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

Leonardo Baldaçara a, b, *, Andrea P. Jackowski a, Aline Schoedl c, Mariana Pupo c, Sergio B. Andreoli d, Marcelo F. Mello c, Acíoly L.T. Lacerda a, Jair J. Mari e, Rodrigo A. Bressan a

a Psychiatry, Laboratório Interdisciplinar de Neurociências Clínicas (LiNC), Universidade Federal de São Paulo (UNIFESP), Brazil
b Medicine, Universidade Federal do Tocantins (UFT), Brazil
c Psychiatry, Programa de Atendimento e Pesquisa em Violência (PROVE), Universidade Federal de São Paulo (UNIFESP), Brazil
d Psychiatry, Núcleo de Estatística e Metodologia Aplicadas (NEMAP), Universidade Federal de São Paulo (UNIFESP), Brazil
e Psychiatry, Universidade Federal de São Paulo (UNIFESP), Brazil

A R T I C L E   I N F O

Article history:
Received 27 May 2011
Received in revised form 14 July 2011
Accepted 14 July 2011

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

A B S T R A C T

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 human fear perception, anticipation, and recollection. 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 resilient controls, 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 < 0.01) volumes persisted after controlling for gender, age, and brain volume. In PTSD group, left cerebellar hemisphere volume correlated negatively with PTSD (p = 0.01) and depressive symptoms (p = 0.04). Vermal volume correlated negatively with PTSD symptoms (p < 0.01), early traumatic life events (p < 0.01), depressive symptoms (p = 0.04) 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 Ressler, 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., 2010) and trauma load, (Kolassa et al., 2010) and affect vulnerability in the aftermath of trauma exposure.

Findings from magnetic resonance imaging (MRI) studies have demonstrated neurostructural alterations in PTSD that suggest volumetric reductions or atrophy of the hippocampus (Bremner et al., 2003; Lindauer et al., 2004; Pavic et al., 2007; Stein et al., 1997), amygdala (Pavlisa et al., 2006; Rogers et al., 2009), anterior
cingulate gyrus (Rogers et al., 2009; Woodward et al., 2006), corpus callosum (Carrion et al., 2009; Villarreal et al., 2004), and temporal and frontal gray matter (Geuze 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 affect and efferent connections to the brainstem and limbic system provide a neuroanatomical substrate (Schmahmann and Pandya, 1997; Schutter and van Honk, 2005). 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 (Osuch et al., 2001) and vermis (Anderson et al., 2002; Pissiota 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, superior temporal gyrus, and pituitary differences have been reported in maltreated children and adolescents with PTSD (De Bellis et al., 2002; De Bellis and Kuchibhatla, 2006; Thomas and De Bellis, 2004).

In an MRI study with nonhuman primates, enlarged vermis, dorsomedial prefrontal cortex and dorsal anterior cingulate cortex were observed in peer-reared monkeys (Spinelli et al., 2009). Peer 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 (Spinelli et al., 2009). In humans, MRI studies have reported a smaller bilateral cerebellar volume in children with PTSD secondary to maltreatment (De Bellis et al., 2002; De Bellis and Kuchibhatla, 2006), and smaller vermis in children (aged 7–14) 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 trauma onset (De Bellis and Kuchibhatla, 2006). Only one study has evaluated the cerebellum (more specifically vermis) in adults. This study only examined combat-related PTSD (Levitt 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 to 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 not developed PTSD), were identified through an epidemiological survey that studied PTSD among the civilian population in the city of São Paulo (Andreoli et al., 2009). To identify trauma victims in the community, a professional team specializes in household surveys from Brazilian Institute of Public Opinion and Statistics, conducted interviews. Interviewers were trained on the Composite International Diagnostic Interview (CIDI) (Wittchen et al., 1998) 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 (Andreoli et al., 2009; Bressan 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 after 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 (6 weeks for fluoxetine); 4) body mass index below 20; 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 specialist used Structured Clinical Interview 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 Interview for DSM-IV (SCID-I). SCID I is a semi-structured interview for the DSM-IV. It facilitates 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) (Pupo et al., 2011). 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. CAPS 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., 1974). Scores range from 0 to 63, with depression classified as minimal when scores range from 0 to 11, mild from 12 to 19, moderate from 20 to 35, and severe from 36 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 Sigma scanner. Structural MRI images were acquired using a sagittal T1 acquisition series (TR = 9.8 ms, TE = 3.1 ms, flip angle = 30°, NEX = 1, matrix size = 256 × 256, FOV = 24 cm, thickness = 1.0 mm), yielding 160 slices. Before scanning, a sagittal scout series (nine to eleven 5-mm-thick slices with a 1-mm interslice 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 (dbm.neuro.uni-jena.de/vbm) 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 (Ashburner and Friston, 2005). 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 as the cerebellum appeared laterally to the pons. The tentorium cerebelli acted as the superior limit and the base of the cerebellum as the inferior limit. The cisterna magna and transverse sinus were excluded (De Bellis and Kuchibhatla, 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 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 Kuchibhatla, 2006).

To evaluate inter-rater and test-retest reproducibility, two raters repeated the cerebellar measurements twice, at least one week apart, for 10 randomly selected subjects. Inter-rater reliability and test-retest was found to be high (ICC > 0.96) for all cerebellar and vermal regions.

2.4. Data analysis

Data were codified 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–Wilk 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), ETI (early trauma life events), BDI (depressive symptoms), and BAI (anxiety symptoms) scores were analyzed using a multivariate regression model. Alpha was set at $p < 0.05$.

3. Results

There were no age ($t = 1.74, p = 0.08$) or gender ($\chi^2 = 1.42, df = 1, p = 0.34$) 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 ($t = 6.22, p < 0.01$), avoidance and numbing symptoms ($t = 7.12, p < 0.01$), hyperarousal symptoms ($t = 6.445, p < 0.01$), total CAPS score ($t = 7.88, p < 0.01$), anxiety ($t = 4.65, p < 0.01$), and depressive symptoms ($t = 4.46, p < 0.01$). For details, please see Table 1.

Of the PTSD patients, 81% (34 subjects; $\chi^2 = 42.60, p < 0.01$) 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% (16 subjects) reported no psychological abuse, and other traumatic life experiences as follows: assault (38.1%), sexual and physical abuse (28.6%), sudden death of a loved one (19%), kidnapping (7.1%) and others (14.3%).

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 ($\beta = -0.36, t = -3.44, p < 0.01$), re-experiencing symptoms ($\beta = -0.34, t = -3.11, p < 0.01$), avoidance and numbing symptoms ($\beta = -0.39, t = -3.65, p < 0.01$), hyperarousal symptoms ($\beta = -0.25, t = -2.30, p = 0.02$), early traumatic life events ($\beta = -0.32, t = -2.86, p < 0.01$), anxiety ($\beta = -0.29, t = -2.544, p = 0.013$), and depressive symptoms ($\beta = -0.23, t = -2.04, p = 0.045$) (Fig. 1). A negative correlation between left cerebellum volume and CAPS total score ($\beta = -0.43, t = -2.77, p = 0.01$), re-

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>$F$/$t^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male (n, %)</td>
<td>Mean 95% CI*</td>
<td>Mean 95% CI*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.91 (35.71%)</td>
<td>38.30 (35.21–41.51)</td>
<td>1.42</td>
<td>0.34</td>
</tr>
<tr>
<td>Reexperiencing symptoms</td>
<td>19.72 (16.85–22.63)</td>
<td>7.23 (4.41–10.12)</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>Avoidance and numbing symptoms</td>
<td>26.71 (22.72–30.70)</td>
<td>8.41 (5.06–11.71)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Hyperarousal symptoms</td>
<td>24.14 (20.42–27.71)</td>
<td>9.41 (6.84–12.04)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>CAPS total score</td>
<td>70.53 (61.82–79.23)</td>
<td>25.06 (17.20–32.81)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Early trauma life events (ETI total score)</td>
<td>107.65 (73.74–141.42)</td>
<td>52.11 (25.12–81.43)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Anxiety symptoms (BAI)</td>
<td>29.20 (24.50–33.91)</td>
<td>14.33 (9.83–18.81)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Depressive symptoms (BDI)</td>
<td>25.61 (21.01–30.22)</td>
<td>12.57 (8.73–16.22)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

* CI = Confidence interval.

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experiencing symptoms ($\beta = -0.36, t = -3.30, p = 0.02$), avoidance and numbing symptoms ($\beta = -0.37, t = -2.42, p = 0.02$), hyper-arousal symptoms ($\beta = -0.42, t = -2.74, p = 0.01$), and anxiety ($\beta = -0.32, t = -2.03, p = 0.04$) was also observed (Fig. 2). CAPS total score correlated positively with ETI ($\beta = 0.32, t = 3.02, p < 0.01$). Albeit, when both variables were controlled in linear regression analysis, vermal volume continue correlate negatively with CAPS total score ($\beta = -0.25, t = -2.14, p = 0.04$) and ETI ($\beta = -0.25, t = -2.14, p = 0.04$).

### 4. Discussion

The evidence of structural alterations in cerebellum volume in neuropsychiatric disorders is not novel. Previous data demonstrated a cerebellar volume reduction in schizophrenia (Ichimiya et al., 2001; Lee et al., 2007), bipolar disorder (DelBello et al., 1999), dementia (Baldaçara et al., in press), epilepsy (Bilevicius et al., 2010), attention deficit hyperactivity disorder (Berquin et al., 1998), autism (Courchesne et al., 2001), and anxiety disorder (De Bellis 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 (Nashold 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 nuclei 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, 2009). 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 vermal 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 (Carrion et al., 2009; De Bellis and Kuchibhatla, 2006). However, these studies were conducted with children and adolescents with PTSD. Only one study has examined adults, and no Table 2 Brain measurement in PTSD patients and resilient control group.

<table>
<thead>
<tr>
<th>Volumes</th>
<th>PTSD (n = 42)</th>
<th>Controls (n = 42)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>95% C.I.</td>
<td>Mean</td>
<td>95% C.I.</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>1096.27</td>
<td>1069.05–1123.48</td>
<td>1161.03</td>
<td>1133.82–1188.24</td>
</tr>
<tr>
<td>Total cerebellum</td>
<td>101.93</td>
<td>98.97–104.88</td>
<td>105.52</td>
<td>102.55–108.46</td>
</tr>
<tr>
<td>Left cerebellar hemisphere</td>
<td>50.55</td>
<td>48.89–52.20</td>
<td>53.61</td>
<td>51.95–55.26</td>
</tr>
<tr>
<td>Right cerebellar hemisphere</td>
<td>51.38</td>
<td>49.89–52.88</td>
<td>51.89</td>
<td>50.40–53.39</td>
</tr>
<tr>
<td>Vermis</td>
<td>7.04</td>
<td>6.70–7.39</td>
<td>8.74</td>
<td>8.34–9.08</td>
</tr>
</tbody>
</table>

* Volumes are in cm$^3$.
* Confidence interval.
* Adjusted for age, gender and comorbidity.
* Adjusted for brain volume, age, gender and comorbidity.

Fig. 1. Correlation between vermis volume and CAPS total score and early traumatic life events.
volumetric cerebellar differences were observed between the PTSD and non-PTSD war veterans (Levitt et al., 2006). Moreover, no correlations between CAPS scores and cerebellar, and vermis measurements were observed. However, the last one was observed in males 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 (Carrion et al., 2009; De Bellis and Kuchibhatla, 2006; Levitt et al., 2006) and functional (Bonne et al., 2003; Fernandez 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 antecedent vulnerability for developing PTSD upon exposure to a traumatic event or a consequence of PTSD symptoms.

Spinelli et al. (2009) 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, dorsomedial 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 months 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 (LeardMann et al., 2010). Evidence has suggested that the developing cerebellum is vulnerable to environmental insults, including physical and psychological insults (Ferguson and Holson, 1999; Finkelstein 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 (Sanders et al., 2009), chronic irradiation (Altman, 1987), low birth weight (Martinussen et al., 2009), and neonatal exposure to dexamethasone (Ferguson and Holson, 1999), preferentially damage cerebellar structures.

The dysregulation of the limbic-hypothalamic-pituitary-adrenal (LHPA) 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 primate mothers show this dysregulation (Coplan 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 (Llorente et al., 2009). Maternal deprivation induces neuronal degeneration and astroglial changes in the hippocampus 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 (Llorente et al., 2009).

Thus, children exposed to trauma (early trauma) may experience chronically elevated CRH during pituitary development. Elevated CRH may lead to pituitary hypertrophy, 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 hypertrophy, 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) (Baldacara et al., 2008; Bonne 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, although our results suggest that PTSD indicates more severe brain structural anomalies, our findings do not necessarily indicate that they are restricted to PTSD patients. Second, the cross-sectional study 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.

5. 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 (re-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 theorized previously [Schutter and van Honk, 2005; Teicher 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 (1026/06). 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: 2004/15039-0, and the National Research Council (CNPq) Millenium Institute of Violence and Mental Health by the grant: 420122/2005-2. 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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