An fMRI study of negative emotion processing and cognitive reappraisal in major depressive disorder and borderline personality disorder

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Abstract

Background. One common denominator to the clinical phenotypes of borderline personality disorder (BPD) and major depressive disorder (MDD) is emotion regulation impairment. Although these two conditions have been extensively studied separately, it remains unclear whether their emotion regulation impairments are underpinned by shared or distinct neurobiological alterations.

Methods. In the present study we contrasted the neural correlates of negative emotion regulation across an adult sample of BPD patients (n=19), MDD patients (n=20) and healthy controls (HCs; n=19). Emotion regulation was assessed using an established functional magnetic resonance imaging (fMRI) cognitive reappraisal paradigm. We assessed both task-related activations and modulations of interregional connectivity (i.e., Psychophysiological Interactions, PPI).

Results. When compared to HCs, patients with BPD and MDD displayed a homologous decreased activation in the right ventrolateral prefrontal cortex (vlPFC) during cognitive reappraisal. Additionally, the MDD group presented decreased activations in other prefrontal areas (i.e., left dorsolateral and bilateral orbitofrontal cortices), while the BPD group was characterized by a more extended pattern of alteration in the connectivity between the vlPFC and cortices of the visual ventral stream during reappraisal.

Conclusions. Decreased activation of the vlPFC underlays emotion regulation deficits in MDD and BPD, although, beyond this finding, these groups are characterized by specific neurobiological underpinnings. Alterations in patients with MDD suggest a primary deficit in the strength of prefrontal activations, while patients with BPD are better characterized by connectivity disruptions between the prefrontal cortex and temporal emotion processing regions. These findings substantiate in neurobiological terms the different profiles of emotion regulation alteration observed in these disorders.

Keywords. Emotion regulation, borderline personality disorder, major depressive disorder, fMRI, prefrontal cortex, functional connectivity, cognitive reappraisal, transdiagnostic psychiatry, neuroimaging.

Introduction

Emotion is a complex and multifaceted process that involves different evaluative components, including appraisal processes evaluating the meaning and relevance of actual or imagined events (Peil, 2014). These appraisals may be consciously modulated to regulate emotions, such as during the reappraisal of negative emotion scenarios into neutral or positive terms, and this is an important factor influencing wellbeing and successful functioning (Cicchetti, Ackerman & Izard, 1995; Thompson-Schill, 2005). One way to modulate such emotion appraisals is cognitive reappraisal, an antecedent-focus cognitive control strategy that allows reframing emotion-inducing stimuli or scenarios in positive terms, which leads to decreased sympathetic activity and negative affect, better interpersonal functioning, and increased physical and psychological wellbeing (Gross and John, 2003; Steward, et al, 2016).

In neurobiological terms, emotion regulation is characteristically implemented by the circuits linking different regions of the prefrontal cortex (PFC) with subcortical structures, such as the amygdala or the hypothalamus, related to emotional responding (Beauregard et. al., 2001; Goldin et al., 2008; Ochsner et al., 2004; Phan et al., 2005). More specifically, regulatory input to subcortical structures is assumed to originate in dorsolateral prefrontal (dlPFC) and orbitofrontal cortices (OFC), being disturbances in these circuits associated to changes in the emotional experience and social behaviour (Scheuerecker, et.al. 2010). Moreover, other PFC regions such as the ventrolateral prefrontal cortex (vlPFC) has been shown to be implicated in selecting goal-appropriate responses and retrieving information from semantic memory, which will then be used to develop new appraisals (Badre, 2007; Thompson-Schill, 2005).

Several studies have demonstrated that patients with psychiatric disorders have difficulties in using cognitive reappraisal (Campbell-Sills et al., 2014), although the mechanisms of alteration may differ across conditions. Thus, despite alterations in emotion regulation are central to both Major Depressive Disorder (MDD) and Borderline Personality Disorder (BPD), these may be underpinned by different pathophysiological mechanisms. Firstly, subjects with BPD show fluctuations in subcortical systems functioning, which results in failure to habituate and hypersensitivity to threat cues (Brasfield, 1994). Importantly, this has been suggested to underlie many of the pathological manifestations of this disorder, including affective instability, intense and tumultuous relationships, difficulty controlling anger, impulsivity, suicidal tendencies, and deliberate self-harm (thought to serve an emotion-regulating function) (Cooper 2001; Rothschild, Haslam, Cleland, & Zimmerman, 2003). Patients with MDD, in contrast, show a different clinical profile, and portray cognitive impairments related to basic elements of emotional processing (Heinzel, 2010), which has been linked to decreased prefrontal recruitment during voluntary behavioural and cognitive control (Beauregard et. al. 2006). Indeed, during early, automatic stages of emotion regulation, MDD subjects capable of recruiting lateral prefrontal neuronal resources have been shown to successfully regulate emotions (Rive, et. al. 2013). Nevertheless, such putatively distinct neurobiological mechanisms of altered emotion regulation have been never directly compared. This comparison may be however of great interest not only to further understand the different mechanisms of psychological maladjustment in BPD and MDD, but also to develop disorder-specific approaches to improve emotion regulation capacities.

The present study is, to our knowledge, the first to investigate these neurobiological aspects in both disorders during an emotional processing paradigm with functional magnetic resonance imaging (fMRI). Moreover, given the central role of interregional connectivity

alterations in neurobiological models of emotion regulation disruption, we decided to not only assess task-related brain activations, but also task-modulations of interregional connectivity. Overall, we anticipated that both MDD and BPD groups, in comparison with healthy controls (HCs), would display greater difficulties in regulating emotions. More specifically, we also hypothesized that patients with BPD would show increased subcortical activations related to inefficient regulatory input from prefrontal areas, while patients with MDD would recruit fewer prefrontal areas during regulation of emotions. Finally, we also anticipated that such neurobiological alterations would be specifically correlated to core clinical measurements in both groups of patients.

Methods

Sample

The study included three groups of participants: patients with BPD (n=19), patients with MDD (n=20) and HCs (n=19), which were recruited at *Fundación Lucha contra las Enfermedades Neurológicas en la Infancia* (FLENI foundation) in Buenos Aires, Argentina. There was a total of 19 males and 39 females, ranging from 21 to 63 years of age (Mean=41.26, SD=13.11). Patients were consecutively recruited when attending the Department of Psychiatry at FLENI if they met DSM-V diagnostic criteria for BPD or MDD. All participants were evaluated via a clinical interview in order to confirm their DSM-V diagnosis (patients) or the absence of any present or past diagnostic (HCs). Table 1 summarizes sociodemographic and clinical features of study participants. Exclusion criteria for patients included current or past presence of other psychiatric diagnoses (including psychotic symptoms but excluding nicotine addiction), or current or past presence of major neurological or medical conditions (including episodes of loss of consciousness > 30 min). Controls were recruited form the same sociodemographic environment, and were excluded not only because of the current or past presence of any psychiatric, neurological or major medical condition, but also if they reported current of past treatment with psychotropic medication. Subjects from all groups were also excluded if they were not able to undergo the MRI exam or gross anatomical abnormalities were detected in the MRI scan.

The present study was carried out in accordance with the latest version of the Declaration of Helsinki. The ethics committee in clinical research of Bellvitge University Hospital approved the study. Signed informed consent was obtained from all participants.

Psychometric assessment

All participants completed the validated Spanish versions of the Emotion Regulation Questionnaire (ERQ) and the Difficulties in Emotion Regulation Scale (DERS) to evaluate emotion dysregulation. Likewise, all subjects also completed the Hamilton Depression Rating Scale and Hamilton Anxiety Rating Scale to assess severity of depression and anxiety symptoms, respectively (Hervas et al., 2018; Gómez-Ortiz et al., 2016; Gross & John, 2003; Gratz & Roemer, 2004).

MRI acquisition

Functional Magnetic Resonance Imaging (fMRI) data was acquired on a 3T General Electric HDx scanner with an 8-channel head coil. Change in blood-oxygenation-level-dependent (BOLD) T2* signal was measured using a gradient echo-planar imaging (EPI) sequence. Thirty-three contiguous slices were obtained in the AC-PC plane (TR=2s, TE=30ms, flip angle=90°, FOV=24cm, 64x64 matrix, voxel size=3.75 x 3.75 x 4, 247 volumes). A

structural MRI was also acquired (for image pre-processing and detection of gross anatomical abnormalities) with the T1-weighted 3D fast SPGR-IR sequence (166 slides, 1.2mm thick slices, TR=6.988ms, TE=2.848ms, flip angle=8°, FOV=26cm, 256 x 256 matrix).

fMRI task, emotional paradigm

We used a well-validated paradigm to evaluate brain activations during emotion regulation with functional magnetic resonance imaging (fMRI) using negative images and in-scanner behavioural ratings (Phan et al., 2005). Picture stimuli were obtained from the International Affective Picture System (Lang et al. 1995; IAPS). The task consisted of three conditions ("observe," "maintain" and "regulate") presented in an ABC design with four blocks per condition (i.e., a total of twelve blocks). At the beginning of each block, a word appeared in the middle of the screen for four seconds to provide instructions to participants for the upcoming block. If the instruction was to "observe", the images that followed were neutral in content and participants were required passively observe them without trying to alter their emotional response. If the instruction was to "maintain", the presented images that followed were negative and participants were instructed to actively sustain the negative emotions elicited by the images. Finally, if the instruction was to "regulate," the images were always negative in content and participants had to reappraise and reduce the intensity of negative emotions by means of previously trained cognitive reappraisal techniques (distancing or reappraisal/reinterpretation). All blocks consisted of two consecutive images (each image was presented on screen for ten seconds, with no inter-stimulus interval), and each block was followed by 10 seconds of baseline during which a cross fixation was presented on the screen to minimize carryover effects (Steward et.al. 2016). Images were presented thru a system…

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Comentario [2]: Mirta/Agustina, me dice Salvador que vosotras podéis completar esta información. Gracias!

After the presentation of the second picture of each block during the emotion regulation task, the intensity of the negative emotion experienced was self-rated by participants on a 1–5 number scale (1 being 'neutral' and 5 being 'extremely negative'). These in-scanner ratings were recorded through an fMRI-compatible response pad (Lumina 3G Controller, Cedrus Corporation).

fMRI pre-processing and analysis

All fMRI images were initially preprocessed using the Wavelet Despike procedure within the BrainWavelet Toolbox to remove high and low frequency artifacts induced by abrupt physical movements (Patel et al. 2014). Remaining image processing was performed using Statistical Parametric Mapping software (SPM12, Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk/spm) running on MATLAB R2017a. Functional images were realigned to the mean position of all scans and co-registered to their respective T1 images, which were used for normalization to MNI space. Subsequently, normalization parameters were applied to the functional time-series, which were finally smoothed with an 8-mm full width at half maximum (FWHM) kernel.

Regulate vs. maintain was defined as the contrast of interest for first-level (single-subject) analysis. This contrast allows for the delineation of brain activations associated with cognitive reappraisal (Phan et al. 2005). Conditions were modeled for the 20 seconds that the images were displayed and did not include instruction, rating and rest periods. The BOLD response at each voxel was convolved with the SPM12 canonical hemodynamic response function (HRF) using a 128-s high-pass filter.

Contrast images from first-level comparisons were carried forward to second-level analyses. Between-group comparisons in task activations were conducted with a one-way ANOVA model including the three groups (HC, MDD and BPD patients) as the main factor. Age was introduced as a nuisance covariate in these analyses.

To investigate between-group differences in task-induced connectivity between the brain regions activated during the emotion regulation task, we also performed psychophysiological interactions (PPI) analyses in SPM12. Specifically, the impact of the contrast of interest (the 'psychological' factor) on the strength of time-course correlations of our empirically obtained region of interests (ROI, the 'physiological' factor) was explored. In first level analyses, functional connectivity maps were estimated for the selected seeds by including the signal of interest in interaction with the task blocks, while controlling for the raw signal of the seed and the task blocks (Steward et. al., 2016). Resulting images were then included in a one-way ANOVA model (second-level) to assess between-group effects.

Our whole-brain analyses were corrected for multiple comparisons using a voxel-wise nonparametric permutation testing with the threshold-free cluster enhancement (TFCE) method (Smith & Nichols 2009) as implemented in the SPM-TFCE toolbox v174 (http://dbm.neuro.uni-jena.de/tfce/). Significance threshold was set at $p<0.05$, family-wise error (FWE) whole-brain corrected.

Analysis of psychometric data were carried out with SPSS v. 25 (IBM Corp; Armonk, NY). Specifically, we first extracted with SPM the first eigenvariate from peak voxels of above analyses, and these values were compared between-groups with independent sample t-tests, while linear associations with psychometric data were estimated using Pearson's correlations. In these last analyses, associations were considered significant if significance p values were below 0.05 and effect sizes were moderate to large ($|r|>0.24$; Rosnow & Rosenthal 1996).

Results

The demographic and clinical characteristics of the sample are displayed in Table 1. Because of patients were consecutively recruited, groups significantly different in age (patients with MDD were older). Because of this, age was introduced as a nuisance covariate in all analyses.

Ximena Goldberg 10/3/21 12:31
Comentario [3]: How would consecutive recruitment affect mean age? Difference in mean age could be due to other expected factors (volunteers are usually younger, mean age MDD is usually over 45 and BPD is usually younger than MDD in general)

Sample			
	HCs (n =19)	BPD (n =19)	MDD (n=20)
Gender	N(%)	N(%)	N(%)
Female	15(79)	10(53)	14(70)
	(Mean ± S.D.)	**(Mean ± S.D.)**	**(Mean ± S.D.)**
Age	35.84±10.38	37.68±11.25^	49.80±13.24º^
Psychometric Evaluations			
CERQ Reappraisal	10.37±4.57	8.32±4.74	8.00±3.65
CERQ Rumination	8.89±3.16	9.74±2.60	9.65±3.11
DERS Total	58.21±15.10	96.95±33.05*	89.15±21.88º
HDRS Total	0.16±0.68	5.58±5.80*	6.70±6.35º
HARS Total	0.68±1.63	9.89±9.27*	5.40±4.10

Table 1. Demographic and clinical characteristics of the study group. Abbreviations = CERQ = Cognitive Emotion Regulation Questionnaire, Scale; DERS = Difficulties in Emotion Regulation; HARS= Hamilton Anxiety Rating Scale; HDRS = Hamilton Depression Rating Scale; RRS = Reappraisal and Rumination Subscales. Symbol references for significant correlations among groups = *HC-BPD; ºHC-MDD; ^BPD-MDD.

Intra-Scanner ratings

Overall, in-scanner emotion ratings showed the highest values during the maintain blocks (mean = 3.08, SD=0.89), followed by regulate (mean = 2.56, SD=0.90) and observe (mean = 1.860, SD=0.99) blocks. We did not observe, however, significant across-group differences in these ratings.

fMRI task-related activations

In the contrast regulate vs. maintain, a direct between-group comparison showed that when compared to HCs, individuals of BPD and MDD groups presented overlapping decreased activations in the right ventrolateral prefrontal cortex (vlPFC) during cognitive reappraisal. Additionally, patients with MDD, also in comparison to HCs, showed decreased activations in the left dorsolateral prefrontal cortex (dlPFC) and in the bilateral orbito-frontal cortex (OFC) (Figure 1A, Table 2).

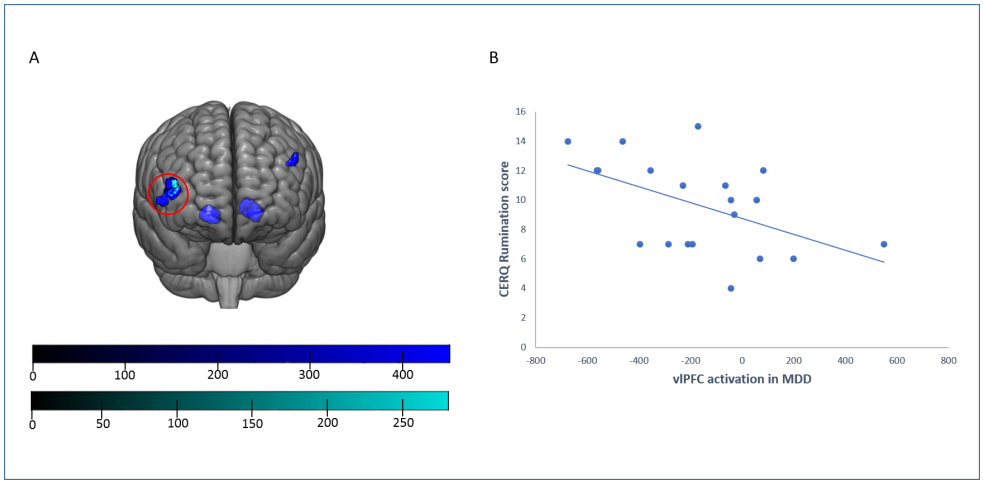

Figure 1. *Between-group differences in task-related activations*. **A)** Patients with BPD (cyan) and patients with MDD (blue) showed overlapping decreased activations in comparison to HCs during emotion regulation in right vlPFC (red circle). Patients with MDD showed additional hypoactivations in left dlPFC and the OFC (bilaterally). **B)** Correlation between CERQ rumination score and right vlPFC activation in patients with MDD. Color bars represent TFCE values.

Ximena Goldberg 10/3/21 12:37
Comentario [4]: There is no cyan in the brain figure. That does mean no specific results for BPD?

Ximena Goldberg 10/3/21 12:38
Comentario [5]: Do you mean the slope line? Could be useful to repeat here what TFCE means.

Activations: Regulate>Maintain						
Contrast	Anatomical Area	MNI Coordinates			k_E	P_{FWE}
		X	Y	Z		
HC>BPD	Right vlPFC	45	60	6	117	0.030
HC>MDD	Right vlPFC	47	56	8	393	0.008
	Right OFC	18	38	-9	342	0.011
	Left OFC	-17	42	-9	443	0.011
	Left dlPFC	-47	45	33	65	0.018

Table 2. Regions showing significance between-group differences activations during Regulate>Maintain. Abbreviations = BPD = Borderline Personality Disorder HC= Healthy Controls; Left dlPFC = Left Dorsolateral Prefrontal Cortex; Left OFC = Left Orbitofrontal Cortex; MDD = Major Depressive Disorder; Right OFC = Right Orbitofrontal Cortex; Right vlPFC = Right Ventrolateral Prefrontal Cortex.

PPI analyses

Regarding psycho-physiological interactions (PPI), we observed significant between-group differences when assessing connectivity from the right vlPFC. Specifically, in comparison to HCs, individuals from both the BPD and MDD groups showed a similar pattern of reduced connectivity with right posterior temporal areas. Nevertheless, the BPD group showed an additional cluster of decreased connectivity with the right vlPFC involving the left inferior temporal cortex. In addition, when directly comparing both clinical groups, patients with BPD showed decreased connectivity values in comparison to patients with MDD within these same clusters (Figure 2A, Table 3).

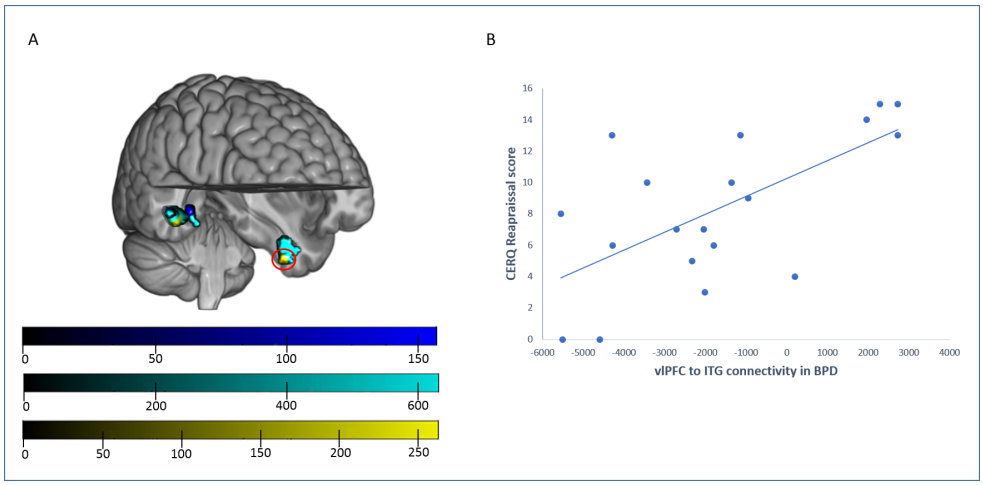

Figure 2. *Between-group differences in PPI analyses from the right vlPFC seed.* **A)** In comparison to HCs, patients with MDD showed a decreased connectivity with right posterior temporal areas, involving the medial temporal gyrus (MTG) and the parahippocampal gyrus (PHG) (blue). Patients with BPD (cyan) showed also decreased connectivity with posterior temporal areas (in this case, with peak differences in the fusiform gyrus (FG)) and, specific to these subjects, with the left inferior temporal gyrus (ITG). Moreover, patients with BPD showed, in comparison to the MDD group (yellow), decreased connectivity between the right vlPFC and the left ITF and the right FG. **B)** CERQ reappraisal scores correlated positively with right vlPFC-left ITG (red circle) connectivity in the BPD group. Color bars represent TFCE values.

Ximena Goldberg 10/3/21 12:40
Comentario [6]: MDD? HC?

Ximena Goldberg 10/3/21 12:41
Comentario [7]: Same as before

Connectivity (PPI) → vlPFC: Regulate>Maintain						
Contrast	Anatomical Area	MNI Coordinates			k_E	P_{FWE}
		X	Y	Z		
HC>BPD	FG	48	-36	-14	475	0.001
	ITG	-39	-9	-33	364	0.002
HC>MDD	PG	33	-36	-6	58	0.007
	MTG	53	-35	-11	42	0.033
MDD>BPD	ITG	-35	-9	-39	54	0.024
	FG	45	-45	-8	161	0.009

Table 3. Regions showing significant area connectivity (PPIs) during Regulate>Maintain; Anatomical area interaction, MNI coordinates, cluster size (kE) and one-sample p-values showing significant differences between the groups; healthy controls compared to borderline personality disorder patients (HC>BPD); healthy controls compared to major depressive disorder patients (HC>MDD); major depressive disorder patients compared to borderline personality disorder patients (MDD>BPD); Fusiform Gyrus (FG); Inferior Temporal Gyrus (ITG); Parahippocampal Gyrus (PG); Medial Temporal Gyrus (MTG). Abbreviations= BPD = Borderline Personality Disorder; HC = Healthy Controls; ITG = Inferior Temporal Gyrus; FG = Fusiform Gyrus; MDD = Major Depressive Disorder; MTG = Medial Temporal Gyrus; PG =Parahippocampal Gyrus.

Correlations between clinical and imaging data

We observed a significant negative correlation between right vlPFC activation and CERQ rumination scores in the MDD group (Pearson's r= -0.505; p= 0.023; Figure 1B), which significantly differed from the same correlation in the BPD group (Pearson's r= 0.099; p= 0.686 and z=-1.881; p= 0.03), although the difference with the correlation in HCs did not reach statistical significance (Pearson's r= -0.22; p= 0.365 and z=-0.954; p= 0.17). Also, we observed that patients with BPD showed a significant positive correlation between CERQ reappraisal scores and right vlPFC-left ITG connectivity (Pearson's r= 0.644; p= 0.003; Figure 2B). This correlation differed from what was observed both in MDD (Pearson's r= 0.004; p= 0.986 and z=-2.208; p= 0.014) and HC (Pearson's r= -0.112; p= 0.648 and z=-1.846; p= 0.032) groups.

Discussion

Our results showed that both individuals with MDD and individuals with BPD display a decreased activation of the vlPFC during cognitive reappraisal. Nevertheless, such hypoactivation was more extensive in the MDD group, who also showed a negative correlation between reappraisal-related vlPFC activity and rumination. Likewise, patients with MDD displayed other clusters of significant hypoactivation during emotion regulation, including the left dlPFC and the bilateral OFC. Conversely, patients with BPD showed larger connectivity decreases between the vlPFC and left inferior and right posterior temporal regions during reappraisal, being this connectivity alterations significantly associated with emotion regulation capacities. Overall, this pattern of results confirms our a priori hypotheses, since patients with MDD seem to recruit fewer prefrontal areas during regulation of emotions, while the BPD group displayed inefficient regulatory input from prefrontal areas.

Our findings of a decreased vlPFC activation during in emotional processing in both patient groups are in agreement with previous research (Chechko et al., 2016). The vlPFC plays a crucial role in response selection and inhibition (Aron et al., 2014), and, particularly, in the inhibition of emotional appraisals (Wager et al., 2009). Our present results therefore indicate that emotion regulation impairments in MDD and BPD may be partly a consequence of ineffective management of inhibitory resources. Notably, the vlPFC has been related to the use

of reinterpretation strategies during reappraisal, as opposed to the use of distancing strategies engaging parietal regions (Ochsner et al., 2004; Ochsner et al., 2012, Pico-Pérez et al., 2017). Consequently, MDD and BPD seem to share a weakened reinterpretation capacity, although we observed a larger cluster of alteration in MDD. Moreover, in this group, decreased vlPFC activation was inversely correlated with rumination scores, which, in addition to suggest that such hypoactivation is a core feature of the depression phenotype, concurs with reports in healthy control samples (Hooker et al., 2010) and other findings indicating that the lateral prefrontal cortex plays a general inhibitory role limiting the impact, or carryover effects, of an emotional state onto emotional states evoked by subsequent events (Waugh et al., 2017). On the other hand, the lateralization of this finding to the right hemisphere is in agreement with previous reports in MDD (Bruder et al., 2015) and BPD (Visintin et al., 2016) patients, but not with recent meta-analytic evidence in anxiety and depression groups (Picó-Pérez et al., 2017). The recruitment of the left vlPFC has been however associated to a greater use of linguistic and semantic strategies (Ochsner et al., 2012), which may be less relevant in emotion regulation protocols using visual cues, such as the one of the present study.

Decreased activation of the dlPFC has been also previously reported in clinical samples, including not only depression and anxiety patients (Campbell-Sills et al., 2014; Johnstone & Walter, 2014), but also individuals with substance abuse disorders (Kober et al., 2014). This region participates in different executive functions (Wager & Smith, 2003), and, in the context of emotion regulation, its role seems to be related to the active manipulation of information to reappraise emotional stimuli (Ochsner et al., 2012). This alteration concurs with the executive function alterations commonly described in depression samples (Rock et al., 2013). In this case, however, findings were lateralized to the left hemisphere. This may be partially accounted for by the role of right dlPFC activation in negative emotion appraisal, which is related to depression severity and may therefore compensate for the executive function-related hypoactivations allegedly occurring during reappraisal (Phan et al., 2005; Grimm et al., 2008).

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Regarding the hypoactivations also observed in the medial orbitofrontal cortex in patients with MDD, it should be noted that this region, as other medial prefrontal structures, has been shown to downregulate activity in subcortical limbic structures (Etkin et al. 2009), and, indeed, its functional connectivity with the amygdala is increased during threat-induced anxiety in healthy controls (Gold et al. 2015). According to our findings, the medial OBF of patients with MDD is probably not exerting this downregulatory input into subcortical limbic structures.

Patients with BPD did however not show such extended prefrontal hypoactivation, but rather a decreased functional connectivity between the vlPFC and visual association cortices of the ventral stream, implicated in complex visual feature detection and recognition of facial expression (George et al., 1993). Different studies have consistently described a hyperresponsiveness of the visual system in BPD patients when processing emotional information, especially, emotional faces, extending from primary cortices to association cortices of the temporal lobe (Chechko et al., 2016; Scherpiet et al., 2014; Guitart-Masip et al., 2009; Koenigsberg et al., 2009; Herpertz et al., 2001). Although we here have not observed such increased activation in the visual system, the regulatory input from the vlPFC cortex was diminished in patients with BPD, which seems to be a plausible mechanism to account for the visual hyperresponse described with other emotional tasks in the above studies. Likewise, although patients with MDD also showed some degree of decreased connectivity from the vlPFC to early visual perception areas, their clusters were less extended and, at least for some of these clusters (i.e., right posterior fusiform gyrus), we also observed a significant difference

between the clinical groups, with MDD patients showing significant connectivity increases in comparison to the BPD group.

According to these results, it can be concluded that alterations in emotion regulation in patients with BPD (and to a lesser extent, in patients with MDD) start at perceptive stages, before information reaches proper limbic structures (i.e., the amygdala). Nevertheless, since information is conveyed from these visual association cortices to the amygdala (Dolan et al., 2002; Cardoner et al., 2011), it is expected that such (lack of) modulation of the perceptive input into the amygdala will indirectly weaken the regulatory input from prefrontal structures to the amygdala. In this sense, it is worth mentioning that only patients with BPD, but not patients with MDD, showed in our study decreased connectivity between the vlPFC and more rostral parts of the ITG, anatomically closer to the amygdala. It can therefore be suggested that as information progresses through the ventral stream, alterations in prefrontal modulation of visuo-emotional processing are exclusively observed in patients with BPD. Interestingly, alterations in the white matter tracts linking anterior brain areas with visual association cortices (i.e., the inferior fronto-occipital and the inferior longitudinal fasciculi) have been described in patients with BPD (Ninomiya et al., 2018).

Overall, the above notions concur with recent reports suggesting that, in comparison to patients with MDD, patients with BPD show an exaggerated amygdala response in emotional induction paradigms (Schulze et al., 2019). It is also remarkable that correlations between inter-regional connectivity alterations and emotion regulation scores were only observed in patients with BPD. Specifically, we observed a positive association between reappraisal capacity and vlPFC-rostral ITG connectivity, indicating that prefrontal input at this particular stage of visuo-emotional processing within the ventral stream may critically determine emotion regulation success in this clinical group. In sum, these prefronto-visual association cortices connectivity alterations observed in BPD are likely to account for the increased sensitivity to emotional aspects of the environment (Herpertz et.al., 1997) and the general higher sensitivity to emotional stimuli and slow return of emotional arousal to baseline that characterize patients with BPD (Johnson et al., 2003).

The results of this study have to be interpreted in the context of the following limitations. Firstly, our overall sample was small (n=58, with 19/20 subjects per group), which may have limited the power of our analyses to detect significant findings. Nonetheless, we would like to stress that our subjects were carefully recruited according to strict inclusion criteria, and we have obtained several significant differences between the study groups. Secondly, patients with MDD were older than the other two groups, although this was a consequence of the consecutive recruitment strategy. Moreover, we controlled for age in all the analyses, and, therefore, reported findings do not depend on this variable. Thirdly, we observed no significant across-group differences in intra-scanner ratings, although this is commonly observed in emotion regulation studies and should not be interpreted as evidence of spared emotion regulation capacities (Pico-Pérez et al., 2017). Indeed, our groups differed from healthy controls in psychometric measurements of emotion regulation (i.e., DERS scores). Moreover, intra-scanner ratings showed that emotions were successfully induced to all groups of participants, who also engaged in the regulation protocol (i.e., higher scores during maintain and lower scores during observe blocks). There are, nevertheless, different reasons for this lack of across-group differences in intra-scanner ratings, such as the inherent limitations of subjective behavioral assessments, social desirability effects, or impaired self-awareness of emotional experience, as suggested by Zilverstand et al. (2016). Lastly, we assessed emotion regulation strategies with a retrospective self-report measure. Although previous research has

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shown that such measurements may significantly predict real-life outcomes such as well-being and depressive symptomatology (Gross and John 2003), future research can benefit from real-time and real-life approaches, such as ecological momentary assessments.

Taken together, our findings indicate that MDD and BPD share an altered neural response during cognitive reappraisal involving the right vlPFC, indicating that this region is implicated in the emotion regulation shortcomings that characterize both disorders. Nevertheless, MDD patients showed a more widespread pattern of reduced prefrontal activation, which may be interpreted in the context of a pervasive alteration in executive functioning probably stemming from a primary deficit in the strength of prefrontal activations. On the other hand, BPD patients showed a more extended pattern of dysfunctional connectivity between prefrontal areas and visual association cortices that may lead to the higher sensitivity to emotional stimuli typically observed in these patients. These findings substantiate in neurobiological terms the existence of dissimilar profiles of emotion regulation alteration between these disorders, and may ultimately be of relevance for the development or optimization of clinical interventions aimed at restoring emotion regulation capacities.

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XG: Health Department of the Generalitat de Catalunya (SLT002/16/00237)

Conflict of interest.

None

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Con formato: Inglés (americano)

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