Reduced cerebellar left hemisphere and vermal volume in adults with PTSD from a community sample

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ARTICLE INFO
Article history:
Received 27 May 2011
Revised in revised 1st
Accepted 14 July 2011

Keywords:
Cerebellum
Early trauma
Posttraumatic stress disorder
Neuromaging
Magnetic resonance imaging
Volumetry

ABSTRACT

Background: Traumatic events exposure is a necessary condition for developing posttraumatic stress disorder (PTSD), but not all individuals exposed to the same trauma will develop PTSD. Human studies have suggested that the cerebellum is involved in emotional perception, anticipation, and recognition. In this context, the current study evaluated whether cerebellar volume is associated with PTSD. Methods: Eighty-four victims of violence, 42 who fulfilled the DSM-IV-TR criteria for PTSD and 42 resident control, were identified through an epidemiologic survey conducted in the City of São Paulo. Subjects were evaluated using the Clinician-Administered PTSD Scale (CAPS), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), and Early Trauma Inventory (ETI). All subjects underwent a magnetic resonance imaging (MRI) scan to evaluate their cerebellar hemispheres and vermis. Results: PTSD subjects had relative smaller left hemisphere (p < 0.04) and vermis (p < 0.05) volumes persisted after controlling for gender, age, and brain volume. In PTSD group, left cerebellar hemisphere volume correlated negatively with PTSD symptoms (p = 0.01), early traumatic life events (p = 0.03), depressive symptoms (p = 0.004), and anxiety (p = 0.01). Conclusion: The cerebellum is involved in emotion modulation, and our results suggest that cerebellar volumetric reduction is associated with mood, anxiety and PTSD symptoms. Early traumatic life experiences are related to vermal volume reduction and may be a risk factor for future PTSD development.

1. Introduction

Posttraumatic stress disorder (PTSD) is a psychiatric disease that is associated with exposure to a traumatic event followed by the appearance of three symptom clusters: re-experiencing of the event, avoidance/numbing, and hyperarousal (American Psychiatric Association, 1994). Since the first reports of PTSD in war veterans, and its introduction as a diagnostic category, research on the phenomenology, neurobiology, and treatment of PTSD has grown exponentially, primarily in the non-military population (Bernik et al., 2003). Curiously, not all individuals who are exposed to traumatic events develop PTSD. Therefore, the factors that mediate risk, resilience, and other stress-related psychopathology are of paramount importance to the further understanding of trauma-related symptoms as well as the development of new treatment approaches (Jovanovic and Resler, 2010). The current knowledge points to multiple factors, such as genotype and nervous system dynamics, that interact with environmental factors, such as childhood background (LeardMann et al., 2016) and trauma load (Kolata et al., 2010) and affect vulnerability in the aftermath of trauma exposure.

Findings from magnetic resonance imaging (MRI) studies have demonstrated neuroanatomical alterations in PTSD that suggest volumetric reductions or atrophy of the hippocampus (Bremner et al., 2003; Lindauer et al., 2004; Fava et al., 2007; Stein et al., 1997), amygdala (Parisi et al., 2006; Regers et al., 2005), anterior...
cingulate gyrus (Roizen et al., 2009; Woodward et al., 2005), corpus callosum (Carrion et al., 2009; Villareal et al., 2004), and temporal and frontal gray matter PTSD (Lauter et al., 2008), functional imaging evaluation has shown that PTSD affects regions that support emotion processing and autobiographical memory retrieval, such as the hippocampus, amygdala, and ventromedial prefrontal cortex (St Jacques et al., 2010).

It has been proposed that the also cerebellum is involved in the experience and regulation of emotions, and intimate affairs and affective connections to the brainstem and limbic system provide a neuroanatomical substrate (Schmahmann and Pandya, 1997; Scharf and von Brock, 2003). More recently, it has been postulated that the cerebellum plays a role in PTSD, and some studies have observed altered functioning of the left cerebellar hemisphere (Ou et al., 2004) and vermis (Anderson et al., 2002; Fossati et al., 2002) in PTSD patients. This evidence suggests a possible role for this structure in the pathophysiology of the disease. To a lesser extent, cerebellar, temporal, superior gyms, and parietal differences have been reported in maltreated children and adolescents with PTSD (De Bellis et al., 2002; De Bellis and Kuchibhata, 2006; Thomas and De Bellis, 2004).

In a MRI study with nonhuman primates, enlarged vermis, dorsomedial prefrontal cortex and dorsal anterior cingulate cortex were observed in pre-reared monkeys (Spiegelt et al., 2005). Poor rearing during infancy seems to induce the enlargement of stress-sensitive brain regions, and these changes may be a structural phenotype for increased risk of stress-related neuropsychiatric disorders (Spiegelt et al., 2005). In humans, MRI studies have reported a smaller bilateral cerebellar volumes in children with PTSD secondary to maltreatment (De Bellis and Kuchibhata, 2006), and smaller vermis in children (age 1–11) with PTSD (Carrion et al., 2009). These cerebellar differences persisted after adjusting volumes for cerebral volume, sociodemographic, and IQ variables. In addition, there was a positive correlation between cerebellar volume, and age of onset (De Bellis and Kuchibhata, 2006). Only one study have evaluated the cerebellum (more specifically vermis) in adults. This study only examined cerebellar function with MRI (Luthra et al., 2006), and found negative results. Finally, no studies have evaluated whether early-life trauma is related to PTSD in adulthood.

In the present research, we hypothesized that cerebellar hemispheres and vermis are reduced in subjects with PTSD and resilient controls exposed trauma in community. A major strength of this investigation is the identification of participants through an epidemiological survey rather than from clinical referrals. Moreover, we assessed whether cerebellar reduction is related to early-life trauma experience and the severity of PTSD symptomatology (i.e., re-experiencing symptoms, avoidance, and numbing symptoms, hyperarousal symptoms), as measured by clinical scales.

2. Methods

2.1. Participants

Forty-two PTSD cases (patients) and 42 resilient matched controls (people exposed to one or more traumatic events after age 18 that did not develop PTSD), were identified through an epidemiological study that surveyed PTSD among the civilian population in the city of São Paulo (Andreaty et al., 2008). To identify trauma victims in the community, a professional team specializes in house surveys from Brazilian Institute of Public Opinion and Statistics, conducted interviews. Interviewers were trained on the Composite International Diagnostic Interview (CIDI) (Wittchen et al., 1996) in the Federal University of São Paulo, a World Health Organization (WHO) accredited center. Training procedures were conducted in accordance with the WHO guidelines (World Health Organization, 2004). Interviews were carried out in the participants’ households using printed questionnaires. Individuals who met inclusion criteria during the epidemiological study were invited to participate in the case-control study. Subjects exposed to traumatic life experiences resulting in PTSD (cases) were compared to resilient subjects who were victims of traumatic life experiences, but who did not have PTSD (controls). The aim was to identify biological variables that might protect or predispose subjects to PTSD. Subjects were informed about the procedures of the studies, and were asked to formally consent to participation. Further details of the study design have been reported previously (Andreaty et al., 2008; Bergman et al., 2009).

Patients were eligible to participate if they met the following inclusion criteria: 1) DSM-IV criteria for a diagnosis of PTSD (American Psychiatric Association, 1994); 2) 18–60 years old (women and men); 3) women of childbearing age who were not pregnant or breast-feeding, and who were practicing reliable contraception during the course of the study; and 4) primary traumatic event that occurred before age 18. The exclusion patient criteria were as follows: 1) lifetime history of bipolar, psychotic, borderline personality disorder or substance dependence or abuse (excluding nicotine and caffeine) in the previous 6 months; 2) serious or unstable concurrent illness; 3) use of psychotropic medications in the previous 2 weeks (5 weeks for fluoxetine); 4) body mass index above 30; 5) current suicidal ideation or the presence of psychotic symptoms; 6) or history of head trauma. Substance dependence or abuse was evaluated by a psychiatrist prior to MRI. This special use of structured Clinical Interviews for DSM-IV as parameter. Controls subjects without PTSD inclusion and exclusion criteria were the same the ones used for patients.

2.2. Measures

1) Sociodemographic data were obtained using an adapted form of the Composite International Diagnostic Interview (CIDI) sociodemographic section (Quintana et al., 2007).

2) Structured Clinical Interviews for DSM-IV (SCID-I). SCID-I is a semi-structured clinical interview that screens for the diagnosis of mental health disorders according to DSM-IV criteria, and has been validated for the Brazilian population (Del-Ben et al., 2001).

3) Clinician-Administered PTSD Scale (CAPS) (Pars et al., 2013). CAPS is a clinician rating scale that assesses current and lifetime PTSD. It is a structured clinical interview designed to be applied by clinicians, and its validation was included as part of the first phase of this protocol. This scale is a 30-item scale that investigates the frequency and intensity of PTSD symptoms, and traumatic life experiences. Scores range from 0 to 136, with scores classified as follows: subclinical, from 0 to 19; mild, from 20 to 39; moderate, from 40 to 59; severe, from 60 to 79; and extreme, 80 and above. Symptoms were divided into the following clusters: re-experiencing symptoms, avoidance and numbing symptoms, and hyperarousal symptoms.

4) Beck Anxiety Inventory (BAI). The BAI is a self-administered 21-item questionnaire that assesses the intensity of anxiety symptoms (Beck et al., 1988).

5) Beck Depression Inventory (BDI). The BDI is used to assess depressive symptoms in clinical settings. The BDI is a self-administered 21-item questionnaire, and it has been validated for the Brazilian population (Beck et al., 1991). Scores range from 0 to 63, with depression classified as minimal when scores range from 0 to 10, mild from 11 to 19, moderate from 20 to 25, and severe from 26 to 63.

6) Early Trauma Inventory (ETI). The ETI is a semi-structured interview comprising 56 items that measure early traumatic life experiences in the following domains: sexual, physical and...
psychological abuse, and other traumatic life experiences (Bremner et al., 2000; Mello et al., 2010).

2.3. Image acquisition and analysis

Imaging data were acquired at the Instituto do Sono, using a GE 1.5T Signa scanner. Structural MRI images were acquired using an axial T1-weighted scan (TR = 540 ms, TE = 11 ms, flip angle = 90°, NEX = 1, matrix size = 256 × 256, FOV = 24 cm, thickness = 10 mm), yielding 160 slices. Before scanning, a sagittal scout series (nine to eleven 5-mm-thick slices with a 1-mm inter-slice gap) was performed to determine image quality and clarity, as well as subject head position.

Total brain volume was measured using voxel-based morphometry (VBM) methodology, which was implemented with the VBM Toolbox in SPM5 (www.fil.ion.ucl.ac.uk/spm) as described previously (Ashburner and Friston, 2005). T1-weighted images were segmented in the original space. The sum of all voxel values within the segmented image approximates the total volume within the corresponding partition. Total brain volume was computed from the sum of gray and white matter volumes (Ashburner and Friston, 2005).

The cerebellum was measured using region of interest (ROI) methodology. First, the ROI tracing was performed using the BrainS 2 semi-automated model, then manually corrected based on previous studies (De Bellis and Risch, 2006; Laakso et al., 1996; Friston et al., 2004). The cerebellar hemispheres and vermal volumes were calculated by summing the areas of successive coronal slices after tracing the region of interest (ROI) and excluding cerebrospinal fluid (CSF). The measurements began at the cerebellum appeared laterally to thepons. The tentorium cerebelli acted as the superior limit and the base of the cerebellum as the inferior limit. The cistern magna and transverse sinuses were excluded (De Bellis and Risch, 2006). The last slice included was the one at which the cerebellum was no longer distinguishable from the transverse sinuses or was no longer visible. The measurement of the vermis began at the slice where the anterior and/or inferior posterior lobes appeared. Measurements were made until the vermis was no longer visible (De Bellis and Risch, 2005).

2.4. Data analysis

Data were coded and analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, version 15.0). Prior to conducting the analyses, the measures were examined for normality using the Shapiro–Wilks test. The level of significance was set at p < 0.05, using a 2-tailed test.

Comparisons between groups were made with chi-square (for categorical variables) and Student’s t-tests (for continuous variables). Brain and cerebellar volumes were analyzed using the General Linear Model (GLM). Cerebellar measurements were adjusted for gender, age and total cerebral volume. The relationship between cerebellar measurements and CAPS (PTSD symptoms); E (early trauma life events); BRI (panic symptoms); and BDI (anxiety symptoms) scores were analyzed using a multivariate regression model. Alpha was set at p < 0.05.

3. Results

There were no age (t = 1.34, p = 0.18) or gender (t = 1.42, df = 41, p = 0.34) differences between the PTSD and resilient control groups. The PTSD group presented significantly higher scores for history of early traumatic life events (t = 2.49, p = 0.01) and all clinical variables as follows: re-experiencing symptoms (t = 5.92, p < 0.01), avoidance and numbing symptoms (t = 7.12, p < 0.01), hyperarousal symptoms (t = 6.445, p < 0.01), total CAPS score (t = 7.86, p < 0.01), anxiety (t = 4.65, p < 0.01), and depressive symptoms (t = 4.046, p < 0.01). For details, please see Table 1.

Of the PTSD patients, 81% (34 subjects; x² = 42.60, p < 0.01) presented comorbid major depressive disorder (MDD), 9.5% (4 subjects) presented panic disorder (PD), and 2.4% (1 subject) presented alcohol abuse disorder (AAD). Of the resilient controls, 78.6% (31 subjects) did not fulfill criteria for any psychiatric disorder but 9.5% (4 subjects) reached MDD, 7.1% (2 subjects) PD, and 2.4% (1 subject) fulfilled the criteria for AAD. The PTSD sample included a heterogeneous range of traumatic experiences as follows: assault (38.1%), sexual and physical abuse (28.6%), sudden death of a loved one (19%), kidnapping (7.1%) and others (7%). The average duration of the trauma was 43 months (from 1 month to 18 years). The controls were also primarily victims of assault (35.7%), sexual and physical abuse (26.2%), sudden death of a loved one (16.7%), kidnapping (7.1%) and none (14.2%).

Brain volume was smaller in the PTSD group (F = 4.50, p = 0.01). PTSD patients also presented reduced left cerebellar hemisphere (F = 2.55, p = 0.04) and vermal volumes (F = 13.49, p < 0.01) compared to resilient controls. For more details see Table 2.

In PTSD group (but not in control group), a significant negative correlation was observed between vermal volume and CAPS total score (ρ = -0.30, t = -2.44, p < 0.01), re-experiencing symptoms (ρ = -0.34, t = -3.11, p < 0.01), avoidance and numbing symptoms (ρ = -0.39, t = -3.45, p = 0.01), hyperarousal symptoms (ρ = -0.25, t = -3.90, p = 0.021), early traumatic life events (ρ = -0.32, t = -2.86, p < 0.01), anxiety (ρ = -0.29, t = -2.54, p < 0.01), and depressive symptoms (ρ = -0.21, t = -1.24, p = 0.094) (Fig 1). A negative correlation between left cerebellar volume and CAPS total score (ρ = -0.43, t = -2.77, p = 0.01) re-

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Table 1: Demographic and Clinical variables of PTSD subjects and resilient controls.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PTSD (n = 42)</th>
<th>Controls (n = 42)</th>
<th>t</th>
<th>p</th>
<th>( \bar{x} )</th>
<th>( SE )</th>
<th>( \bar{S} )</th>
<th>( SE )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male (n, %)</td>
<td>151 (37.1)</td>
<td>10 (23.8)</td>
<td>1.42</td>
<td>0.14</td>
<td>10.12</td>
<td>0.01</td>
<td>10.08</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.91</td>
<td>32.32 ± 17.41</td>
<td>38.30</td>
<td>21.51 ± 6.91</td>
<td>3.33</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain-perpetuating symptoms</td>
<td>18.72</td>
<td>16.65 ± 12.64</td>
<td>7.23</td>
<td>4.91 ± 0.12</td>
<td>3.89</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance and numbing symptoms</td>
<td>26.71</td>
<td>22.72 ± 10.79</td>
<td>8.41</td>
<td>5.96 ± 1.71</td>
<td>7.40</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperarousal symptoms</td>
<td>24.14</td>
<td>20.42 ± 17.71</td>
<td>9.41</td>
<td>6.34 ± 0.04</td>
<td>6.04</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPS total score</td>
<td>79.53</td>
<td>61.82 ± 70.21</td>
<td>25.06</td>
<td>17.20 ± 3.80</td>
<td>6.73</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early trauma life events (ETLE total score)</td>
<td>107.85</td>
<td>72.94 ± 48.42</td>
<td>52.11</td>
<td>21.4 ± 6.42</td>
<td>10.45</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety symptoms (ASI)</td>
<td>29.29</td>
<td>24.09 ± 13.61</td>
<td>14.33</td>
<td>9.43 ± 2.81</td>
<td>12.42</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms (BDI)</td>
<td>25.61</td>
<td>21.81 ± 10.22</td>
<td>12.57</td>
<td>8.73 ± 3.42</td>
<td>6.41</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Confidence interval.

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Table 2
Brain measurement in PTSD patients and resilient control group.

<table>
<thead>
<tr>
<th>Volumes*</th>
<th>PTSD (n = 42)</th>
<th>Control (n = 42)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI</td>
<td>Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>Brain</td>
<td>1096.27</td>
<td>1069.95–1121.48</td>
<td>1105.03</td>
<td>1113.82–1188.24</td>
</tr>
<tr>
<td>Total cerebellum*</td>
<td>101.53</td>
<td>99.97–104.08</td>
<td>105.52</td>
<td>102.75–108.46</td>
</tr>
<tr>
<td>Left cerebellar hemisphere*</td>
<td>50.55</td>
<td>48.29–52.82</td>
<td>53.61</td>
<td>51.05–56.24</td>
</tr>
<tr>
<td>Right cerebellar hemisphere*</td>
<td>51.58</td>
<td>49.35–53.88</td>
<td>51.91</td>
<td>50.16–53.64</td>
</tr>
<tr>
<td>Vermis*</td>
<td>7.68</td>
<td>6.70–8.79</td>
<td>8.74</td>
<td>8.33–9.08</td>
</tr>
</tbody>
</table>

*Volumes are in cm³.  |
| Confidence interval.  |
| Adjusted for age, gender and connectivity.  |
| Adjusted for brain volume, age, gender and connectivity.  |

experiencing symptoms (β = −0.36, t = −3.30, p = 0.02), avoidance and numbing symptoms (β = −0.37, t = −2.42, p = 0.02), hyper-arousal symptoms (β = −0.42, t = −2.73, p = 0.04), and anxiety (β = −0.22, t = −2.01, p = 0.04) was also observed (Fig 1). CAPS total score correlated positively with ERI (β = 0.32, t = 3.02, p = 0.01). Overall, when both variables were controlled in linear regression analysis, vermis total volume remained negatively associated with CAPS total score (β = −0.34, t = −3.11, p < 0.01) and ERI (β = −0.25, t = −2.14, p = 0.04).

4. Discussion

The evidence of structural alterations in cerebellum volume in neuropsychiatric disorders is not novel. Previous research demonstrated a cerebellum volume reduction in schizophrenia (Ichimura et al., 2003; Lee et al., 2017), bipolar disorder (Bettinello et al., 1999), dementia (Baldara et al., in press), epilepsy (Bilevicius et al., 2010), attention deficit hyperactivity disorder (Berquin et al., 1998), autism (Cournia et al., 2011), and anxiety disorder (De Bells and Kuchibhatla, 2006).

The proposal that the cerebellum is involved in the experience and regulation of emotions was posited more than half a century ago (Schutter and van Honk, 2009) and intimate afferent and efferent connections to the brainstem and limbic system have provided a neuroanatomical substrate (Schutter and van Honk, 2005). The cerebellum has monosynaptic projections not only to the hypothalamus, septum, hippocampus, amygdala, and basal ganglia, but also to the brainstem nuclei, where the cerebellar projections stimulate dopamine and noradrenaline release by innervating the substantia nigra and locus coeruleus (Schutter and van Honk, 2005).

One of the first reports to relate the cerebellum to emotional experience involved a patient who reported unpleasant feelings after electrical stimulation of the dentate nucleus and superior peduncle (Naishold and Slaughter, 1969; Schutter and van Honk, 2009). Furthermore, electrophysiological responses in several limbic structures, including the hippocampus, amygdala, and septum were recorded following electrical stimulation of the fastigial portion of the deep cerebellar nucie in mammals (Schutter and van Honk, 2009). Additional support for the connection between the cerebellum and emotions in humans is provided by reports of an emotionally disturbed patient who received electrical stimulation in the fastigial nucleus (Schutter and van Honk, 2005, 2006). It was found that electrical discharges induced by electric stimulation correlated with the patient’s experience of anger and tension. Moreover, there is evidence that chronic stimulation of the vermis using implanted subdural electrodes can normalize behavior in severely emotionally (severe anxiety or depression) dysregulated patients (Schutter and van Honk, 2005, 2009).

The current study evaluated the cerebellar volume of PTSD subjects and victims of trauma who did not develop the disorder (resilient controls). PTSD subjects exposed to community traumatic events were found to have significantly reduced left cerebellar hemisphere and vermis volumes compared to resilient controls. These differences persisted after controlling for gender, age and brain volume. The results are in agreement with two previous studies (Cernon et al., 2009; De Bells and Kuchibhatla, 2006). However, these studies were conducted with children and adolescents with PTSD. Only one study has examined adults, and no...
volumetric cerebellar differences were observed between the PTSD and non-PTSD war veterans (Levit et al., 2006). Moreover, no correlations between CAPS scores and cerebellar, and vermis measurements were observed. However, this last one was observed vermic volume in twins, and did not found differences. Comparing with our results, we could suppose that early trauma may be related with this volume reduction.

Although previous studies have demonstrated structural (Cavian et al., 2009; De Bellis and Kuchibhatla, 2006; Levin et al., 2006) and functional (Bromm et al., 2003; Fernández et al., 2001) cerebellar changes in PTSD subjects, none of them have found a relationship between early-life traumatic experiences and cerebellar alterations in adulthood. The correlations between early-life trauma and CAPS with cerebellar volumes found in the current study suggest that both traumatic events and PTSD symptoms have an effect on cerebellar structure. However, it is not yet clear whether reduced brain regions (e.g., the cerebellum) represent an incident vulnerability for developing PTSD upon exposure to a traumatic event or a consequence of PTSD symptoms.

Spinelli et al. (2006) conducted a study to identify structural abnormalities that may predict increased risk of stress-related neuropsychiatric disorders. In this study, mother-reared Rhesus monkeys were compared to peer-reared offspring. An enlarged vermis, thalamic, prefrontal cortex, and dorsal anterior cingulate cortex were encountered in peer-reared monkeys; however, there were no differences in the corpus callosum or the hippocampus (Spinelli et al., 2009). Comparing the present results with those from previous studies, we speculate that cerebellar hyperactivity is present during the first month after the stress factor and cerebellar volume reduction is a consequence of this chronic hyperactivity that appears later.

Adverse childhood factors may lead to an increased risk for later PTSD (Leer-Mann et al., 2010). Evidence has suggested that the developing cerebellum is vulnerable to environmental insults, including physical and psychological stressors (Ferguson and Helson, 1981; Finkelson et al., 1998; Schutter and van Honk, 2005; Teicher et al., 2006; Thomas and De Bellis, 2004). Environmental insults encountered during childhood, such as exposure to toxic levels of lead (Saders et al., 2008), chronic irradiation (Aftman, 1987), low birth weight (Martinussen et al., 2009), and neonatal exposure to desamethasone (Ferguson and Helson, 1981) contribute to cerebellar damage or cerebellar structures.

The dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis with elevated levels of corticotrophin releasing hormone (CRH) has been consistently reported in traumatized individuals (Mello et al., 2009; Thomas and De Bellis, 2004). Adults with PTSD, maltreated children with symptoms of mood and anxiety disorders, children with PTSD secondary to maltreatment, and infant primates models show this dysregulation (Epkan et al., 2006; De Bellis, 2001; Mello et al., 2009; Thomas and De Bellis, 2004). One hypothesis to explain PTSD is that childhood abuse acts as a severe stressor that unleashes a cascade of events that affect brain development (Thomas and De Bellis, 2004). Adult animals submitted to a single prolonged episode of early maternal deprivation show stress-induced corticosterone responses (Lioine et al., 2009). Maternal deprivation induces neural degeneration and atrophic changes in the hypothalamic and cerebellar cortex of neonatal rats. Maternal separation may impair learning and memory in adult males by altering normal developmental changes in glucocorticoid receptor expression (Jouvent et al., 2005).

Thus, children exposed to trauma (early trauma) may experience chronically elevated CRH during pituitary development. Elevated CRH may lead to pituitary hyperactivity, which may be most pronounced during puberty, due to trophic factors (Thomas and De Bellis, 2004). Chronic exposure to CRH may result in the downregulation of pituitary CRH receptors over time. This downregulation may be an adaptive mechanism that regulates pituitary hyperactivity, as the resultant high cortisol levels would otherwise result in medical illness, and damage to the brain (Thomas and De Bellis, 2004) and cerebellum (MacKenzie et al., 2008).

The finding of smaller cerebellar volumes in subjects with PTSD is not novel. Despite evidence suggesting that the cerebellum might play a role in anxiety manifestations such as hyperarousal symptoms, which are present in various disorders such as posttraumatic stress disorder (PTSD) and generalized anxiety disorder (GAD) (Baltazara et al., 2008; Bromm et al., 2003; De Bellis and Kuchibhatla, 2006), little is known about cerebellar structure and function in DSM-IV-Axis I anxiety disorders.

There are several limitations of this study that are worth considering. First, the study sample size is too small to detect significant differences between groups. Second, the cross-sectional design precludes causal interpretation of the cerebellar reduction on PTSD or consequence of the disease PTSD or other life events. Finally, since sample size was not sufficient we could not observe if cerebellar volume could be related to the type of trauma. However, the main strength of the
current study is that the sample is from a community epidemiological study, which enabled the observation of differences in a representative sample and the generalizability of the results.

3. Conclusion

In summary, the present study provides evidence that cerebellar volume is smaller in adult PTSD subjects than in resilient controls (both groups were previously exposed to trauma events), and that volume reductions in the left hemisphere and vermis are associated with the magnitude of the PTSD symptoms (experiencing the trauma, avoidance and numbing, hyperarousal, and anxiety and depressive symptoms). Moreover, the study found an association between these cerebellar reductions and early traumatic life experiences, posing the question of whether the changes are a consequence of abnormal neurodevelopmental adaptations in subjects that later develop PTSD. Cerebellar impairment may be related to the dysfunction of circuits that project to the limbic system or may be secondary to high levels of cortisol as theoretically proposed (Schneider and van Honk 2005; Trichter et al., 2006). We propose that the cerebellum participates, at least partially, in the pathophysiology of PTSD symptoms and mood modulation. In addition, the role of the cerebellum in the pathophysiology of PTSD should be investigated in the future by means of longitudinal studies and clinical trials.

Ethical issues

Participants were informed about the research procedures and risks and signed an informed consent that was fully approved by the Ethical Committee of the Federal University of São Paulo: 20268-96. Subjects diagnosed as having any mental health disorder were offered a referral to the outpatient clinic at the Federal University of São Paulo.

Role of funding sources

This study was supported by the State of São Paulo Funding Agency (FAPESP) by the Grant 2004/15030-0, and the National Research Council (CNPq) Millennium Institute on Violence and Mental Health by the grant 20122/2005-2. The FAPESP and CNPq had no further role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

There are no contributors to declare.

Conflict of interest

The authors report no financial or other relationship relevant to the subject of this article.

Acknowledgment

There are no acknowledgments to declare.

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Artigo IV: Is cerebellar volume a trait-related to bipolar disorder?

Artigo publicado na Journal of Affective Disorders, 2011
Preliminary communication

Is cerebellar volume related to bipolar disorder?

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ABSTRACT

Background: Recent data suggest that cerebellar influences emotion regulation in humans. The findings of cerebellar anomalies in bipolar disorder (BD) are especially intriguing given the link between the cerebellum emotional and behavioral regulation. The purpose of this study was to evaluate cerebellar volume in patients with euthymic BD type I compared to controls. Moreover, we investigated the possible relationship between cerebellar volume and suicidal behavior.

Methods: Forty patients with euthymic BD type I, 20 with and 20 without history of suicide attempt, and 22 healthy controls underwent an MRI scan. The participants were interviewed using the Structured Clinical Interview with the DSM-IV axis I (SCID-I), the Hamilton Depression Rating Scale (HDRS), the Young Mania Rating Scale (YMRS) and the Barratt Impulsiveness Scale (BIS-11).

Results: Groups were age, gender and years of schooling-matched. The left cerebellum (p = 0.002), right cerebellum (p = 0.012) and vermis (p = 0.001) were significantly smaller in the BD group, however, there were no volumetric differences between the BD subjects with and without suicidal attempt. There was no correlation between cerebellar measurements and clinical variables.

Limitations: The main strength is that our sample consisted of patients with euthymic BD type I, without any comorbidity, however, these results cannot establish causality as the cross-sectional nature of the study.

Conclusions: Our findings suggest that the reduction in cerebellum volumes observed in BD type I might be a trait-related characteristic of this disorder. Additional studies with large samples and subtypes of this heterogeneous disorder are warranted to determine the possible specificity of this cerebellar finding.

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1. Introduction

Structural imaging studies suggest that, although patients with BD exhibit relatively healthy-appearing brains overall, corticol and subcortical brain structures may be impaired. Cerebellar abnormalities go either way (i.e., volumes may be larger or smaller) in amygdala volume (Brambilla et al., 2003; Rosso et al., 2007), hippocampus (Alda et al., 1994; Bouyer et al., 2004; Blomberg et al., 2003), basal ganglia (Pap et al., 2007; Bieau et al., 2005; Yuan et al., 2006), and prefrontal cortex (Najt et al., 2007; Shurma et al., 2003) are the most common findings in BD. However, these results are not consistent between studies. Multiple factors could contribute to the variability in these findings, including gender-related
differences, volumetric changes related to the use of mood stabilizers, and genetic variation (Weiner et al. 2006).

Since the 1960s, studies have posited that the cerebellum plays a role in the experience and regulation of emotion (Van Hout and Sautter, 1969; Schutter and van Honk, 2009), and cerebellar findings have also been reported in BD. Cerebellar atrophy (Uippmann et al., 1982; Narudahall et al., 1981, 1982; Westerberg et al., 1982), cerebellar gray matter reduction (Moorhead et al., 2007), and smaller vermal subregion V2 and V3 are the main findings in patients with BD (Defelice et al., 1999; Hilti et al., 2005; Munkul et al., 2008).

In this study, we use the region of interest (ROI) MRI approach to evaluate whether cerebellar volume in patients with euthymic BD type 1 is reduced compared to healthy controls. In a second analysis, we assess the association between cerebellar volume and suicidal behavior.

2. Methods

2.1. Participants

We screened a total of 48 patients with euthymic BD type 1 and 25 healthy controls. Eight patients and three controls were excluded due to a history of neurological illness, head trauma, or inability to complete the MRI exam. Additional exclusion criteria included the lifetime history of substance abuse or a serious, current medical problem within the preceding 6 months. The final sample consisted of 40 patients with euthymic BD type 1 (20 with a history of suicide attempt and 20 with no history of suicide attempt) and 22 healthy controls.

Patients were recruited from the Mood and Anxiety Program of the Federal University of Bahia and were screened using the Structured Clinical Interview for the DSM-IV axis I (SCID-I) (First et al., 2002), the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), the Young Mania Rating Scale (YMRS) (Young et al., 1978), and the Barratt Impulsiveness Scale (BSI-11) (Barratt, 1983). The euthymia criterion was scores for both the YMRS and the HDRS under 7 points. Sociodemographical and clinical data were collected through a questionnaire. Patients were classified as having positive suicidal history if they reported one or more self-termination acts committed with the intent to die.

Healthy controls were recruited from patients’ social network. None of the healthy subjects had a current or previous history of Axis I DSM-IV psychiatric disorder or a first-degree relative with an Axis I psychiatric disorder.

2.2. Magnetic Resonance Imaging

Imaging data were acquired at the Image Memorial Medicina Diagnóstica-Bahia-Brazil using a 1.5T Symphony Master/Intera Siemens. Structural MR images were acquired using a sagittal T1 acquisition series (TR = 1850 ms, TE = 3.45 ms, flip angle = 13°, matrix size = 256 × 256, FOV = 24 cm, thickness = 1.0 mm) rendering 160 slices.

2.3. Brain volume

Brain volume was measured using voxel-based morphometry (VBM) methodology, as implemented in the VBM toolbox in SPSS (dpm.s.uoe.anl.jena.de/Vbm). This methodology has been described previously (Ashburner and Friston, 2005). The sum of all voxel values within the segmented image approximates the total volume within the corresponding partitions. Total brain volume was computed from the sum of gray and white matter volumes (Ashburner and Friston, 2005).

3.4. Cerebellar volumes

The cerebellar ROI tracing was performed using the Brains2 semi-automated model and was manually corrected based on previous studies (Lutfi et al., 1999; Son et al., 2002). The cerebellar hemispheres and vermis were manually traced using protocol, which have been described elsewhere (De Bellis and Kuchar, 2005; Lutfi et al., 1999; Son et al., 2002). The cerebellar ROI measurements were obtained at the point that the cerebellum appeared lateral to the pons. The anterior cerebellum was considered to be the superior limit of the cerebellum, while the base of the cerebellum itself was considered to be the inferior limit. The cuneate magna and transverse sinus were excluded (De Bellis and Kuchar, 2006). The last slice included was the one at which the cerebellum was no longer distinguishable from the transverse sinus or was no longer visible. The tissue measurement started at the slice where the anterior and/or inferior posterior lobes appeared. Measurements were made until the vermis was no longer visible (De Bellis and Kuchar, 2006).

2.3. Reproducibility

To evaluate intra-rater reproducibility, each rater repeated the cerebellar measurements twice, at least 1 week apart, for ten randomly selected subjects. Intra-rater reliability was found to be high (Kc = 0.96) for all cerebellar and vermal regions.

6. Data Analysis

Data were codified and analyzed using the Statistical Package for Social Sciences (SPSS for Windows, version 15.0). Prior to conducting analyses, measures were examined for normality using the Shapiro–Wilk test. The level of significance was set at p < 0.05 using a two-tailed test.

Differences in proportion were compared using the chi-square test. Continuous variables were compared using Student’s t-test and the Analysis of Variance (ANOVA). By employing the General Linear Model, analyses of covariance (ANCOVAs) were performed to investigate volume differences in the brain and cerebellar subregions across groups, after which Duncan’s post hoc test was performed. The level of significance was set at p < 0.05 using a two-tailed test.

3. Ethical Issues

Participants who agreed to participate after the explanation of the study signed an informed consent form. The study was fully approved by the Institutional Ethics Committee of Federal University of Bahia (16/2005).

Please cite this article as: Baldujara, L. et al., Is cerebellar volume related to bipolar disorder? J. Affect. Disord. (2011). doi:10.1016/j.jad.2011.06.099
4. Results

There was no age, gender or years of schooling differences among patients with BD and healthy controls. The mean number of suicide attempts was 1.64 ± 1.8. There was no difference between patients with BD who exhibited suicidal behavior and those who did not in terms of age, gender, and years of schooling. For more details, see Table 1. BIS scores were higher in BD subjects with a history of suicide attempts (67.3 ± 14.08) as compared to those without attempts (58.3 ± 8.64) and control group (58.5 ± 9.65) (p = 0.05).

There were no differences in intracranial and brain volumes between the BD group and the healthy controls. The left cerebellum (p = 0.02), right cerebellum (p = 0.02) and vermis (p = 0.01) were smaller in the BD group (Table 2). Ventricular volume was smaller in the BD group than the healthy control group (p = 0.03), although it was similar between the BD groups without and with suicide behavior groups. For more details, see Table 2.

There was no correlation between vermal and cerebellar hemisphere volumes and BIS, number of suicide attempts, or number of mood episodes (manic, depressive or mixed episodes).

5. Discussion

In this study, we examined anatomical abnormalities in the cerebellum of patients with euthymic BD type I compared to healthy controls. The volumes of the cerebellar hemispheres and the vermis were reduced in the BD group. However, there were no differences between BD subjects with and without a history of suicide attempts.

The cerebellum is reciprocally connected to limbic structures, including the amygdala, hippocampus, septum, as well as the cerebral cortex, including prefrontal areas (Heath and Harper, 1974; Insler and Mett, 1976). This feature provides a strong neuroanatomical basis for the involvement of the cerebellum in emotion regulation.

As BD is a multi-state heterogeneous syndrome, a variety of neuroimaging findings are observed in the literature (Emsell and McDonald, 2005; Langan and McDonald, 2009; Liu et al., 2010; Mahouti et al., 2009; Monkul et al., 2008). Early Computed Tomography (CT) studies have found cerebellar atrophy in patients with BD. The importance of these findings, however, was limited as only qualitative assessments were performed (Lppard et al., 1982; Nasrallah et al., 1981, 1982; Weinberger et al., 1982). While cerebral atrophy was more frequent in patients with schizophrenia, cerebellar atrophy was more frequent in patients who were currently with mania compared to controls (Lppard et al., 1982; Nasrallah et al., 1981, 1982; Weinberger et al., 1982). One study did not find differences in cerebellar volume between patients with schizophrenia, bipolar disorders, and healthy controls (Yates et al., 1987), whereas another found that cerebellar atrophy was associated with alcohol use/ history. This finding has not been consistently controlled for in other studies (Lppard et al., 1982).

In our study, alcohol abuse was an exclusion criterion.

In a voxel-based MRI study, Adler and colleagues (2007) observed increased volumes in the cerebellum bilaterally in first-episode BD subjects (Adler et al., 2007). In a longitudinal VBM study, patients with BD showed a decrease in cerebellar gray matter density over 4 years, and this decline was more rapid than observed in healthy control subjects (Noolhara et al., 2007). McDonald and colleagues (2005), however, found no abnormalities in BD patients who had experienced psychotic symptoms compared to controls (McDonald et al., 2005).

Our results are in agreement with previous ROI studies. Vermal subregions V2 and V3 were smaller in BD subjects (Monkul et al., 2008), mainly in those with a history of multiple episodes (DelBello et al., 1999; Mills et al., 2005). In contrast to earlier CT studies (Lppard et al., 1982; Nasrallah et al., 1981, 1982; Weinberger et al., 1982) and our data, bipolar patients from the former study (Monkul et al., 2008) did not exhibit significantly smaller cerebellar hemispheres compared with healthy subjects. However, these results, as in the present study, suggest that cerebellar vermal atrophy may occur during the course of BD, either as a result of medication exposure or illness progression. Interestingly, Brumbilla et al. (2001) found that patients with at least one first-degree relative with a history of mood disorders had smaller cerebellar hemispheres and vermis volumes and larger left lateral ventricle volumes compared with patients with BD without a first-degree family history of BD (Brumbilla et al., 2001).

Finally, Arcudi et al. (2000) reported right cerebellar hemisphere and vermis agenesis in autopsy findings in a case of suicide behavior, low IQ, and personality disorder. In a MRI functional study, Jabbar et al. (2008) observed reduced activity in the right cerebellum in euthymic men with a history of major depressive disorder and suicidal behavior. Moreover, there is evidence that the cerebellum is involved in

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls (n = 22)</th>
<th>Bipolar disorder (n = 40)</th>
<th>Bipolar disorder without history of suicide attempts (n = 20)</th>
<th>Bipolar disorder with history of suicide attempts (n = 20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (54.5)</td>
<td>29 (72.5)</td>
<td>16 (80.0)</td>
<td>13 (65.0)</td>
<td>0.3 1</td>
</tr>
<tr>
<td>Female</td>
<td>10 (45.5)</td>
<td>11 (27.5)</td>
<td>4 (20.0)</td>
<td>7 (35.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>37.7 ± 11.3</td>
<td>40.9 ± 10.6</td>
<td>39.4 ± 11.2</td>
<td>11.4 ± 11.2</td>
<td>0.29</td>
</tr>
<tr>
<td>Years of schooling</td>
<td>11.2 ± 3.8</td>
<td>11.8 ± 3.2</td>
<td>11.3 ± 3.8</td>
<td>11.3 ± 3.8</td>
<td>0.39</td>
</tr>
<tr>
<td>N. episodes</td>
<td>8.4 ± 5.0</td>
<td>6.1 ± 5.8</td>
<td>5.1 ± 5.8</td>
<td>10.9 ± 5.8</td>
<td>0.24</td>
</tr>
</tbody>
</table>

impulsive behavior (Moore-Hornsby et al. 2009), which strongly correlates with suicide. However, our results are not in agreement with this previous data.

There are several limitations of this study that are worth considering. First, although the overall sample size of BD patients was reasonable for a study using neuroimaging data, the examined bipolar I patients with a history of suicide attempt was rather small. Thus, there was insufficient statistical power to examine psychopathological phenomena in our BD group. Second, although our findings suggest that BD indicates more severe brain structural anomalies, our findings do not necesarily indicate that these findings are exclusive to BD patients. Third, the cross-sectional design precluded the opportunity to examine chronological relationships between suicide attempt and BD. Further, the study was conducted in two urban tertiary hospitals serving a low- or middle-income population; therefore, these results may not be generalizable to other care service settings. However, one of the strengths of our sample is that it consisted of patients with euthymic BD type I which diagnosis were well-characterized and without any comorbidities.

In conclusion, cerebellar volumes are reduced in patients with BD as compared to healthy controls. Our results are in agreement with the literature and extend the findings, suggesting that there is no relationship between cerebellar volume and suicide attempts. As BD is a multi-state, heterogeneous disease and different MRI analysis techniques have been employed throughout the literature, there are a variety of conflicting results. Future studies should more thoroughly evaluate the role of the cerebellum in mood disorders.

Role of funding sources

This paper has been supported in part by the Mood and Anxiety Disorders Program (CTPAM), Santa Fe, Brazil, and by the National Council of Technological and Scientific Development (CNPq), registered as a public entity no. 523797/2010-1, and CNPq had no further role in the study design in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Conflict of interest

The authors have no financial disclosures or conflicts of interest relevant to the subject of this article to report.

Acknowledgments

The authors would like to thank all of the patients who agreed to be included in this study for their cooperation and resilience in completing the assessment. We also thank the professionals at Image Memorial for their technical assistance.

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Physical copy not available.
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Please cite this article as: Bakalacu, L., et al., Cerebellar volume related to bipolar disorder? J. Affect. Disord. (2011), doi:10.1016/j.jad.2011.06.059

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CONSIDERAÇÕES FINAIS

O cerebelo contribui não só no controle dos movimentos voluntários, da coordenação, do equilíbrio, da marcha e da postura, mas também das funções cognitivas (memória, atenção, linguagem e funções executivas), além do controle das emoções e do comportamento. Entretanto, a natureza exata do seu envolvimento nos processos mentais superiores ainda não está totalmente compreendida. Nesse contexto, técnicas de neuroimagem estrutural e funcional mostram-se como ferramentas valiosas no estudo da contribuição do cerebelo na cognição e seu papel nos transtornos psiquiátricos.

Anormalidades na estrutura e nas funções cerebelares têm sido relatadas em alguns transtornos psiquiátricos. Nos indivíduos com prejuízo cognitivo foi observado que o volume cerebelar está reduzido e correlacionado com o prejuízo da atenção e linguagem, mesmo antes do desenvolvimento da demência do tipo Alzheimer. Esses dados corroboram estudos prévios que demonstraram anormalidades cerebelares em portadores de Alzheimer, mas também acrescenta que tais alterações já estão presentes nos estágios precoces da doença.

No transtorno do estresse pós-traumático foi observada a redução do volume do hemisfério cerebelar esquerdo associada aos sintomas de revivência, evitação, hiperatividade e ansiedade. Apesar de lesões em hemisférios cerebelares associadas e alterações emocionais já terem sido descritas, ainda não há suporte na literatura para compreender o motivo de tal lateralização. Também foi observada a redução do volume do vérmis cerebelar associada aos mesmos sintomas, além de sintomas depressivos e trauma no início da vida. Tal achado confirma dados da literatura, que observaram a relação das regiões posteroinferiores do cerebelo, mais precisamente do vérmis, com o controle das emoções. Estende-se ainda os dados para a relação entre eventos precoces
de vida na gênese de transtornos mentais, teoria muito discutida na literatura, entretanto de difícil comprovação.

No transtorno bipolar foi observada a redução do volume total do cerebelo, dos hemisférios e do vérmis comparado a controles. Também foi observada a redução em portadores dessa doença com história de suicídio, mas, ao contrário do que seria esperado baseado em dados da literatura, não houve relação com os sintomas de impulsividade, número de episódios de humor ou tempo de doença. Nesse último transtorno fica então o questionamento: Seria a redução volumétrica do cerebelo um traço relacionado diretamente ao curso da doença ou uma alteração precoce que poderia predispor a doença?

Pesquisas futuras ainda são necessárias para investigar a importância das alterações estruturais cerebelares em pacientes com transtornos psiquiátricos de forma mais aprofundada. Para tal, serão necessárias amostras maiores, com testes neuropsicológicos mais minuciosos e unindo técnicas de neuroimagem estrutural e funcional (como o volume de interesse – VOI). Também, seria importante que se observasse diferentes grupos no mesmo transtorno, baseado nas diferentes formas de ativação do cerebelo durante a mesma tarefa.

Para o Século 21 ainda há muito o que ser descoberto. Talvez uma molécula nova, um novo processo celular, um processamento de sinal exclusivo em redes neuronais, ou como um princípio de controle ainda desconhecidos, que podem mudar os conceitos atuais e compreender de forma mais aprofundada como essa estrutura regula e complementa as demais funções do sistema nervoso. O cerebelo se mostra como um local propício a tais descobertas, principalmente para o esclarecimento do funcionamento de circuitos alternativos e de refimento.
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ANEXOS
Aprovações em Comitê de Ética
CEP 0407/07

PARECER DO COMITÉ DE ÉTICA INSTITUCIONAL

Ref: Projeto de pesquisa intitulado: “Relação entre achados de neuroimagem estrutural do cerebelo e desempenho funcional em pacientes idosos com prejuízo cognitivo”.

CARACTERÍSTICA PRINCIPAL DO ESTUDO: ESTUDO CLÍNICO OBSERVACIONAL COM INTERVENÇÃO DIAGNÓSTICA

RISCOS ADICIONAIS PARA O PACIENTE: Risco mínimo, desconforto mínimo.

OBJETIVOS: O objetivo do presente estudo é observar possíveis associações entre o volume do cerebelo além do volume de estruturas que compõem circuitos do quais o cerebelo faz parte, com o desempenho funcional de pacientes idosos apresentando graus variados de prejuízo cognitivo.

RESUMO: O estudo será realizado no Laboratório de Neuroimagem e Cognição (LINC) do Departamento de Psiquiatria da UNIFESP. Serão utilizados dados provenientes do estudo EPIDOSO que seguiu por dois anos 1667 idosos residentes em São Paulo. Dentre esses indivíduos da coorte, 158 foram encaminhados a um outro protocolo de demência, dentro do projeto, e foram objeto de outro estudo, que avaliou clinicamente e neurologicamente esses pacientes. Essas avaliações foram realizadas entre os anos de 1999 e 2003 e os dados estão armazenados no banco de dados do estudo. Neste estudo atual, serão incluídos pacientes do protocolo de demência, com diagnóstico de Alzheimer, Transtorno cognitivo leve e sem prejuízo cognitivo.

FUNDAMENTO E RACIONAL: O presente estudo aborda as possíveis associações entre o volume total e segmentar do cerebelo com o volume das estruturas cerebrais, que fazem parte de seus circuitos. O estudo da importância do cerebelo permitiria uma maior compreensão do funcionamento dessa estrutura, da evolução da doença e também contribuiria para a criação de novos tratamentos...

MATERIAL E MÉTODO: Estão apresentados todos os procedimentos que serão utilizados...

TCLE: não se aplica.

DETALEHAMENTO FINANCEIRO: Sem financiamento específico.

CRONOGRAMA: 4 anos.

OBRIGADO ACADEMICO: MESTRADO.

O Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo **ANALISOU e APROVOU**

o projeto de pesquisa referenciado.

1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê após análise das mudanças propostas.

2. Comunicar imediatamente ao Comitê qualquer evento adverso ocorrido durante o desenvolvimento do estudo.

3. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possível auditoria dos órgãos competentes.

Atenciosamente,

Prof. Dr. José Osmar Medina Pestana
Coordenador do Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/ Hospital São Paulo
PARECER DO COMITÊ DE ÉTICA INSTITUCIONAL

Ref.: Projeto de pesquisa intitulado: "Avaliação neuroestrustral do transtorno do estresse pós-traumático através de imagens de ressonância magnética".

CARACTERÍSTICA PRINCIPAL DO ESTUDO: Estudo clínico, observacional envolvendo o aprimoramento de novas formas diagnósticas (diagnóstico por imagem).

RISCOS ADICIONAIS PARA O PACIENTE: sem risco, desconforto mínimo.

OBJETIVOS: Avaliar alterações neuroestrutrasais no córtex orbitofrontal e hipocampo de pacientes com TEPT através de imagens de ressonância magnética.

RÉSUMO: Estudo transversal com 50 indivíduos com transtorno de estresse pós-traumático (TEPT) e 40 indivíduos, também vítimas de violência, sem diagnóstico de TEPT. Esses pacientes serão provenientes do estudo epidemiológico que será realizado na cidade de São Paulo pela equipe do Prof. Sérgio B Andreoli. O TEPT será diagnosticado segundo critérios do DSM-IV -SCID IV. Serão então submetidos aos seguintes instrumentos de avaliação: 1- questionário sócio demográfico; 2- Inventario de Eventos da Vida traumáticos; 3- CIDI (versão 2.1), 4- Risk and Resiliency Factor Questionnaire, 5- Questionário sobre capital Social e 6- Migration History Questionnaire. Após isso, os pacientes deverão ser encaminhados para a realização das imagens de ressonância magnética, que serão realizadas no Instituto do Sono, UNIFESP.

FUNDAMENTOS E RACIONAL: Estudo que visa relacionar prejuízos neuropsicológicos apresentados por pacientes que sofreram estresse pós-traumático aos relacionados por pacientes que apresentam lesões no hipocampo ou córtex orbitofrontal permitindo avaliar os danos causados pelo TEPT no tamanho de algumas regiões do cérebro.

MATERIAL E MÉTODO:

TCLE: Adequado de acordo com a Res. 195/96

DETALHAMENTO FINANCEIRO: Trabalho financiado pelo CNPq (R$ 82.750,00).

CRONOGRAMA: 24 MESES

OBJETIVO ACADEMICO: MESTRADO


O Comitê de Ética em Pesquisa da Universidade Federal de São Paulo/Hospital São Paulo ANALISOU e APROVOU o projeto de pesquisa referenciado.

1. Comunicar toda e qualquer alteração do projeto e termo de consentimento livre e esclarecido. Nestas circunstâncias a inclusão de pacientes deve ser temporariamente interrompida até a resposta do Comitê, após análise das mudanças propostas.

2. Comunicar imediatamente ao Comitê qualquer evento adverso ocorrido durante o desenvolvimento do estudo.

3. Os dados individuais de todas as etapas da pesquisa devem ser mantidos em local seguro por 5 anos para possibilidade de auditoria dos órgãos competentes.

Atenciosamente,

Prof. Dr. José Osmar Medina Pestana
Coordenador do Comitê de Ética em Pesquisa da
Universidade Federal de São Paulo/Hospital São Paulo

Rua Botucatu, 572 - 1º andar - conj. 14 - CEP 04023-062 - São Paulo / Brasil
Tel: (011) 5571-1062 - 5539.7162
PARECER/RESOLUÇÃO ADITIVA N.º 110/2007

Para análise e deliberação deste Institucional a Professora, Doutora, Ângela Marisa de Aquino Miranda-Scipó, Pesquisadora Responsável pelo Projeto de Pesquisa: “Programa da Avaliação Continuada do Centro de Estudos e Tratamento dos Transtornos Afetivos (CETTA) do HUPES”, aprovado através da Resolução Aditiva N.º 16/2005 deste CEP em 23.02.05, solicitou, em 20 de Agosto de 2007, a inclusão de “exames de neuroimagem: Ressonância Magnética de Crânio-RMC” e “Espectroscopia por Ressonância Magnética-ERM” em córtex pré-frontal e amigdala, para avaliação dos pacientes com transtornos afetivos que fazem parte do projeto supra citado. As justificativas para tais procedimentos encontram-se descritas em um consentimento “mini-projeto”, anexado à solicitação.

Inexistindo na proposição analisada conflito administrativo, processual e ético que contraindique a incorporação pretendida e a consequente continuidade executória local do Estudo, fica a mesma aprovada por este Institucional.

Salvador, 3 de Agosto de 2007.

Professor, Doutor Antônio dos Santos Barata,
Coordenador – CEP/MCO/UFBA

Observações importantes. Toda a documentação anexa ao Protocolo proposto e rubricada pelo (a) Pesquisador (a), arquivada neste CEP, e também a outra devolvida com a rubrica da Secretaria deste ao (a) mesmo (a), faz parte intrínseca deste Parecer/Resolução Aditiva e nas “Recomendações Adicionais” apenas, bem como a impostergável entrega de relatórios parciais e final como consta nesta liberação (Modelo de Redação para Relatório de Pesquisa, anexo).