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

De la Peña-Arteaga et al.

Methods

Sample

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 setting and were excluded if they reported the current or past presence of any psychiatric, neurological or major medical condition or if they reported current of past treatment with psychotropic medication. Participants from all groups were also excluded if they were not able to undergo the MRI exam or if anatomical abnormalities were detected in the MRI scan.

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, cognitive reappraisal paradigm

At the beginning of each block of the task, 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.

The paradigm was executed using Presentation software (Neurobehavioral Systems, Inc.) and images were presented to subjects by means of a projector and a screen placed at the feet of participants, who were able to see the images trough a mirror system mounted on the head coil.

After the presentation of the second picture of each block, the intensity of the negative emotion experienced by was self-rated by participants on a 1–5 number scale (1 being 'neutral' and 5 being 'extremely negative'). Subjects provided these responses through an fMRI-compatible response pad (Lumina 3G Controller, Cedrus Corporation) placed near their right hand.

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 artefacts induced by abrupt physical movements (1). 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 (2). Conditions were modelled 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 (HCs, 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 cognitive reappraisal task, we also performed a generalized form of psychophysiological interactions (gPPI) 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. First-level design matrices (subject-wise level) included the regressors of the different task blocks (i.e., observe, maintain and regulate), and 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. 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 (3) 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 ($|r|>0.24$) (4).

Results

Activations: Regulate>Maintain						
Contrast	Anatomical Area	MNI Coordinates			k_E	P_{FWE}
		x	y	z		
HCs>BPD	Right vlPFC	45	60	6	28	0.042
HCs>MDD	Right vlPFC	47	56	8	210	0.017
	Right OFC	18	38	-9	172	0.031
	Left OFC	-17	42	-9	234	0.025
	Left dlPFC	-47	45	33	11	0.040

Supplementary Table 1. *Regions showing significant activation differences during Regulate>Maintain (controlling for age and sex).* Abbreviations: BPD = Borderline Personality Disorder; dlPFC = Dorsolateral Prefrontal Cortex; FWE = Family-Wise Error; HCs= Healthy Controls; k_E = Cluster extent; MDD = Major Depressive Disorder; MNI = Montreal Neurological Institute; OFC = Orbitofrontal Cortex; vlPFC = Ventrolateral Prefrontal Cortex.

Activations: Maintain>Observe						
Contrast	Anatomical Area	MNI Coordinates			T	$P_{uncorrected}$
		x	y	z		
Maintain>Observe	Right Amygdala	21	-5	-18	2.25	0.014

Supplementary Table 2. *Regions showing across-group activation in the in Maintain>Observe contrast.*
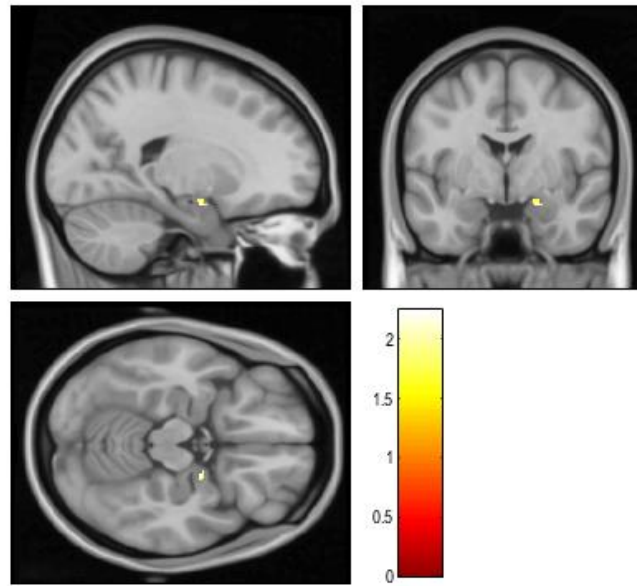
Supplementary Figure 1. *Across-group activation in right amygdala in the Maintain>Observe contrast.*
Colour bar indicates t-value.

Activations: Maintain>Observe						
Contrast	Anatomical Area	MNI Coordinates			k_E	P uncorrected
		x	y	z		
MDD>HCs	Right vlPFC	50	54	5	62	0.005
	Right OFC	12	39	-15	190	0.016
	Left OFC	-3	35	-14	336	0.007
BPD>HCs	Right vlPFC	45	59	11	237	<0.001
	Right OFC	14	36	-12	183	0.012
	Left OFC	-17	42	-9	471	0.002

Supplementary Table 3. *Regions showing significant activation differences during Maintain>Observe*
within the vlPFC cluster. Abbreviations: BPD = Borderline Personality Disorder; HCs= Healthy Controls;
k_E = Cluster extent; MDD = Major Depressive Disorder; MNI = Montreal Neurological Institute; OFC =
Orbitofrontal Cortex; vlPFC = Ventrolateral Prefrontal Cortex.

References

1. Patel A, Kundu P, Rubinov M, Jones P, Vértes P, Ersche K, et al. A wavelet method for modeling and despiking motion artifacts from resting-state fMRI time series. Neuroimage. 2014; 95: 287-304.
2. Phan KL, Fitzgerald DA, Nathan PJ, Moore GJ, Uhde TW, Tancer ME. Neural substrates for voluntary suppression of negative affect: A functional magnetic resonance imaging study. Biol Psychiatry. 2005; 57(3): 210–219.
3. Smith S, Nichols T. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage. 2009; 44(1): 83-98.
4. Rosnow R, Rosenthal R. Computing contrasts, effect sizes, and counternulls on other people's published data: General procedures for research consumers. Psychol Methods. 1996; 1: 331-340.