Brief report

Dorsolateral prefrontal cortex and hippocampus sustain impulsivity and aggressiveness in borderline personality disorder


* Corresponding authors. Sala is to be contacted at the Department of Mental Health, Azienda Sanitaria Locale di Alessandria, viale Giolitti 2, 15033 Casale Monferrato (AL), Italy. Brambilla, Inter-University Center for Behavioural Neurosciences, Department of Pathology and Experimental & Clinical Medicine, Section of Psychiatry, University of Udine, Udine, Italy. E-mail addresses: michelosalacap@yahoo.it (M. Sala), paolo.brambilla@uniud.it (P. Brambilla).

1. Introduction

Impulsivity and aggressiveness are heritable traits that may contribute to the psychopathology of borderline personality disorder (BPD) (Lieb et al., 2004; Siever and Weinstein, 2009). Impulsive aggression has recently been conceptualised as an imbalance between the “top-down” control or “brakes” provided by the frontal cortices and excessive “bottom-up drives” triggered or signaled by limbic regions (Siever, 2008). Specifically, the hippocampus may play an important role in the regulation of aggressive behaviours. Tumours and infections involving hippocampus are associated to changes in aggressive behaviours (Malamud, 1967) while regional stimulation of hippocampus has been shown to facilitate or inhibit aggressiveness (Gregg and Siegel, 2001). Furthermore, an
inverse correlation between hippocampal volumes and aggressive traits (i.e. provoked and explosive hostility) in BPD patients has been shown (Zetsche et al., 2007).

Regarding prefrontal cortices, the dorsolateral prefrontal cortex (DLPFC) may represent a key structure, along with the orbitofrontal cortex, in impulsivity regulation (Bellani et al., 2010; Chanen et al., 2008; Matsuo et al., 2009; Soloff et al., 2003). Particularly, reduction of DLPFC grey matter volumes has recently been shown in BPD patients compared to healthy subjects (Brunner et al., 2010; Tomoda et al., 2009). Moreover, a recent PET study on BPD subjects, showed that DLPFC failed to activate during the top-down cognitive control of aggression (New et al., 2009). Finally, the interplay between DLPFC and hippocampus appears to play a key role for memory, emotional, and behavioural control in BPD (Anderson et al., 2004; New et al., 2007; Sala et al., 2009; Schmahl et al., 2003, 2004).

In this study we aim to study the structural integrity of hippocampus and DLPFC in BPD patients and their possible correlations with aggressive and impulsive traits.

2. Methods

2.1. Subjects

Fifteen DSM-IV BPD patients were recruited at the Center for Research on Personality Disorders of the University of Pavia, Pavia, Italy (mean age ± S.D. = 32.8 ± 7.6 years; 11 females; 12 right-handed; Caucasians; length of illness ± S. D. = 6.9 ± 3.9 years, years of education = 13.4 ± 2.8). Handedness was detected with the Oldfield handedness questionnaire (Oldfield, 1971). The diagnosis was determined with the SCID-II (Williams et al., 1992), the Diagnostic Interview for Borderline Patients (DIB) (Gunderson et al., 1981), and successively confirmed with the clinical consensus of two staff psychiatrists. The Zanarini Scale for Borderline Personality Disorders (ZAN-BPD) (Zanarini et al., 2003) was used to assess the severity of the illness. The SCID-I was administered in order to detect any Axis I disorders (Spitzer et al., 1992). Patients with any comorbid personality disorder, current medical problems, alcohol or substance abuse within six weeks preceding the study were excluded. Three patients were not taking any medication at the time of testing; four were treated only with antidepressants, two only with a mood stabilizer, one only with an antipsychotic. The other five patients were treated with a combination of antidepressant and antipsychotics, antidepressant and mood stabilizers or antipsychotics and mood stabilizers. Two patients did not have any lifetime comorbid conditions, while eight had major depression, two anorexia nervosa, four dysthymia.

Fifteen healthy subjects 1:1 matched with patients for race, age, gender, handedness, and years of education were recruited (mean age ± S.D. = 34.2 ± 8.1 years; 11 females; 12 right-handed; Caucasians; years of education = 14.9 ± 3.6). They had no past or current history of any axis I or II disorders as determined by the SCID non-patient version (SCID-NP), the SCID-II and the ZAN-BPD. Also they had no current medical problems, no history of substance/alcohol abuse, and no history of psychiatric disorders among first-degree relatives. The same scales as for the BPD patients were administered to healthy controls.

All subjects provided signed informed consent, after having understood all issues involved in participation in the study protocol. This research study was approved by the biomedical Ethics Committee of the IRCCS S. Matteo Hospital.

2.2. Diagnostic instruments

To assess aggressive and impulsive behaviour the Buss–Durkee Hostility Inventory (BDHI) (Buss and Durkee, 1957) and the Barratt Impulsivity Scale (BIS-11) (Patton et al., 1995) were, respectively, used. The HRDS-24 (Hamilton, 1960) and the BPRS (Andersen et al., 1989) were used to rate the clinical symptoms. They were administered by trained raters with extensive experience, being fully reliable blindly and independently with a senior investigator for at least 10 HDRS and 10 BPRS. Also, we regularly assured reliability scale ratings by holding consensus meeting with psychiatric residents and a senior investigator. Moreover, the Child Abuse Scale (CABUSE) (Soloff et al., 2002) was utilized to evaluate childhood abuse.

2.3. MRI collection and processing

MRI scans were acquired with a 1.5 Tesla Siemens Symphony Maestro Class. A T1-weighted sagittal scout image was obtained to verify subject’s head position and image quality (TR = 2300 ms, TE = 3.93 ms, slice thickness = 1). PD and T2-weighted images were successively acquired in order to exclude focal lesions (TR = 2500 ms, TE1 = 24, TE2 = 121 ms, slice thickness = 5 mm). Subsequently, a coronal 3D MPR sequence according to Charcot’s plane was performed (TR = 1400 ms, TE = 3.49 ms, slice thickness = 1 mm).

2.4. Anatomical measurements and landmarks

Anatomical measurements were conducted on a PC workstation (Dell Dimension, Pentium II 400, Windows NT 4.0) using the semi-automated software Brains2. Hippocampus, DLPFC, and intracranium volumes (ICV) were obtained manually in the coronal plane by well trained evaluators blind to group assignment and to subjects’ identity. The intraclass correlation coefficients (ICCs), which were calculated by having two raters trace 10 training scans, were >0.90 for all measurements.

Intracranial volumes (ICV). ICV was traced in the coronal plane, along the border of the brain and included the cerebrospinal fluid, dura mater, sinus, optic chiasma, brainstem, cerebral and cerebellar matter. The inferior border did not extend below the base of the cerebellum.

Hippocampus. The corona radiata and then the ambient cistern were used as the superior border; the white matter acted as the inferior border, and the inferior horn of the lateral ventricle as the lateral one (Baiano et al., 2008). Both the fimbria and the subiculum, but not the parahippocampal gyrus, were included in the tracing.

DLPFC. The tracing was started where the genu of the corpus callosum was formed, constituting the posterior limit. The anterior limit was marked by moving anteriorly nine slices. The superior and inferior borders were the superior frontal sulcus and the superior temporal sulcus, respectively (Brambilla et al., 2004).
2.5. Statistical analyses

All analyses were conducted using the SPSS for Windows software, version 11.0 (SPSS Inc., Chicago), and the 2-tailed statistical significance level was set at \( p \leq 0.05 \). GLM multivariate with ICV as covariate was performed to compare the volumes of the anatomical structures of interest between BPD patients and healthy controls. Spearman’s correlation analyses were used to examine the correlations between scores at the BIS and at the BDHI and hippocampal and DLPFC volumes.

3. Results

3.1. Volumes

Right hippocampal volumes showed a significant effect of diagnosis (\( F = 5.31, \ p = 0.03 \)) (Table 1). No significant differences were found between the two groups for left hippocampus and DLPFC volumes (GLM multivariate with ICV as covariates, \( p > 0.05 \)). Also, BPD patients with a history of childhood abuse (\( n = 6 \)) had significantly reduced right hippocampal volumes (\( F = 8.97, \ p = 0.01 \)) in comparison to those patients without history of childhood abuse (\( n = 9 \)). No volume differences were reported between BPD patients with comorbid lifetime major depression or dysthymia and those without such comorbidities (GLM multivariate with ICV as covariates \( p > 0.05 \)).

3.2. Correlations of hippocampal and DLPFC volumes with aggressive and impulsive traits

Right hippocampal volumes significantly inversely correlated in BPD patients with BDHI total score patients (\( r = -0.6, \ p = 0.02 \)), assaults subscale (\( r = -0.6, \ p = 0.01 \)), and irritability subscale (\( r = -0.6, \ p = 0.01 \)), but not in healthy subjects (BDHI total score: \( r = -0.03, \ p = 0.9 \); assaults subscale: \( r = -0.2, \ p = 0.5 \); irritability subscale: \( r = -0.2, \ p = 0.5 \)). Also, bilateral DLPFC grey matter volumes significantly inversely associated in the BPD group with the BIS total score (left side: \( r = -0.7, \ p = 0.005 \); right side: \( r = -0.6, \ p = 0.03 \)), attention subscale (left side: \( r = -0.6, \ p = 0.02 \); right side: \( r = -0.6, \ p = 0.01 \)), motor subscale (left side: \( r = -0.5, \ p = 0.03 \); right side: \( r = -0.5, \ p = 0.04 \)), but not in the control group (BIS total score left side: \( r = 0.20, \ p = 0.60 \); right side: \( r = 0.4, \ p = 0.08 \); attention subscale left side: \( r = 0.3, \ p = 0.2 \); right side: \( r = -0.4, \ p = 0.1 \); motor subscale left side: \( r = -0.2, \ p = 0.4 \); right side: \( r = -0.03, \ p = 0.9 \)).

No significant correlations were found between hippocampal or DLPFC volumes and illness duration, severity of symptoms (measured by the ZAN-BPD), number of hospitalisations, and medication dosages (\( p > 0.05 \)), with only significant inverse associations between illness duration/severity and right hippocampus (\( r = -0.39, \ p = 0.03 \); \( r = -0.44, \ p = 0.01 \), respectively).

4. Discussion

As expected and consistently with previous studies (Brambilla et al., 2004; Driessen et al., 2000; Schmahl et al., 2003; Soloff et al., 2008; Zetzsche et al., 2007), we found that hippocampal volumes are significantly reduced in BPD patients, especially in those with a childhood history of abuse. We also replicated the previous finding by Zetzsche et al. (2007) confirming the correlation between hippocampal volumes and BDHI scores, both with the subscale that measures provoked or retaliatory hostility (Assault subscale) and with the subscale measuring uncontrolled hostility (Irritability subscale). Interestingly, we showed for the first time the correlation between DLPFC grey matter and white matter volumes and impulsivity as measured with the BIS scale. This result is quite important since there is confusion in the literature concerning the concept of impulsive aggression. Though impulsivity and aggression may be related, they do not actually have the same dimension (Garcia-Forero et al., 2009), being possibly sustained by different anatomical regions. Importantly, some authors suggest that the reduction of hippocampal volumes in BPD patients may characterize the later stages of the disease and may be linked to history of traumatic events (Schmahl et al., 2009; Weniger et al., 2009). In contrast, anatomical alterations of the orbitofrontal cortex and DLPFC may be present at the earlier stages of the illness (Brunner et al., 2010; Chanen et al., 2008), potentially representing a risk factor for the development of BPD. DLPFC is crucially involved in modulating hippocampal activity, particular memory (Sala et al., 2009) and behavioural control (New et al., 2009). Failure of DLPFC functioning may therefore facilitate the development of impulsive behaviours and of aggressiveness discontrol.

It is of interest to note that studies on primates revealed that increased aggressive behaviours and stress share environmental, social and genetic influences (Honess and Marin, 2006a,b). Thus a vicious circle may link aggressiveness and stressful events in BPD which, along with hippocampal disruption, may finally support behavioural disturbances, memory impairment and neuropsychological deficits. It should also be noted that in some other psychiatric disorders like post-traumatic stress disorder (PTSD) and major depression, hippocampal reduction seems to be related to duration of illness and lifetime traumatic experience (Sala et al., 2004). It has been supposed that the elevated activity of stress-associated neurobiological systems such as the hypothalamic-pituitary-adrenal axis determines the shrinkage of hippocampus in stress-related disorders, such as PTSD, major depression and BPD (De Bellis et al., 2001; Bremner 2006), particularly in patients with history of traumatic events (Sapolsky 2001; Sala et al., 2004; Wingenfeld

Table 1: Volumes in borderline personality disorder (BPD) patients and healthy controls.

<table>
<thead>
<tr>
<th>Volumes (ml)</th>
<th>BPD patients (n=15)</th>
<th>Healthy controls (n=15)</th>
<th>F</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hippocampus</td>
<td>1.23±0.23</td>
<td>1.27±0.22</td>
<td>0.27</td>
<td>0.60</td>
</tr>
<tr>
<td>Right hippocampus</td>
<td>1.24±0.26</td>
<td>1.42±0.15</td>
<td>5.43</td>
<td>0.027</td>
</tr>
<tr>
<td>Left DLPFC grey matter</td>
<td>6.63±2.09</td>
<td>6.30±2.08</td>
<td>0.08</td>
<td>0.78</td>
</tr>
<tr>
<td>Left DLPFC white matter</td>
<td>8.99±4.05</td>
<td>8.27±3.60</td>
<td>0.09</td>
<td>0.76</td>
</tr>
<tr>
<td>Right DLPFC grey matter</td>
<td>6.14±1.99</td>
<td>5.42±1.78</td>
<td>0.96</td>
<td>0.34</td>
</tr>
<tr>
<td>Right DLPFC white matter</td>
<td>8.1±2.89</td>
<td>7.57±2.77</td>
<td>0.25</td>
<td>0.62</td>
</tr>
</tbody>
</table>

DLPFC = dorsolateral prefrontal cortex. GLM multivariate with ICV as covariate was performed.

*\( p < 0.05 \).
et al., 2010). In this regard, it will be crucial to further understand how early epigenetic events, such as traumatization, influence hippocampal development in these illnesses, particularly focussing on DLPFC and hippocampus before and after treatment modulation.

Two major specific limitations should be considered for interpretation of our findings. Firstly, the sample size was relatively modest, although comparable to previous neuro-anatomical studies in this field (Monarch et al., 2004). Secondly, the majority of BPD patients had other comorbid diagnoses, as it is often seen in the real world (Skodol et al., 2002; Soloff et al., 2002, 2000). Therefore, excluding subjects with Axis I comorbidity would create a non-representative BPD sample that could ultimately limit the generalizability of the findings.

In conclusion, DLPFC and hippocampus may have different roles in sustaining aggressiveness and impulsiveness in BPD. Future longitudinal imaging studies should further investigate the structural and functional neural correlates of impulsive–aggressive behaviour in young BPD patients, in particular focussing on DLPFC and hippocampus before and after treatment modulation.

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Conflict of interest

No authors of this manuscript have fees and grants from, employment by, consultancy for, shared ownership in, or any close relationship with, an organisation whose interests, financial or otherwise, may be affected by the publication of the paper.

None of these funding agencies had any further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report, and in the decision to submit the paper for publication.

References


