclusions:** The identification of a specific network of neurochemical dysfunction and slight structural abnormalities in patients with JME, with diverse involvement of particular structures within the thalamocortical circuitry, suggests that cortical hyperexcitability in JME
is not necessarily diffuse, supporting the knowledge that the focal/generalized distinction of epileptogenesis should be reconsidered and reinforcing the concept of 'system epilepsies'.
Esta tese está de acordo com as seguintes normas, em vigor no momento da publicação:


Abreviaturas dos títulos dos periódicos de acordo com List of Journals Indexed in Index Medicus.
acquisition, quantification, and analysis were performed by one investigator (KL) and reviewed by an experienced neuroradiologist/spectroscopist (HJC).

**Statistics**

All results were presented as mean ± standard deviation (SD) to define dispersion. Statistical analysis was performed with the following packages SPSS for Windows 10.01 Standard Version (SPSS Inc., Chicago, IL, U.S.A.) Statistica for Windows 4.2 (StatSoft Inc., Tulsa, OK, U.S.A.) and STATA Statistics Data Analysis 5 (Stata Corporation, College Station, TX, U.S.A.). Difference between patients and controls with respect to age was assessed using Student’s t-test. Comparison of age at seizure onset and duration of epilepsy between patients with and without PD was performed with Student’s t-test. The gender distribution, manual dominance, and treatment of epilepsies were examined by the Fisher’s exact test. Association between the number of positive scores in SCID-II and clinical variables were examined by Pearson coefficient of correlation (r). Furthermore, a multiple correlation analysis with stepwise method was performed to evaluate a possible relation between the number of positive scores in SCID-II and values of NAA/Cr and GLX/Cr ratios among JME patients. Group differences for each spectroscopic ratio between JME and healthy controls were compared using one-way analysis of variance (ANOVA) and post hoc analysis with least significant difference (LSD) test (two-tailed). Given that concentrations of measured metabolites vary among different regions (Helms, 1999; Savic et al., 2000) and between different sides assessed by paired ANOVA paired, only values from the same region and from the same side were compared among groups. With the aim of providing a normal distribution of data, we excluded individuals with abnormal regional concentrations of the metabolites from statistical analysis. Abnormality of the regional concentration of a given metabolite in individual patients was defined as a value outside the 2 SD of the mean of normal controls. This procedure, however, did not compromise statistical analysis, once the data loss was <5% of our sample. The results were also corrected for multiple comparisons using a false discovery rate (FDR) analysis [q = 0.15; c(V) = 1]. Once there are no data describing adequate parameters of FDR in spectroscopy, the q value of 0.15 would be reasonable to use in most situations regarding neuroimaging studies according to literature (Genovese et al., 2002).

**RESULTS**

**Demographic and clinical data**

In the JME group, 16 patients fulfilled criteria for only cluster B PDs, whereas 41 did not have any PD. The MRS of these 57 patients and of 30 healthy controls was analyzed. Groups were homogeneous according to age (p = 0.20), gender distribution (p = 0.74), and manual dominance (p = 0.67). Table 1 shows the demographic data for the three groups.

When the clinical variables of the two JME groups were compared, there were no differences in duration of disease, age at epilepsy onset, photosensitivity, and the proportion of patients with adequate treatment, which was defined by the use of therapeutic doses of a first-line drug for generalized epilepsies, in monotherapy or in association, such as valproate (VPA), topiramate (TPM), lamotrigine (LTG), and clonazepam (CNZ). Inadequate treatment was defined by the use of non-recommended drugs for this type of epileptic syndrome, such as phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), clobazam (CLB), and phenobarbital (PB). The number and types of seizures, like myoclonia, absences, and GTCS were also compared to investigate seizure control in the two groups. According to seizure control, patients who presented more than four GTCS per year or more than 15 myoclonia or absences, either isolated or in clusters, per month were considered to have inadequate control of seizures (Prasad et al., 2003). The JME group with PD presented significantly more patients with inadequate control of both myoclonic (p = 0.007) and absence (p = 0.04) seizures. There was no difference regarding the control of GTCS between the groups (p = 0.28). There was a positive correlation between the number of positive scores in SCID-II, an indicator of PD severity, and worse control of myoclonia (r = 0.69, p < 0.0001), absences (r = 0.52, p < 0.0001), and GTCS (r = 0.63, p < 0.0001). This was made comparing the number of positive scores and the degree of control of

| Table 1. Demographic data of patients with juvenile myoclonic epilepsy and a control group |
|---------------------------------|-----------------|-----------------|-----------------|------------------|
| Demographic data                | JME without PDs | JME with PDs    | Control group   | p-value          |
| Number of patients              | 41 (47.1)       | 16 (18.4)       | 30 (34.5)       |                  |
| Age (mean ± SD)                 | 26.1 ± 9.4      | 28.3 ± 8.2      | 30.1 ± 9.0      | 0.201            |
| Gender (females)                | 19 (46.3)       | 9 (56.3)        | 14 (46.7)       | 0.748            |
| Number of right-handed (%)      | 34 (82.9)       | 15 (93.8)       | 28 (93.3)       | 0.679            |

Values within parenthesis represent percentages.

JME, juvenile myoclonic epilepsy; PD, personality disorder; SD, standard deviation.

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each type of seizure. Table 2 shows the differences in clinical data.

MRS values

A synopsis of metabolite concentrations (mean and SD) in different groups and regions is given in Tables 3 and 4, showing the amplitude values of NAA/Cr and GLX/Cr ratios. A general tendency of lower values of NAA/Cr and higher values of GLX/Cr in the group of JME with PDs was observed, mainly in frontal regions. The results were described according to the differences found in regions of interest between JME versus controls and JME with PDs versus JME patients without any psychiatric disorder, as follows:

JME patients versus controls

The comparison of NAA/Cr values showed a significant reduction in JME patients when compared with controls in right medial primary motor region (p = 0.01). There was also an increase of GLX/Cr in the JME group when compared with controls in left insula (p = 0.02) and in left striatum (p = 0.03). There were no significant differences between JME patients and controls in other regions.

JME with PDs versus JME without PDs

Patients with JME and PDs had significantly lower concentrations of NAA/Cr in the right thalamus (p = 0.03), in the left medial primary motor region (p = 0.003), and in the left parietal region (p = 0.007) when compared with JME patients without PDs. An increase of the GLX/Cr in the right medial primary motor (p = 0.03) and in the left lateral primary motor (p = 0.02) regions in the JME group with PDs was also observed. The same analysis showed an important reduction of NAA/Cr in the right medial supplementary motor region (p = 0.05) in JME with PDs.

A multiple regression analysis with stepwise method was performed to evaluate a possible relation between

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<table>
<thead>
<tr>
<th>Table 2. Clinical data of patients with juvenile myoclonic epilepsy with and without personality disorder</th>
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<tr>
<td><strong>Clinical data</strong></td>
</tr>
<tr>
<td>Number of patients (%)</td>
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<tr>
<td>Time of disease (mean ± SD)</td>
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<tr>
<td>Age at epilepsy onset (mean ± SD)</td>
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<tr>
<td>Adequate treatment (%)</td>
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<tr>
<td>Photosensitivity (%)</td>
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<tr>
<td>Inadequate control of myoclonia (%)</td>
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<tr>
<td>Inadequate control of absences (%)</td>
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<td>Inadequate control of GTCS (%)</td>
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</table>

| GTCS, generalized tonic–clonic seizures; JME, juvenile myoclonic epilepsy; PD, personality disorder; SD, standard deviation.
*Significant; corrected for multiple comparisons using false discovery rate [q = 0.15; c(V) = 1].

<table>
<thead>
<tr>
<th>Table 3. Values of NAA/Cr ratio</th>
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<tr>
<td><strong>Areas</strong></td>
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<tr>
<td>Thalamus</td>
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<tr>
<td>Striatum</td>
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<tr>
<td>Cingulate gyrus</td>
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<td>Insula</td>
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<tr>
<td>Medial primary motor</td>
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<td>Lateral primary motor</td>
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<tr>
<td>Medial supplementary motor</td>
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<td>Lateral supplementary motor</td>
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<tr>
<td>Parietal</td>
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<td>Occipital</td>
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| **Right**                      | **Controls** (mean ± SD) | **JME with PD** (mean ± SD)  | **JME without PD** (mean ± SD) | **p-value** |
| Thalamus                       | 1.64 ± 0.19              | 1.79 ± 0.58                   | 1.97 ± 0.68                     | 0.053       |
| Striatum                       | 1.24 ± 0.20              | 1.36 ± 0.25                   | 1.32 ± 0.21                     | 0.178       |
| Cingulate gyrus                | 1.67 ± 0.58              | 1.74 ± 0.46                   | 1.57 ± 0.38                     | 0.497       |
| Insula                         | 1.33 ± 0.13              | 1.30 ± 0.24                   | 1.33 ± 0.23                     | 0.873       |
| Medial primary motor           | 2.07 ± 0.16              | 1.87 ± 0.19                   | 2.02 ± 0.18                     | 0.003*      |
| Lateral primary motor          | 1.89 ± 0.15              | 1.78 ± 0.19                   | 1.84 ± 0.21                     | 0.199       |
| Medial supplementary motor     | 1.69 ± 0.14              | 1.66 ± 0.22                   | 1.75 ± 0.21                     | 0.346       |
| Lateral supplementary motor    | 1.92 ± 0.16              | 1.81 ± 0.17                   | 1.85 ± 0.28                     | 0.242       |
| Parietal                       | 1.95 ± 0.16              | 1.87 ± 0.29                   | 2.11 ± 0.30                     | 0.007*      |
| Occipital                      | 1.80 ± 0.38              | 1.89 ± 0.56                   | 2.08 ± 0.55                     | 0.094       |

Cr, creatine; JME, juvenile myoclonic epilepsy; NAA, N-acetyl-aspartate; PD, personality disorder; SD, standard deviation.
*Significant; corrected for multiple comparisons using false discovery rate [q = 0.15; c(V) = 1].

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positive scores in SCID-II and values of NAA/Cr and GLX/Cr ratios among JME patients. The strongest correlations based on beta % value occurred in left medial primary motor region (r = 0.28, p = 0.03) and right thalamus (r = 0.22, p = 0.08) for NAA/Cr. For GLX/Cr, the strongest correlations occurred in the right medial primary motor (r = 0.35, p = 0.01) and in the left lateral primary motor (r = 0.25, p = 0.08) regions. A synopsis of multiple regression data is given in Table 5.

## Discussion

The aim of this study was to perform a functional controlled correlation of possible neuronal dysfunctions between a group of patients with JME and cluster B PDs and JME patients without any psychiatric diagnosis treated in a tertiary center through the use of the technique of quantitative multivoxel MRS. We also aimed to find specific network-region associated dysfunction in relation to specific personality traits and to correlate the findings with a number of clinical variables, such as seizure type and frequency, number and types of AED, and duration of epilepsy. To the best of our knowledge this is the first study using a combined analysis of MRS and psychiatric evaluation to investigate such personality traits in JME.

Although it is generally accepted that there is no neuroimaging abnormality in patients with IGE, quantitative MRI studies suggest that subtle structural abnormalities may in fact exist among them (Woermann et al., 1998, 1999; Duncan, 2005; Betting et al., 2006). Proton quantitative MRS is a technique that provides MR signals from a number of cerebral metabolites, such as NAA, GLX, and Cr. Previous studies have suggested that these metabolite signals may be valuable in the assessment of certain brain disorders (Bottomley, 1992; Prichard & Brass, 1992). NAA is found exclusively in neurons and neuronal processes and is considered an indicator of neuronal function. Its reduction is thought to represent neuronal and axonal loss, injury, or metabolic dysfunction (Duncan, 2005; Betting et al., 2006). Glutamate is another neurotransmitter for which higher levels indicate increased neuronal excitability, whereas Cr is relatively homogeneously distributed throughout the brain and is not significantly influenced by the epileptic state (Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005). Because metabolites are measured in voxels, units of volume, their increase or reduction could be related to a large variety of confounding factors, such as neuronal shrinkage or increase/decrease in water content (Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005).

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### Table 5. Correlations between NAA/Cr and GLX/Cr ratios and number of SCID-II scores

<table>
<thead>
<tr>
<th>Areas</th>
<th>NAA/Cr</th>
<th>GLX/Cr</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>R2</td>
<td>CI 95%</td>
</tr>
<tr>
<td>Left medial primary motor</td>
<td>0.29 ± 0.04</td>
<td>5.54–1.33</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>0.29 ± 0.04</td>
<td>4.65–3.38</td>
</tr>
<tr>
<td>Right medial primary motor</td>
<td>0.27 ± 0.04</td>
<td>1.21–9.26</td>
</tr>
<tr>
<td>Left lateral primary motor</td>
<td>0.27 ± 0.04</td>
<td>-0.59–9.02</td>
</tr>
</tbody>
</table>

Beta %, regression coefficient percentage; CI, confidence interval; Correlation coeff, partial correlation coefficient; Cr, creatine; GLX, glutamate–glutamine; NAA, N-acetyl-aspartate; SCID, Scheduled Clinical Interview for DSM-IV. *Significant at p < 0.05.
of frontal lobe injury (Doval et al., 2001; Koepp, 2005). To prevent possible mistakes in their measuring that could lead to incorrect interpretations of the results, we performed an analysis of the NAA/Cr and GLX/Cr ratios, providing more reliability to all the comparisons performed. The method used to calculate the values of metabolites is another matter of controversy, and different studies have discussed what would be the more sensitive and specific to apply (Savic et al., 2000; Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Haki et al., 2007). However, the majority of recent studies in epilepsy have used the amplitude NAA/Cr and GLX/Cr values as a valid method to compare the differences found in their respective analyses (Simister et al., 2003; Haki et al., 2007; Hetherington et al., 2007). Therefore, we preferred to use the same methodology, aiming to unify our results with the current literature, making future comparisons possible.

Different types of anxiety and mood disorders, such as generalized anxiety disorder (GAD), phobias, major depression, dysthymia, and somatization disorders have been described as psychiatric comorbidities in JME (Gelisse et al., 2001; de Araújo Filho et al., 2006; Trinka et al., 2006; de Araújo Filho et al., 2007). We previously found a general prevalence of 49% of PDs among 100 JME patients and also diagnosed in 17% of them mild to moderate cluster B PD, particularly histrionic, borderline, and passive-aggressive, which share most psychopathological characteristics and are clinically described by a marked impulsivity, humor reactivity, emotional instability, unsteadiness, and difficulty in accepting social rules (American Psychiatric Association, 2000; Gelisse et al., 2001; de Araújo Filho et al., 2007).

As mentioned before, the association between JME and some personality traits has already been suggested in the pivotal description of Janz and Christian (1957). These traits were characterized by emotional instability and immaturity, unsteadiness, lack of discipline, hedonism, frequent and rapid mood changes, and indifference toward the disease (Simonsen et al., 1976; Janz, 1985; Janz & Christian, 1994; Trimble, 2000; Trimble et al., 2000; Swinkels et al., 2003). Clinical and electroencephalographic studies have referred to these as “typical” traits and “psychiatric symptoms” (Leder, 1967; Lund et al., 1976; Tsuboi, 1977). Therefore, the description of symptoms and clinical manifestations provided by authors in the past among JME patients could correspond to the cluster B PD cited earlier and described in the DSM-IV-TR (American Psychiatric Association, 2000), since these patients share almost the behavioral characteristics already mentioned for JME.

These manifestations may correspond to frontal lobe impairment, once there have been descriptions of similar behavioral abnormalities in patients with different types of frontal lobe injury (Doval et al., 2001; Koepp, 2005). There is evidence in that literature that such regions involved in those PDs could correspond to the frontal lobes and thalamus, which already have been involved in the pathophysiology of JME (Devinsky et al., 1997; Woermann et al., 1998, 1999; Gelisse et al., 2001; Koepp, 2005; Betting et al., 2006; Pascalicchio et al., 2007). However, we performed a study of other regions over thalamus and frontal lobes aiming to verify possible dysfunctions in cerebral cortex also related to PDs, once JME is generalized epilepsy syndrome and there are no data in literature of MRS findings in PD related to JME.

Studies utilizing the technique of MRS have demonstrated a significant decrease of thalamic and frontal lobe NAA in JME (Savic et al., 2000) and to other types of IGE (Savic et al., 2004) when compared with normal controls. Although the neurochemical abnormality underlying JME is not fully determined, evidence exists to support that a hypersynchrony within the thalamocortical circuitry maintained through γ-aminobutyric acid (GABA) and GLX-mediated mechanisms may play an important role in this epileptic syndrome (Savic et al., 2000; Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005; Haki et al., 2007). Therefore, current evidence of frontal lobe involvement provided by neuroimaging techniques suggests that JME could be a frontal lobe variant of a multiregional, thalamocortical “network” epilepsy, rather than simply a generalized epilepsy syndrome (Duncan, 2005; Koepp, 2005).

The amplitude analysis of the values of metabolite showed significant alterations of the NAA/Cr and GLX/Cr values in JME patients with cluster B PDs, predominantly in the thalamus and frontal lobes. Such differences particularly present on the left side could be explained by differences in gray matter volumes between both cerebral hemispheres. Frontal gray matter volumes have been shown to be higher in the right hemisphere in human brain, which would generally be associated with higher metabolite concentrations. MRI studies have already suggested lower concentrations of all metabolites in the left side when right–left comparisons are made (Amunts et al., 1996; Watkins et al., 2001). Another explanation could be the hemispheric dominance, once manual dominance of almost the totality of patients (85.9%) and controls (93.3%) of this study was located on right side. However, these findings could demonstrate a dysfunction in those cited areas, since NAA reduction may indicate neuronal damage (Savic et al., 2000; Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005; Haki et al., 2007). We also found an increase of GLX/Cr ratio in the same areas that could correspond to increased neuronal excitability and/or increased number of glutamatergic neurons (Duncan, 2005). These findings possibly confirm a more intense thalamic and frontal lobe dysfunction among JME patients with cluster B PDs. In addition, quantitative MRI studies in patients with cluster B PDs without
epilepsy demonstrated significant reductions in frontal lobe structures when compared to normal controls (Lyoo et al., 1998; Raine et al., 2000; Rüsch et al., 2003). Other MRS studies that measured frontal lobe NAA in borderline personality have also described a significant decrease of this metabolite among these patients (Tebartz van Elst et al., 2001). These behavioral characteristics could be, therefore, a consequence of frontal lobe damage, being a constituent of JME or at least be present in more severe forms of this syndrome (Devinsky et al., 1997; Gelisse et al., 2001; Koepp, 2005; de Araújo Filho et al., 2007).

Recent studies have demonstrated that JME patients with PDs have more difficulty in seizure control and worse functional performance when compared to those without these behavioral traits (de Araújo Filho et al., 2007). The importance of seizure control for the mental health of these patients is already defined, and previous studies have associated a higher seizure frequency and the appearance of psychiatric symptoms in generalized epilepsies and consequent worsening in quality of life (Trimble, 2000; Kanner & Weisbrot, 2001; Mula & Trimble, 2003). On the other hand, treatment with VPA for more than 2 years appears to be a protective factor against psychiatric disorders, confirming previous data (de Araújo Filho et al., 2001; Koepp, 2005; de Araújo Filho et al., 2007).

In conclusion, data from MRS might aid support of the hypothesis that PD in JME could represent a more severe form of thalamic and frontal lobe dysfunction as an underlying mechanism of epilepsy generation, consequently producing neuronal damage and PDs (Savic et al., 2000; Bernasconi et al., 2003; Simister et al., 2003; Savic et al., 2004; Koepp, 2005; Haki et al., 2007). More studies involving neuroimaging and psychiatric evaluation in JME are, therefore, highly encouraged.

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We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure: None of the authors has any conflicts of interest to disclose.

References


Personality traits related to juvenile myoclonic epilepsy: MRI reveals prefrontal abnormalities through a voxel-based morphometry study

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Keywords: Magnetic resonance imaging
Voxel-based morphometry
Idiopathic generalized epilepsy
Juvenile myoclonic epilepsy
Psychiatric disorders
Cluster B personality disorders

1. Introduction

Juvenile myoclonic epilepsy (JME) is a well-defined type of idiopathic generalized epilepsy (IGE) that comprises 5–11% of patients with epilepsy, characterized by myoclonic jerks, generalized tonic–clonic seizures (GTCS), and typical findings of generalized 4–6 Hz spike and wave or poly-spike and wave discharges in the electroencephalogram (EEG) [1,2]. Studies involving JME patients have highlighted difficulties in their treatment, which have been attributed to some specific psychological and personality traits, described as emotional instability, immaturity, unsteadiness, lack of discipline, and rapid mood changes. We aimed to verify a possible correlation between structural brain abnormalities in magnetic resonance image (MRI) and the PD in JME using voxel-based morphometry (VBM). Sixteen JME patients with cluster B PD, 38 JME patients without psychiatric disorders, and 30 healthy controls were submitted to a psychiatric evaluation through SCID I and II and to a MRI scan. Significant reduction in thalami and increase in mesiofrontal and frontobasal regions’ volumes were observed mainly in JME patients with PD. Structural alterations of the orbitofrontal cortex (OFC), involved in regulation of mood reactivity, impulsivity, and social behavior, were also observed. This study supports the hypothesis of frontobasal involvement in the pathophysiology of cluster B PD related to JME.

In the last decades there has been an increased interest in characterizing these manifestations that could correspond to frontal lobe impairment, once these behavioral abnormalities have been described among patients with different types of frontal lobe lesions [15,16].

Neuroimaging studies in JME, such as magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), have suggested the presence of structural and functional brain abnormalities among these patients, particularly in the thalamus and frontal lobes [16–25]. While studies using morphometric MRI techniques have demonstrated reduction of gray matter concentration (GMC) in thalamus [16,17] and increase in mesiofrontal and frontobasal areas [18–20], MRS studies have highlighted the thalamocortical circuitry dysfunctions [21–25]. Neuropsychological evaluation has confirmed these frontal lobe dysfunctions in patients with JME [26,27], which could be related to pathophysiological mechanisms involved in the generation of epileptic activity [21–25].

The voxel-based morphometry (VBM) is an MRI technique that measures brain tissue concentrations and volume and makes inferences about the brain on the basis of differences in tissue classifications [18–20,28]. It is a postprocessing method of morphological images which can provide detailed information relating to changes in gray-white matter composition within the brain, which has been reliably used in psychiatric and neurological studies for many
years [28]. Based on the previous neuroimaging studies in JME, the VBM was performed aiming to investigate thalamic and frontal lobe gray matter abnormalities related to PD in JME patients. We hypothesized that JME would be associated with smaller thalamus and increased frontalobasal and mesiofrontal gray matter and greater alterations in these areas would be observed in JME patients with PD. An exploratory VBM analysis was also performed to investigate possible additional differences in white matter volume (WMV) between controls and JME patients with and without PD.

2. Methods

2.1. Subjects

All patients included in this study were followed up in the outpatient clinic of a tertiary center (Epilepsy Section of the Universidade Federal de São Paulo, São Paulo, Brazil), from July 2005 to July 2007. After the Ethical Committee approval, advantages and risks for participation were explained and informed consent was obtained. The inclusion criteria for the patients’ group were the presence of electroclinical diagnosis of JME based on ILAE classification [2] and having been treated in our unit for at least 6 months. JME patients had typical EEG showing generalized 3–6 Hz spike and wave or poly-spike and wave activity maximum in frontocentral regions. We excluded patients with clinical illnesses besides epilepsy. Caffeine or nicotine use on the day of psychiatric interview, differently from that usually taken, were also considered exclusion criteria.

2.2. Psychiatric evaluation

A clinical and socio-demographic questionnaire including age, gender, schooling, duration of epilepsy, neurological and psychiatric family antecedents, previous psychiatric treatment, type and frequency of seizures, occurrence of status epilepticus, and drug treatment was applied before imaging acquisition. The psychiatric evaluation was performed through two structured questionnaires—Schedule Clinical Interview for DSM, axis I and II (SCID I and SCID II, respectively) [29,30]. These are psychiatric scales based on DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) and on DSM-III-R, respectively, and have been internationally used to evaluate psychiatric disorders. The axis I refers to the evaluation of most psychiatric diseases (e.g., mood, anxiety, and psychotic disorders), while the axis II refers to the evaluation of all types of PD. Each patient could have had more than one psychiatric diagnosis in each axis (I and II).

2.3. Procedures

The MRIs of 16 patients that fulfilled criteria for the diagnosis of cluster B PD only (histrionic, borderline, and passive-aggressive) were compared to 38 patients without any psychiatric diagnosis. The control group consisted of 30 age- and sex-matched healthy volunteers who were also evaluated by the same psychiatrist (GMAF). None of them presented any seizures, antihistamine administration, or alcohol consumption within 72 hours prior to the psychiatric evaluation.

2.4. MRI data acquisition

The MRI examination of the brain was obtained from all subjects using a 1.5 T (Magnetom Sonata [Maestro class] – Siemens AG, Medical Solutions, Erlangen, Germany) using an eight-channel head coil. To minimize variation, the subjects were positioned by the same investigator using the orbito-meatal line as landmark.

Two conventional sequences were performed in order to exclude structural lesions: (a) Axial T2-weighted FLAIR (fluid-attenuated inversion recovery) in a plane parallel to the anterior commissure-posterior commissure (AC-PC) line [TR (repetition time) = 8500 ms, TE (echo time) = 107 ms, IT (inversion time) = 2500 ms, slice thickness = 5.0 mm, slice interval = 1.5 mm, FOV (field of view) = 240 mm, matrix size = 256 × 256, NEX = 1]; (b) Sagittal T1-gradient echo volumetric acquisition for multiplanar reconstruction [TR = 2000 ms, TE = 3.42 ms, flip angle = 15°, FOV = 245 mm, 1.0-mm slice thickness with no gaps, totaling 160 slices per slab, matrix size = 256 × 256, NEX = 1]. All patients and controls had normal images on visual inspection.

2.5. MRI data preprocessing and analysis

The present study employed the VBM5 toolbox (http://dbm.neuro.uni-jena.de), which utilizes and extends the new unified segmentation approach implemented in SPM 5 (Ashburner and Friston, 2005; Wellcome Department of Imaging Neuroscience, London, http://www.fil.ion.ucl.ac.uk/spm), executed in Matlab 7.0. (Mathworks, Sherborn, MA). Unified segmentation provides a generative model of VBM preprocessing that integrates tissue classification, image registration, and MRI inhomogeneity bias correction. The DICOM files (TI images) were converted to NIFTI-1 (http://nifti.nimh.nih.gov) format. The converted files were then segmented into gray and white matter and normalized using the unified model cited above. Voxel values were modulated by the Jacobian determinants derived from the spatial normalization, thus allowing brain structures that had their volumes decreased after spatial normalization to have their total counts decreased by an amount proportional to the degree of volume discounted. The final tissue maps of gray and white matter were modulated with the Jacobian determinants of the deformation parameters obtained by normalization to the Montreal Neurological Institute (MNI) standard space. The final voxel resolution after normalization was 1 × 1 × 1 mm. The obtained gray and white matter images were finally smoothed with a Gaussian filter at full width at half maximum equal to 8 and 12 mm, respectively, and entered in statistical analysis. Additionally, intracranial volume was computed from the sum of gray, white, and cerebrospinal fluid volume and entered as a covariate in the statistical analysis.

2.6. Statistics

Clinical and demographic results were presented as mean ± standard deviation (SD) to define dispersion. Statistical analysis was performed with the following packages: SPSS for Windows 10.01 Standard Version, SPSS Inc., Statistica for Windows 4.2, StatSoft Inc., and STATA Statistics Data Analysis 5, Stata Corporation. Difference between patients and controls with respect to age was assessed using Student’s t test. Comparison of age at seizure onset and duration of epilepsy between patients with and without PD was performed with Student’s t test. The gender distribution, manual dominance, and treatment of epilepsies were examined by Fisher’s exact test. Group differences between JME and healthy controls were compared using one-way analysis of variance (ANOVA) and post hoc analysis with LSD test. Association between the number of positive scores in SCID-II and clinical variables were examined by Pearson coefficient of correlation (r). The level of statistical significance was set at P < 0.05.

By employing the general linear model an analysis of covariance (Ancova) was designed in order to investigate focal GM and WM volume differences between the JME with PD and without PD and healthy controls groups. Total brain volume was entered as a covariate. Statistical significance was set at P < 0.001, uncorrected for multiple comparisons. Small-volume correction (SVC) for
multiple comparisons, using a sphere radius of 3 mm, corresponding to a volume of 100 mm³, was used for regions that had been predicted in advance regions (thalamus, frontobasal, and mesiofrontal regions) and false discovery rate (FDR) correction was used to correct for multiple comparisons in the exploratory gray and white matter analyses. A voxel-level FDR-corrected \( P < 0.05 \) was used as a criterion for significance.

3. Results

3.1. Demographic and clinical data

In the JME group, 16 patients fulfilled criteria for only cluster B PD, while 38 did not have any psychiatric diagnosis. The MRIs of these 54 patients and of 30 healthy controls were analyzed. Groups were homogeneous according to age (\( P = 0.24 \)), gender (\( P = 0.75 \)), and hand dominance (\( P = 0.68 \)). Table 1 shows the demographic data in the three groups.

Comparing the clinical variables of the two JME groups, there were no differences in duration of the disease, age at epilepsy onset, photosensitivity, and the proportion of patients with adequate treatment, which was defined by the use of nonrecommended drugs for this type of epilepsy syndrome, like phenytoin (PHT), carbamazepine (CBZ), oxcarbazepine (OXC), clonazepam (CLB), and phenobarbital (PB).

According to seizure control, patients who presented more than four GTCS per year or more than 15 myoclonus or absences either isolated or in clusters per month were considered to have inadequate control of seizures [31]. The JME group with PD presented significantly more patients with inadequate control of both myoclonic (\( P < 0.007 \)) and absence (\( P < 0.04 \)) seizures. No differences, however, were observed regarding the control of GTCS between the groups (\( P = 0.28 \)). There was a positive correlation between the number of positive scores in SCID-II, an indicator of PD severity, and an inadequate control of myoclonia (\( r = 0.69, P < 0.0001 \)), absence (\( r = 0.52, P < 0.0001 \)), and GTCS (\( r = 0.63, P < 0.0001 \)). This was made comparing the number of positive scores and the degree of control of each type of seizure. Table 2 shows the differences in clinical data.

3.2. VBM analysis

A synopsis of all regions in which significant differences were found is seen in Tables 3 and 4. The differences were represented by two types of comparisons, which were JME patients versus controls and JME patients with PD versus JME patients without PD, as follows.

3.2.1. JME patients versus controls

There were gray matter volume (GMV) reductions in left (\( P = 0.01 \)) and right (\( P < 0.001 \)) thalamus in JME patients when compared with controls. A significant GMV reduction was also observed in left (\( P = 0.006 \)) and right (\( P = 0.006 \)) insula and in left (\( P = 0.006 \)) and right (\( P = 0.006 \)) cerebellar hemispheres in JME patients. In addition, GMV increases in right superior (\( P < 0.001 \)) and in right medial (\( P = 0.001 \)) frontal gyri were observed in the JME patient group when compared with controls. The exploratory

### Table 1
Demographic data of both juvenile myoclonic epilepsy groups and controls.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>JME without PD</th>
<th>JME with PD</th>
<th>Control group</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>38 (45.2%)</td>
<td>16 (19.0%)</td>
<td>30 (35.8%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>27.1 ± 9.5</td>
<td>28.3 ± 8.2</td>
<td>30.1 ± 9.0</td>
<td>0.23</td>
</tr>
<tr>
<td>Gender (females)</td>
<td>18 (47.3%)</td>
<td>9 (56.3%)</td>
<td>14 (46.7%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Number of right-handed</td>
<td>32 (84.5%)</td>
<td>15 (93.8%)</td>
<td>28 (93.3%)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

JME, juvenile myoclonic epilepsy; PD, personality disorder.

### Table 2
Clinical data of patients with juvenile myoclonic epilepsy with and without personality disorder

<table>
<thead>
<tr>
<th>Clinical data</th>
<th>JME without PD</th>
<th>JME with PD</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>38</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Duration of disease</td>
<td>13.3 ± 9.6</td>
<td>15.4 ± 8.1</td>
<td>0.68</td>
</tr>
<tr>
<td>Age at epilepsy onset</td>
<td>12.3 ± 5.0</td>
<td>13.4 ± 3.1</td>
<td>0.31</td>
</tr>
<tr>
<td>Adequate treatment</td>
<td>32 (84.2%)</td>
<td>15 (93.8%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>11 (28.9%)</td>
<td>6 (37.5%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Inadequate control of myoclonia</td>
<td>3 (7.3%)</td>
<td>7 (43.8%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Inadequate control of absences</td>
<td>2 (4.9%)</td>
<td>5 (31.3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Inadequate control of GTCS (%)</td>
<td>3 (7.3%)</td>
<td>4 (25%)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

JME, juvenile myoclonic epilepsy; PD, personality disorder; GTCS, generalized tonic-clonic seizures.

### Table 3
Voxel-based morphometry evaluation of gray matter regions; \( P \) and \( Z \) scores corresponding to significant group effects.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI coordinates</th>
<th>( P_{uncorrected} )</th>
<th>( P_{corrected} )</th>
<th>( Z ) score</th>
<th>Ke</th>
</tr>
</thead>
<tbody>
<tr>
<td>JME patients &lt; controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right insula</td>
<td>42; -9.6</td>
<td>&lt;0.0001</td>
<td>0.006*</td>
<td>4.14</td>
<td>981</td>
</tr>
<tr>
<td>Left insula</td>
<td>-39; -21.9</td>
<td>&lt;0.0001</td>
<td>0.006*</td>
<td>4.04</td>
<td>476</td>
</tr>
<tr>
<td>Left thalamus</td>
<td>12; -28.9</td>
<td>&lt;0.0001</td>
<td>&lt;0.001*</td>
<td>3.86</td>
<td>61</td>
</tr>
<tr>
<td>Right thalamus</td>
<td>-12; -29.10</td>
<td>&lt;0.0001</td>
<td>0.001*</td>
<td>3.52</td>
<td>42</td>
</tr>
<tr>
<td>Right cerebellar hemisphere</td>
<td>28; -82; -32</td>
<td>&lt;0.0001</td>
<td>0.006*</td>
<td>4.35</td>
<td>38209</td>
</tr>
<tr>
<td>Left cerebellar hemisphere</td>
<td>-29; -70; -50</td>
<td>&lt;0.0001</td>
<td>0.006*</td>
<td>3.95</td>
<td>38209</td>
</tr>
<tr>
<td>JME patients &gt; controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right superior frontal gyrus</td>
<td>21.62; 15</td>
<td>&lt;0.0001</td>
<td>&lt;0.001*</td>
<td>3.86</td>
<td>183</td>
</tr>
<tr>
<td>Right medial frontal gyrus</td>
<td>8.37; -16</td>
<td>&lt;0.0001</td>
<td>0.001*</td>
<td>3.34</td>
<td>17</td>
</tr>
<tr>
<td>JME without PD &gt; JME with PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right thalamus</td>
<td>-12; -29.13</td>
<td>&lt;0.0001</td>
<td>&lt;0.001*</td>
<td>3.20</td>
<td>19</td>
</tr>
<tr>
<td>JME without PD &lt; JME with PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right middle frontal gyrus</td>
<td>13.1; 60</td>
<td>&lt;0.0001</td>
<td>&lt;0.001*</td>
<td>3.69</td>
<td>58</td>
</tr>
<tr>
<td>Left middle frontal gyrus</td>
<td>-34.5; 48</td>
<td>&lt;0.0001</td>
<td>0.002*</td>
<td>3.42</td>
<td>42</td>
</tr>
<tr>
<td>Right orbitofrontal gyrus</td>
<td>10.14; -19</td>
<td>&lt;0.0001</td>
<td>0.004*</td>
<td>3.52</td>
<td>34</td>
</tr>
</tbody>
</table>

JME, juvenile myoclonic epilepsy; PD, personality disorder; \( Z \) score, difference in number of standard deviations; Ke, voxel extent threshold.

\* \( P_{uncorrected} < 0.05 \).

\* \( P_{corrected} < 0.05 \).
white matter analysis showed a significant reduction of left \((P = 0.03)\) and right \((P = 0.03)\) cerebellar hemispheres in the group of JME patients.

3.2.2. JME patients with PD versus JME patients without PD

There was a significant reduction of GMV in right thalamus \((P < 0.001)\) when JME patients with PD were compared with JME without PD (Fig. 1). In addition, there were GMV increases in left \((P = 0.002)\) and right \((P < 0.001)\) middle frontal gyrus in the JME with PD group. There was also a GMV increase in the right orbitofrontal cortex (OFC) of JME patients with PD compared to JME without PD \((P = 0.004)\) (Fig. 2). A significant reduction of the posterior corpus callosum (CC) region in the JME with PD group when compared with JME without PD was also observed \((P = 0.04)\) in the white matter analysis.

4. Discussion

The aim of this study was to perform a controlled investigation of possible structural abnormalities between a group of patients with JME and cluster B PD and JME patients without any psychiatric diagnosis treated in a tertiary center using the VBM approach. The healthy control group from the general population was performed observing specific pairing criteria in order to make all the comparisons reliable. We also aimed to correlate the data to a number of clinical variables, such as seizure type and frequency,

**Table 4**

Voxel-based morphometry evaluation of white matter regions; \(P\) and \(Z\) scores corresponding to significant group effects.

<table>
<thead>
<tr>
<th>Region</th>
<th>MNI coordinates</th>
<th>(P_{\text{uncorrected}})</th>
<th>(P_{\text{corrected}})</th>
<th>(Z) score</th>
<th>Ke</th>
</tr>
</thead>
<tbody>
<tr>
<td>JME patients &lt; controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left cerebellar hemisphere</td>
<td>(-15; -66; -32)</td>
<td>(&lt;0.001)</td>
<td>0.03({}^\dagger)</td>
<td>4.22</td>
<td>4260</td>
</tr>
<tr>
<td>Right cerebellar hemisphere</td>
<td>(14; -63; -32)</td>
<td>(&lt;0.001)</td>
<td>0.03({}^\dagger)</td>
<td>3.69</td>
<td>3752</td>
</tr>
<tr>
<td>JME with PD &lt; JME without PD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus callosum (posterior region)</td>
<td>(5; -27; 23)</td>
<td>(&lt;0.001)</td>
<td>0.04({}^\dagger)</td>
<td>3.76</td>
<td>5837</td>
</tr>
</tbody>
</table>

JME, juvenile myoclonic epilepsy; PD, personality disorder; \(Z\) score, difference in number of standard deviations; Ke, voxel extent threshold.

\({}^\dagger\) FDR < 0.05.

Fig. 1. Bilateral thalamic volume reductions in juvenile myoclonic epilepsy patients with personality disorders.

Fig. 2. Sagittal view (a and b). Right mesiosuperior frontal volume increase in juvenile myoclonic epilepsy patients with personality disorders. Axial view (c and d). Right orbitofrontal volume increase in juvenile myoclonic epilepsy patients with personality disorders.
number and types of AED, and duration of epilepsy. To the best of our knowledge this is the first study using a combined analysis of VBM and psychiatric evaluation to investigate personality traits in JME.

Contrary to the concept that there are no neuroimaging abnormalities in IGE patients, investigations using MRI and MRS have demonstrated the presence of structural and functional alterations among JME patients, particularly in thalami and frontal lobes [18–20,32–34]. Controlled structural MRI studies in JME using the techniques of volumetry and VBM have suggested frontal GMV increase in the superior mesiofrontal and frontotemporal regions, as well as GMV reduction in thalami [18–20,33,34]. These abnormal regions, as the literature has already emphasized, correspond to the thalamocortical circuitry related to the pathophysiology of JME, which involves the thalamus and the cortical mesiofrontal regions [16]. To support this hypothesis, neuropathological studies involving IGE patients have shown the presence of minimal malformations of cortical development called microdysgenesis, with varying regional distribution in gray and white matter and have attributed its participation in the pathophysiology of this type of epilepsy [35,36]. In the present study we have observed such thalamic and frontal structural alterations in patients with JME when compared with controls. In addition, we also observed more accentuated thalamic and frontal abnormalities in the JME with PD group in comparison to JME patients without PD. Such differences particularly present on the right side could be explained by differences in gray matter volumes between both cerebral hemispheres. Frontal gray matter volumes have been shown to be higher in the right hemisphere in human brain, which would generally be associated with higher metabolite concentrations. Functional MRI studies have already suggested lower concentrations of all metabolites in the left side when right-left comparisons are made [37,38].

Different types of anxiety and mood disorders, like generalized anxiety disorder (GAD), phobias, major depression, dysthymia, and somatization disorders have been described as psychiatric comorbidities in JME [11–14]. We previously found a general prevalence of 49% of PD among 100 JME patients [14], including 17% of mild to moderate cluster B PD (histrionic, borderline, and passive-aggressive), clinically characterized by a marked impulsivity, mood reactivity, and immaturity, and difficulty to accept social rules [14,39]. The association between JME and some personality traits had previously been suggested in the pivotal description of Janz and Christian in 1957 being characterized by emotional instability and immaturity, unsteadiness, lack of discipline, hedonism, frequent and rapid mood changes, and indifference toward the disease [3–9]. Clinical and electroencephalographical studies have referred to these characteristics as “typical” traits and “psychiatric symptoms” [40–42]. Thus, the description of symptoms and clinical manifestations provided by authors in the past in JME [6–9,40–42] could correspond to the cluster B PD described in modern psychiatric nosography [39], since these patients share almost the same behavioral characteristics noted above. These manifestations may possibly be related to some degree of frontal lobe impairment, considering the descriptions of similar behavioral abnormalities in patients with different types of frontal lobe injuries [15,16] and evidence of frontal lobe involvement in the pathophysiology of JME [18–22].

The critical role of frontobasal structures and prefrontal regions in several psychiatric disorders such as schizophrenia, depression, and cluster B PD is already known [43]. The OFC, an important subdivision of the prefrontal cortex, is connected with structures directly involved in emotional processing, such as the hippocampal formation and amygdala. Functional neuroimaging studies have suggested that OFC is related to the formation of associations between emotions and cognition [43]. This region also plays a critical role in the regulation of mood reactivity and impulsivity, possibly exercising a modulating effect in other frontal regions related to motor functions [43]. Structural MRI studies have already demonstrated abnormalities of OFC volume in patients with cluster B PD, suggesting a possible role of this region, added to other fronto-limbic structures such as cingulum, amygdale, and hippocampus in the pathophysiology of cluster B PD [44–47]. In this study we observed structural abnormalities in OFC in the JME with PD group when compared with JME patients without PD. Psychiatric effects of AEDs are recognized to be of importance in predisposing to or protecting against psychiatric disorders, which may be predictable based on the patient’s preexisting mental status [48]. The mechanisms that are possibly involved in the pathogenesis of these adverse events are pharmacodynamic problems associated with polytherapy, dosage-related toxic effects, dosage-unrelated idiosyncratic effects in predisposed patients, and effects related to efficacy of treatment, like forced normalization and drug withdrawal [48]. While emotional liability, depression, and psychosis have been associated with TPM and PB, few psychiatric side effects have been seen with VPA or LTG, which have been successfully used in treating psychiatric syndromes, such as mood and anxiety disorders [48–50]. In our study there were no differences in the proportion of patients with adequate AED treatment in both JME groups. We also found no differences regarding the number or type of AED used; however, there was a high number of patients taking VPA in both groups, which made this comparison less reliable.

The GMV in the insula was reduced in JME patients when compared to controls, without any differences when both JME groups were compared. Literature data have already shown the connection of insula to several cortical areas, and a possible insular involvement in focal and generalized epilepsies [51]. Exploratory VBM analysis also showed significant structural alterations of WM in the CC and cerebellum in the group of JME patients. The CC is a major interhemispheric connection pathway and the primary white matter tract in the brain [33]. Reductions in callosal area, an indicator of the degree of white matter lesion and/or the number of crossing axons, could be a structural marker of disruptions in connectivity already impaired among cluster B PD [46,47]. Impaired structural interhemispheric connectivity could possibly lead to poor integration of neural networks that, in turn, is linked to impulsivity and emotional instability [44–47]. Cerebellum involvement in epilepsy has already been emphasized in the literature, since this structure has connections with a large number of afferent and efferent neurological tracts [52,53].

In conclusion, the present study observed GMV alterations in JME patients, particularly in thalami, mesiofrontal, and frontotemporal regions. Such findings, which were more intense in the JME with PD group, are concordant with previous structural and functional JME neuroimaging studies [18–25]. In patients with JME and PD, we also found significant structural abnormalities of the OFC, highlighting the involvement of this structure in the regulation of mood reactivity, impulsivity, and social behavior [43], which has been considered dysfunctional in patients with cluster B PD [44–47]. These data support the hypothesis that those “typical personality traits” found in JME, which correspond to cluster B PD in the modern psychiatric nosography, might represent a more severe form of thalamic and frontal lobe dysfunction as an underlying mechanism of epilepsy generation [16,23–27], consequently producing neurological dysfunction and PD [14,17,26]. More studies involving neuroimaging and psychiatric evaluation in JME are therefore highly encouraged.

Acknowledgments

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References
Provocative and inhibitory effects of a video-EEG neuropsychologic protocol in juvenile myoclonic epilepsy

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SUMMARY

Purpose: Studies suggest that higher cognitive functions could precipitate seizures in juvenile myoclonic epilepsy (JME). The present study aimed to analyze the effects of higher mental activity on epileptiform discharges and seizures in patients with JME and compare them to those of habitual methods of activation. Methods: Seventy-six patients with JME (41 female) underwent a video-EEG (electroencephalography) neuropsychologic protocol (VNPP) and habitual methods of activation for 4–6 h. Results: Twenty-nine of the 76 (38.2%) presented provocative effect, and inhibition was seen in 28 of 31 (90.3%). A mixed effect was observed in 11 (35.5%), and 30 patients (39.5%) suffered no effect of VNPP. Action-programming tasks were more effective than thinking in provoking epileptiform discharges (23.7% and 11.0% of patients, respectively, \( p = 0.03 \)). Inhibitory effect was observed equally in the various categories of tasks, except in mental calculation, which had a higher inhibitory rate. Habitual methods of activation were more effective than VNPP in provoking discharges. Anxiety disorders were diagnosed in 24 of 58 patients (41.4%); anxious patients had greater discharge indexes and no significant inhibitory effect on VNPP. Discussion: Praxis exerted the most remarkable provocative effect, in accordance with the motor circuitry hyperexcitability hypothesis in JME. Inhibitory effect, which had no such task specificity, might be mediated by a widespread cortical–thalamic pathway, possibly involving the parietal cortex. The frequent inhibitory effect found under cortical activation conditions, influenced by the presence of anxiety, supports nonpharmacologic therapeutic interventions in JME. KEY WORDS: Idiopathic generalized epilepsy, Reflex epilepsy, Precipitant factors, Activation methods.

Juvenile myoclonic epilepsy (JME) is the most common age-related idiopathic generalized epilepsy (IGE), corresponding to 5–11% of all epilepsies (Panayiotopoulos et al., 1991). It is characterized by myoclonic jerks, generalized tonic–clonic seizures (GTCS), and absences (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). Bilateral spike or polyspike-wave complexes of 4–6 Hz, more often asymmetric, on a normal background, are the typical electroencephalography (EEG) findings (Panayiotopoulos et al., 1991). Patients with JME frequently recognize that sleep deprivation, fatigue, alcohol intake, stress, and flashing lights may act as precipitant factors for their seizures (Clement & Wallace, 1988; Panayiotopoulos et al., 1991; Oguni et al., 1994; Pedersen & Petersen, 1998; Waltz, 2000; Da Silva Sousa et al., 2005a). Beyond these general factors, some patients report other precipitant factors: being sensitive to situations in which they are obliged to consider complicated spatial tasks in a sequential fashion, specifically with the intention of decision making; and responding practically by using a part of their bodies under stressful circumstances. These were conceptualized as...
praxis induction (Inoue et al., 1994) and include ideation and execution of elaborated movements involving a sequential spatial process such as arithmetic, playing cards and sequential games, drawing, writing, and finger manipulation in more elaborated tasks or those of constructive character. In addition, reflex seizures have been identified during reading and speaking as perioral myoclonia, especially in patients with JME (Mayer et al., 2006).

Neuropsychological methods of EEG activation have been used by groups from Japan (Matsuoka et al., 2000), Germany (Mayer et al., 2006), Italy (Chifari et al., 2004), and Greece (Karachristianou et al., 2004) as an auxiliary method to identify specific seizure patterns in various epileptic syndromes. Some studies suggest that JME would be the most sensitive epileptic syndrome to this form of cognitive activation (Matsuoka et al., 1988, 2000; Senanayake, 1992; Chifari et al., 2004; Karachristianou et al., 2004; Da Silva Sousa et al., 2005b; Mayer et al., 2006).

The aim of this study was to assess the effect of a video-EEG neuropsychological protocol (VNPP), whether precipitant or inhibitory, on epileptiform discharges and seizures in patients with JME, and to compare the effect of this protocol with those of habitual methods of activation.

**METHODS**

Seventy-six patients (41 female) with JME underwent VNPP at the Epilepsy Unit of the Hospital São Paulo, Universidade Federal de São Paulo, São Paulo, Brazil. After ethical committee approval, advantages and risks for participation were explained and written informed consent was obtained. Inclusion criteria were age over 12 years, clinical and electroencephalographic features of JME, and a minimum of 4 years of formal education. Clinical signs of antiepileptic drug (AED) intoxication, occurrence of a GTCS, and use of intravenous AED within the last 72 h were exclusion criteria.

Fifty-eight of the 76 patients were submitted to psychiatric evaluation. To assess patients older than 18 years, Schedule Clinical Interview for DSM-IV, Axes I and II (SCID-I and SCID-II) were performed, and the Brazilian version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS-PL) was used to assess those 18 years old or younger. Because of its high prevalence and the potential role of stress as a trigger of seizures in JME, only anxiety disorders were investigated, and patients were divided in to anxious and nonanxious groups. This division was based upon current anxiety disorders, as opposed to lifetime history of anxiety disorders. All patients presented normal physical and neuropsychological examinations, as well as normal routine blood tests. Forty patients had a 1.5T magnetic resonance imaging (MRI) of the brain, and all had normal results.

Video-EEG was recorded on a 32-channel digital equipment (Ceegraph software, Bio-Logic Systems Corp., Mundelein, IL, U.S.A.) using the 10–20 International Electrode System, in addition to perioral and deltoid electrodes.

Our protocol was based on those reported by Matsuoka et al. (2000) and Mayer and Wolf (2004) and will be referred to as VNPP. After having slept for at least 6 h, all patients were submitted to 30-min awake video-EEG recording starting at 7 a.m. Medications were maintained in all treated patients. Sixty-seven were treated with AED at the time of the examination and nine were not. Among the treated patients, therapeutic scheme was considered appropriate in 49 (73.1%) and inappropriate in 18 (26.9%). As appropriate treatment we included valproate, phenobarbital, benzodiazepines, lamotrigine, and topiramate, in monotherapy or in different combinations. Treatment with carbamazepine, oxcarbazepine, or phenytoin was considered inappropriate.

The VNPP and habitual methods of activation were performed as described in Table 1 and lasted 4–6 h. Video-EEG was registered during lunchtime and postprandial sleep. Upon awakening, patients were submitted to 5-min hyperventilation (HV) and intermittent photic stimulation (IPS).

When a task induced epileptiform discharges or seizures, reproducibility was confirmed by retriial of the same or a modified task. According to the effect of induction or inhibition of discharges, four groups were identified: (1) provocative effect, when there was induction of

**Table I. Video-EEG protocol**

<table>
<thead>
<tr>
<th>Task</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recording of background activity, awake, for 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes opened/closed (5 min)</td>
<td></td>
<td></td>
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<tr>
<td>Reading a Portuguese text (patients read the same sentences aloud that they had read silently); this was a medical text describing seizures</td>
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<td></td>
</tr>
<tr>
<td>10 min silently</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min aloud</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading an English text</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min silently</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min aloud</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Speaking aloud for 5 min (patients described their seizures, their lives, and the impact of epilepsy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Writing for 5 min (patients were asked to write about their seizures)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental calculation: subjects responded aloud with answers to four arithmetic problems (18 – 7, 23 + 46, 11 × 11, 125 + 5); when calculation was difficult, an easier problem was presented</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Written calculation: patients responded in writing to one arithmetic problem (15 × 67 × 23 × 48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drawing: patients were instructed to draw a family, a house, and a clock showing quarter to four</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial construction:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients performed a sequence of tasks, for 10 min each: Rubik’s cube, Jenga tower, Conundrum’s cube, Pyramid puzzle, Hanoi tower</td>
<td></td>
<td></td>
</tr>
<tr>
<td>For 5 min they reproduced a figure with matchstick pattern and for 1 min, plastic models</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photic stimulation for 5 min (flashes 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 30, 33, 50, and recovered)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperventilation for 5 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
discharges; (2) inhibitory effect, when there was reduction; (3) mixed effect, when there was provocative effect in a determined category of task and inhibitory effect in another; and (4) no effect.

The same criteria defined by Matsuoka et al. (2000) were used in the EEG analysis: When no discharge was found on the awake EEG, “a provocative effect” meant that one or more tasks induced paroxysmal discharges and its reproducibility was confirmed by retrial. No discharges either in the awake or in the task EEG was judged as “no effect.” When epileptiform discharges were found on the awake EEG, the discharge index was calculated for each task as follows: The number of discharges per recording time (number/minute) during each task condition was divided by the frequency (number/minute) during awake recording. Discharge indexes greater than 2.0 were considered as “provocative effect”; below 0.5 as “inhibitory effect”; and between 0.5 and 2.0 as “no effect” (Matsuoka et al., 2000). Reproducibility was always mandatory to exclude contamination of incidental seizures or discharges.

In VNPP, the different modalities of tasks were categorized according to Matsuoka et al. (2005) in two groups: action-programming (reading aloud, speaking, writing, written calculation, drawing, and spatial construction) and thinking (reading silently and mental calculation). In each of these groups, we considered tasks to be related to spatial (mental and written calculation, drawing, and spatial construction) or linguistic (reading aloud and silently, speaking, and writing) functions.

When both inhibitory and provocative effects were observed in different tasks within the same group, a mean of discharge indexes on each task was performed using the z-test for single means. Indexes of anxious and nonanxious patients were compared using Student’s t-test. The criterion for statistical significance was \( p < 0.05 \).

### Results

At the time of VNPP the mean age was 24.3 ± 8.33 years (range 12–53 years) and duration of epilepsy 11.3 ± 8.85 (range 1–38); 54 patients (71.0%) had a positive family history of epilepsy, being JME in 9 (11.8%). Demographic and clinical data are in Table 2.

#### Video-EEG neuropsychological protocol effect

Awake EEG was normal in 45 (59.2%) and showed epileptiform discharges in 31 (40.8%), consisting of spike and polyspike-wave complexes. Seizures were observed in 31 patients (40.8%): myoclonia in 23 (74.2%), absences in 16 (51.6%), and GTCS in 4 (12.9%). Myoclonia were observed during VNPP in 13 patients, HV in 7, and IPS in 5. Among those patients with myoclonic seizures, four presented perioral reflex myoclonia during speaking or reading aloud, in two of them accompanied by reflex limb myoclonia during action-programming tasks. Absences were observed in 16, during HV in 12, VNPP in 3, and IPS in one. GTCS were observed in four patients: one during resting, two during habitual methods of activation (somnolence and HV), and the last during spatial construction tasks of the VNPP.

Twenty-nine of the 76 patients (38.2%) presented provocative VNPP effect in at least one task. The rate of provocative effect was similar in patients with paroxysms in the awake EEG (14 of 31, 45.2%) and in those without (15 of 45, 33.3%; \( p = 0.34 \)). Among the former, 11 (35.5%) also had inhibitory effect in another task, thus considered as having a mixed effect. Inhibitory effect was seen in 28 of 31 (90.3%) patients with epileptiform discharges on awake EEG. Thirty of the 76 patients (39.5%) had no effect (Table 3).

Regarding treatment there was no difference among appropriately, inappropriately, and nontreated patients in VNPP effects, both in those with discharges in awake EEG and in the group without (Table 4). The mean discharge rate in awake EEG was similar in the three treatment groups: 0.21 ± 0.25, 0.17 ± 0.25, and 0.23 ± 0.33 discharges/min, respectively (\( p = 0.91 \)).

As for seizure control, VNPP effects were similar for groups with and without persistent seizures (Table 4). There was no difference in discharge rate in awake EEG for these two groups: 0.10 ± 0.42 and 0.25 ± 0.37 discharges/min, respectively (\( p = 0.13 \)).

---

Table 2. Demographic and clinical data of 76 patients with juvenile myoclonic epilepsy

<table>
<thead>
<tr>
<th>Data Category</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (46.1)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (53.9)</td>
</tr>
<tr>
<td>Schooling</td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>27 (35.5)</td>
</tr>
<tr>
<td>Secondary</td>
<td>40 (52.6)</td>
</tr>
<tr>
<td>University level</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Antiepileptic therapy</td>
<td></td>
</tr>
<tr>
<td>Without antiepileptic drugs</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Appropriate treatment</td>
<td>49 (64.5)</td>
</tr>
<tr>
<td>Inappropriate treatment</td>
<td>18 (23.7)</td>
</tr>
<tr>
<td>Type of seizures</td>
<td></td>
</tr>
<tr>
<td>Only myoclonia</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Myoclonia + generalized tonic-</td>
<td></td>
</tr>
<tr>
<td>clonic</td>
<td>41 (54.0)</td>
</tr>
<tr>
<td>Myoclonia + generalized tonic-</td>
<td></td>
</tr>
<tr>
<td>clonic + absences</td>
<td>32 (42.1)</td>
</tr>
<tr>
<td>Myoclonia + absences</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Seizure control</td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>23 (30.3)</td>
</tr>
<tr>
<td>Noncontrolled</td>
<td>53 (69.7)</td>
</tr>
</tbody>
</table>

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Epilepsia, **(**)**:1–10, 2009
The effects obtained in the two categories of tasks (action-programming and thinking), subdivided into four subcategories (action-programming linguistic, action-programming spatial, thinking linguistic, and thinking spatial) are depicted in Fig. 1.

Action-programming tasks were more effective than thinking tasks in provoking discharges (23.7% and 11.0% of patients, respectively, p = 0.03). No difference was observed between linguistic and spatial tasks in both categories (18.7% and 21.1% of patients, respectively, p = 0.43).

Inhibitory effect was more frequently observed than provocative effect. However, no difference was observed either between action-programming and thinking (p = 1.00) or between spatial and linguistic categories (p = 0.31). When comparing the four subcategories, thinking spatial (represented by mental calculation task) more often exerted inhibitory effect than the other three subcategories (p = 0.02). This subcategory showed inhibitory effect in 18 of 27 (66.7%) of the patients (mean discharge index 0.57 ± 1.07).

### Video-EEG neuropsychologic protocol effect according to categories of tasks

The effects obtained in the two categories of tasks (action-programming and thinking), subdivided into four subcategories (action-programming linguistic, action-programming spatial, thinking linguistic, and thinking spatial) are depicted in Fig. 1.

Action-programming tasks were more effective than thinking tasks in provoking discharges (23.7% and 11.0% of patients, respectively, p = 0.03). No difference was observed between linguistic and spatial tasks in both categories (18.7% and 21.1% of patients, respectively, p = 0.43).

Inhibitory effect was more frequently observed than provocative effect. However, no difference was observed either between action-programming and thinking (p = 1.00) or between spatial and linguistic categories (p = 0.31). When comparing the four subcategories, thinking spatial (represented by mental calculation task) more often exerted inhibitory effect than the other three subcategories (p = 0.02). This subcategory showed inhibitory effect in 18 of 27 (66.7%) of the patients (mean discharge index 0.57 ± 1.07).

### Table 3. Video-EEG neuropsychological protocol effects

<table>
<thead>
<tr>
<th>VNPP effect</th>
<th>Provocative</th>
<th>Mixed</th>
<th>Inhibitory</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA absent</td>
<td></td>
<td>15 (33.3)</td>
<td>–</td>
<td>30 (66.7)</td>
<td>45</td>
</tr>
<tr>
<td>DA present</td>
<td>3 (9.7)</td>
<td>11 (35.5)</td>
<td>17 (54.8)</td>
<td>0 (0.0)</td>
<td>31</td>
</tr>
<tr>
<td>MDI</td>
<td>1.10 ± 1.174 (p = 0.483)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>11</td>
<td>17</td>
<td>30</td>
<td>76</td>
</tr>
</tbody>
</table>

Values expressed in parentheses are %.

DA, discharges in awake EEG; MDI, mean of discharge indexes (mean ± SD).

*Z-test for single means = 1 (one-tailed), representing comparison between the mean and a preestablished value (μ0), in this case μ0 = 1.

### Table 4. Effects of Video-EEG neuropsychological protocol according to treatment and seizure control. The mean of discharge indexes in each subgroup is compared to the awake value equal to 1 and to each other

<table>
<thead>
<tr>
<th>VNPP effect</th>
<th>Provocative</th>
<th>Mixed</th>
<th>Inhibitory</th>
<th>None</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without antiepileptic drugs</td>
<td>2 (40.0)</td>
<td>–</td>
<td>–</td>
<td>3 (60.0)</td>
<td>5</td>
<td>0.676</td>
</tr>
<tr>
<td>Appropriate treatment</td>
<td>10 (30.3)</td>
<td>–</td>
<td>–</td>
<td>23 (66.7)</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Inappropriate treatment</td>
<td>3 (42.9)</td>
<td>–</td>
<td>–</td>
<td>4 (57.1)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>DA present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without antiepileptic drugs</td>
<td>1 (25.0)</td>
<td>0 (0.0)</td>
<td>3 (75.0)</td>
<td>0 (0.0)</td>
<td>4</td>
<td>0.224</td>
</tr>
<tr>
<td>MDI</td>
<td>0.46 ± 0.683 (p = 0.106)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appropriate treatment</td>
<td>2 (12.5)</td>
<td>5 (31.3)</td>
<td>9 (52.2)</td>
<td>0 (0.0)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>MDR</td>
<td>1.12 ± 1.393 (p = 0.364)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate treatment</td>
<td>0 (0.0)</td>
<td>6 (54.5)</td>
<td>5 (45.5)</td>
<td>0 (0.0)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td>1.04 ± 0.973 (p = 0.444)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA absent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>5 (25.0)</td>
<td>–</td>
<td>–</td>
<td>15 (75.0)</td>
<td>20</td>
<td>0.230</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>10 (40.0)</td>
<td>–</td>
<td>–</td>
<td>15 (60.0)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>DA present</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0 (0.0)</td>
<td>3</td>
<td>0.308</td>
</tr>
<tr>
<td>MDR</td>
<td>1.21 ± 1.051 (p = 0.380)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>2 (7.1)</td>
<td>10 (35.7)</td>
<td>16 (57.2)</td>
<td>0 (0.0)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>MDI</td>
<td>0.99 ± 1.203 (p = 0.478)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values expressed in parentheses are %.

DA, discharges in awake EEG; MDI, mean of discharge indexes (mean ± SD); MDR, mean discharge rate *Z-test for single means = 1 (one-tailed).
6.3%; and English 5 of 64, 7.8%), and mental calculation 5 of 66 (7.6%).

Habitual methods of activation

The mean discharge rate during sleep (0.73 ± 1.43) was higher than that during awake EEG (0.20 ± 0.39; p = 0.001). Sleep activated discharges in 36 of 62 (58.0%) and inhibited in 2 patients.

HV was effective in activating discharges in 27 of 70 (38.6%; discharge rate mean 0.58 ± 1.14; p = 0.001) and in inhibiting in 2 patients. Photosensitivity was present in 19 of 64 patients (29.7%). Eye closure sensitivity was observed in 13 patients (21.3%), 8 of whom (14.6%) were also photosensitive (Table 5).

Comparison between video-EEG neuropsychological protocol and habitual methods of activation effects

Discharge indexes were higher in habitual methods of activation than in VNPP tasks (sleep p = 0.018, HV p < 0.001), as shown in Table 5 and Fig. 3. No difference was observed in VNPP effect between photosensitive and nonphotosensitive patients (Table 6).

Photosensitive patients were younger than nonphotosensitive. The mean age for each group was 20.4 ± 6.32
and 26.4 ± 8.98 years, respectively (p = 0.01). On the other hand, a correlation between VNPP effects and age was not observed. Patients who had provocative effect of VNPP (22.4 ± 6.92 years) were of a similar age when compared to those without VNPP effect (23.1 ± 7.04) and to patients with inhibitory effects (28.1 ± 11.36, p = 0.09).

**Psychiatric evaluation and discharge indexes**

Anxiety disorders were diagnosed in 24 of 58 patients (41.4%). Twenty-three had generalized anxiety disorder and one had obsessive-compulsive disorder. Regarding the presence of discharges in the awake EEG, there was no difference between anxious (11 of 24, 45.8%) and nonanxious patients (11 of 34, 32.4%; p = 0.41). In addition, there were no differences between these two groups in the mean of discharge indexes in VNPP. However, in all tasks except writing, there was a tendency to greater discharge indexes in anxious patients (Fig. 3).

Although the anxious group had no significant inhibitory VNPP effect in any task, the nonanxious group had inhibition in mental calculation, a thinking spatial task (0.19 ± 0.56; p = 0.001), and in action-programming spatial tasks (0.62 ± 0.64; p = 0.04). Considering individual tasks, the nonanxious group had significant inhibitory effect when doing mental calculation (0.19 ± 0.56; p = 0.001), speaking (0.28 ± 0.56; p = 0.003), spatial construction (0.31 ± 0.65; p = 0.003), and reading English silently (0.63 ± 0.60; p = 0.035). Mental calculation was the only VNPP task exerting inhibitory effect when both groups of JME patients were analyzed together (0.57 ± 1.07; p = 0.02).

**DISCUSSION**

Reflex seizures and epileptiform discharges induced by higher mental function in JME patients have been reported in a few studies (Matsuoka et al., 1988; Senanayake, 1992; Matsuoka et al., 2000; Karachristianou et al., 2004; Mayer & Wolf, 2004; Matsuoka et al., 2005; Mayer et al., 2006). As photosensitivity and eye closure sensitivity, they suggest the presence of regional hyperexcitability and raise questions about the strict concept of JME as an IGE (Wolf & Mayer, 2000; Inoue & Zifkin, 2004; Inoue, 2007).

Among cognitive tasks, linguistic operations and decision-making associated with visuospatial manipulation are the best-characterized triggers (Ritaccio et al., 2002). Matsuoka et al. (2000) reported induction of discharges by cognitive activities almost exclusively in IGE (36 of 38 patients), particularly JME (22 of 36).

We found a VNPP provocative effect in at least one task in 29 of 76 patients (38.2%), a rate much inferior to that described in smaller series such as 21 of 25 (84%) of treated (Matsuoka et al., 1988) and 23 of 30 (76.6%) of non-treated (Karachristianou et al., 2004) JME patients. However, it was closer to 22 of 45 (48.8%) of JME patients reported by Matsuoka et al. (2000).

The rate we found was neither dependent on treatment nor on seizure control. The lack of influence of these factors over the provocative effect might indicate that it is a true reflex trait. According to this idea, two JME patients were reported to remain sensitive to neuropsychological provocative tasks for more than 20 years, indicating that this feature was not transitory (Matsuoka et al., 2002). Indeed, we found no correlation between sensitivity to VNPP provocative effect and age. This did not hold true in relation to photosensitivity, as the mean age was lower in the photosensitive group.

In our series, action-programming tasks were more effective than thinking in exerting provocative effect. This is in accordance with previous reports of Matsuoka et al. (2000, 2005) who also found action-programming as the most crucial provocative task category. In their series, among 38 patients who had EEG discharges activation by neuropsychological tasks, 32 (84.2%), had this effect by action-programming and only 4 (10.5%) by thinking.

On the other hand, in our series, the provocative effect of linguistic and spatial tasks was similar (p = 0.84). Eighteen patients had activation of discharges by action-programming tasks, linguistic in 14 (77.8%), and spatial in 15 (83.3%). These numbers also equal those of Matsuoka et al. (2005), who, within the action-programming category, found 33 of 36 activations (91.7%) by linguistic subtype and 30 of 36 (83.3%) by spatial tasks.

**Table 5. Discharge indexes in habitual methods of activation. The mean of discharge indexes in sleep and hyperventilation was compared to the awake value; photosensitivity and eye closure sensitivity were considered present or absent.**

<table>
<thead>
<tr>
<th>Habitual methods</th>
<th>Provocative</th>
<th>Inhibitory</th>
<th>None</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence/sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA absent</td>
<td>25 (64.1)</td>
<td>–</td>
<td>14 (35.9)</td>
<td>39</td>
</tr>
<tr>
<td>DA present</td>
<td>11 (47.8)</td>
<td>2 (8.7)</td>
<td>10 (43.5)</td>
<td>23</td>
</tr>
<tr>
<td>MDI</td>
<td>7.78 ± 14.881 (p = 0.018)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DA absent</td>
<td>9 (22.5)</td>
<td>–</td>
<td>39 (77.5)</td>
<td>40</td>
</tr>
<tr>
<td>DA present</td>
<td>18 (60.0)</td>
<td>2 (6.7)</td>
<td>10 (33.3)</td>
<td>30</td>
</tr>
<tr>
<td>MDI</td>
<td>4.08 ± 4.353 (p &lt; 0.001)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>19 (29.7)</td>
<td>–</td>
<td>45 (70.3)</td>
<td>64</td>
</tr>
<tr>
<td>Eye closure sensitivity</td>
<td>13 (21.3)</td>
<td>–</td>
<td>48 (78.7)</td>
<td>61</td>
</tr>
<tr>
<td>Photo and eye closure sensitivity</td>
<td>8 (14.6)</td>
<td>–</td>
<td>35 (64.8)</td>
<td>54</td>
</tr>
</tbody>
</table>

Values expressed in parentheses are %.

DA, discharges in awake EEG; MDI, mean of discharge indexes (mean ± SD).

*Z-test for single means = 1 (one tailed).
Among individual tasks, those related to manual praxis were the most provocative. Although in a much higher rate, Matsuoka et al. (2000) also identified as significant triggers tasks involving praxis, such as writing in 26 of 38 (68.4%), spatial construction in 24 (63.2%), and written calculation in 21 (55.3%). In contrast, mental calculation exerted provocative effect in only three (7.9%) and reading in two of their patients (5.3%). In a smaller series of 25 patients with JME, Mayer et al. (2006) did not consider the role of praxis as pivotal in inducing discharges, since in their series reading exerted provocative effect in 20% and praxis and speaking in 16% each.

Considering calculation, in our series, the provocative effect of written was twice that of mental calculation. This has also been a matter of discussion: whereas in the series of Matsuoka et al. (2000), written calculation exerted provocative effect in 55.3% versus only 7.9% in mental calculation, in the report of Mayer et al. (2006) the effect of calculation was irrelevant (1 of 25 JME patients). In the present series, mental calculation was a powerful inhibitor of discharges (18 of 27, 66.7%). The same was seen in written calculation that exerted inhibition in 16 of 25 (64%) of the patients. However, the last also elicited discharges in 12 of 60 (20%) of patients. Wolf (2005) stated that the same function could sometimes be provocative or inhibitory depending on the state of cortical activation; when resting, a task could precipitate discharges and seizures, whereas when already firing, the activation of a nearby network could inhibit its activity. The parietal cortex would be the structure involved in this process from
where the spatial thinking processes would or would not be transformed into voluntary movements (Goossens et al., 1990; Senanayake, 1992; Striano et al., 1993; Inoue et al., 1994). When parietal cortex processes involve the frontal region, for example, in written calculation, it could activate discharges; when there is no recruitment of the motor network, as in mental calculation, the parietal cortex might act as the nearby region, inhibiting the hyperexcitable motor cortex, or on the contrary, promoting discharges on it in the dependency of the state of the network at that moment.

In this series, although tasks involving motor networks exerted excitation, those restricted to thinking had the opposite effect, regardless of spatial or linguistic character. Praxis induction would be the preponderant trigger in JME, implying the role of the motor network in the epileptogenic process (Inoue & Zifkin, 2004). Its hyperexcitability determines the clinical hallmark of this syndrome, the motor manifestations and the great amount of evidence of frontal dysfunction by EEG (Janz, 1985), neuropsychological studies (Devinsky et al., 1997; Pascalicchio et al., 2007; Piazzini et al., 2008), quantitative MRI (Woermann et al., 1990; Senanayake, 1992; Striano et al., 1993; Inoue et al., 1994; Murthy et al., 1998; Pedersen & Petersen, 1998), probably due to the fact that 64.5% of the patients in our series were appropriately treated. In our sample, sleep was the most effective activation method, followed by HV and IPS. In JME patients, Matsuoka et al. (1988) considered the neuropsychological tasks as the most effective provocative method, being observed in 21 of 25 (84%), followed by light drowsiness in 17 (68%), HV in 10 (40%), and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients. In a series of selected JME patients who had complained of perioral myoclonia, Mayer et al. (2006) reported myoclonia induced by linguistic and other neuropsychological tasks in 9 of 25 (36%) followed by HV and IPS in 9 (36%). Inoue and Kubota (2000) found photosensitivity in 47 (22.0%) and praxis sensitivity in 27 (12.7%) among 213 JME patients.
Another interesting application of VNPP is related to the possibility of inhibition of epileptiform discharges through cognitive activity, a fact that beyond helping to clarify physiopathologic aspects may be explored as a therapeutic tool. Unexpectedly, inhibitory (28 of 31, 90.3%) was more prevalent than provocative effect (29 of 76, 38.2%). In a population of 480 patients with epilepsy, Matsuoka et al. (2000) reported 63.9% of inhibitory versus 7.9% of provocative effect. However, the authors decided not to deal with inhibitory effect, since the discharge index under this circumstance did not show a peak clearly separated from that under “no effect” condition. Because inhibitory effect was defined in a very strict manner (between 0 and 0.5), in order to provide a better demonstration of this effect, we decided to consider the inverse of each index.

The stronger inhibitory effect exerted by the subcategory of spatial mental task could be biased, given that this subcategory was composed of only one task—mental calculation—of short duration. Alternatively, the activation of parietal cortex without motor involvement could explain the inhibitory effect by a cortical mechanism as already mentioned. However, considering the great categories of tasks, inhibitory effect was not related to any one of them. This may suggest that the inhibitory cognitive effect might be mediated by a more widespread inhibitory pathway, such as the cortical-thalamic. Normally cortical-thalamic feedback loops regulate the flow of sensory information to the cortex through activation of inhibitory neurons in the reticular nucleus, gating thalamic output to the cortex (Kostopoulos, 2001; Zikopoulos & Barbas, 2006).

In addition to influence of subcortical structures, many authors have emphasized the role of stress in precipitating reflex seizures independent of the epileptic syndrome (Matsuoka et al., 1988; Goossens et al., 1990; Inoue & Kubota, 2000; Inoue, 2007). Furthermore, it was found in JME patients a correlation between the presence of anxiety, lack of seizure control, and antecedent of more than 20 lifetime GTCS (De Araújo Filho et al., 2006). We confirmed this suggestion, once the presence of anxiety determined a less expressive inhibitory effect and a tendency to higher discharge indexes. In addition, a high prevalence of anxiety in JME patients might indicate a common physiopathology of the two morbidities. Recent neuroimaging studies in animal models of anxiety have indicated the participation of the amygdala-prefrontal circuitry in the manifestation of this symptom (Bishop, 2007).

In conclusion, we advise habitual methods of activation for EEG diagnoses in JME. However cognitive tasks, mainly those involving hand praxis, may be useful on an individual basis and for research purposes. The understanding of all these dynamic interactions, including the stress contribution, would help to clarify the physiopathologic mechanisms of this prototype of IGE. At last, it could facilitate the design and development of successful nonpharmacologic therapeutic interventions for the treatment of JME patients as cognitive therapy or antistress programs, as already done in an empirical form (Dahl et al., 1985, 1987; Martinovic, 2001; Wolf, 2002).

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We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure: The authors have no conflicts of interest to declare.

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Abstract

**Purpose:** The neuroanatomical basis and the neurochemical abnormalities that underlie juvenile myoclonic epilepsy (JME) are not fully understood. While the thalamus plays a central role in synchronization of widespread regions of the cerebral cortex during a seizure, emerging evidence suggests that all cortical neurons may not be homogeneously involved. The purpose of this study was to investigate the cerebral metabolic and structural differences between JME patients and normal controls.

**Methods:** All patients had a JME diagnosis based on seizure history and semiology, EEG recording, normal magnetic resonance neuroimaging (MRI) and video-EEG according to the Commission on Classification and Terminology of the International League Against Epilepsy, 1989. Sixty JME patients (JME-P) were submitted to 1.5 T MRI multi-voxel proton spectroscopy and voxel-based morphometry (VBM). The control group consisted of 30 age and sex-matched healthy volunteers. The Institutional Ethics Committee approved the study, and informed consent was obtained from all participants.

**Results:** Group analysis demonstrated lower N-acetyl-aspartate/Creatine (NAA/Cr) ratio among patients compared to controls on prefrontal, frontal cortices and thalamus. Patients had a statistically significant difference in glutamate-glutamine complex (GLX)/Cr on prefrontal and frontal cortices, insula, striatum and posterior cingulate gyrus. When evaluating the relationship among the various components of this epileptic network among JME-P, the strongest correlation occurred between thalamus and prefrontal cortex and a significant negative correlation between NAA/Cr and duration of epilepsy was found. Also, VBM demonstrated significantly reduced gray matter volume (GMV) in thalami, insula cortices and cerebellar hemispheres bilaterally; while significantly increased GMV was observed in right superior frontal, orbitofrontal and medial frontal gyri among JME-P when compared to controls.

**Conclusions:** The identification of a specific network of neurochemical dysfunction and slight structural abnormalities in patients with JME, with diverse involvement of particular structures within the thalamocortical circuitry, suggests that cortical hyperexcitability in JME
is not necessarily diffuse, supporting the knowledge that the focal/generalized distinction of epileptogenesis should be reconsidered and reinforcing the concept of ‘system epilepsies’.
Bibliografia consultada

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