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Altered frontoparietal connectivity in patients with obsessive-compulsive disorder during an fMRI cognitive reappraisal task

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ABSTRACT

Patients with obsessive-compulsive disorder (OCD) present increased brain activity in orbitofrontal and limbic regions when experiencing negative emotions, which could be related to deficits in emotion regulation abilities. 30 OCD patients and 29 healthy controls (HC) performed a cognitive reappraisal functional magnetic resonance imaging (fMRI) task and completed emotion regulation and OCD symptomatology questionnaires. Besides task activation, connectivity was also compared between groups through psychophysiological interaction analysis (PPI), using regions previously reported to be hyperactive in OCD as seeds. Finally, brain-behavior correlations were performed between activation/connectivity strength in group differential regions and the questionnaires' scores, as well as the emotional ratings reported during the task. Behaviorally, patients with OCD were less successful than controls at lowering the emotional impact of negative images. At the brain level, there were no significant between-group differences in brain activation. Contrarily, PPI analyses showed that HC had increased frontoparietal connectivity when experiencing negative emotions in comparison to OCD patients, while this pattern was reversed when regulating emotions (increased connectivity in patients). Finally, frontoparietal connectivity was correlated with measures of emotion regulation success and OCD symptomatology. Our findings point towards frontoparietal altered connectivity as a potential compensatory mechanism during emotion regulation in OCD patients.

1. Introduction

Emotion regulation involves the initiation of new, or the alteration of ongoing, emotional responses through the action of regulatory processes. Emotion regulation strategies include attentional deployment, cognitive reappraisal (reinterpreting the meaning and one's connection to a stimulus), and suppression of the expression or experience of an emotion (Gross, 1998; Ochsner et al., 2012). Functional magnetic resonance imaging (fMRI) studies have shown that reappraisal is associated with higher activation in the dorsomedial and lateral frontal cortices, dorsal anterior cingulate cortex (dACC), and parietal and temporal regions (Buhle et al., 2013; Frank et al., 2014). These frontal and cingulate areas are part of the frontoparietal cognitive control network implicated in effortful regulation, by cognitively reframing the affective meaning of a negative stimulus in more neutral terms (Dosenbach et al., 2007). In turn, this network exerts control over automatic bottom-up ventral and limbic regions (such as the amygdala), involved in the appraisal of emotional stimuli (Ochsner and Gross, 2014). Previous dynamic causal modeling studies have attempted to characterize the functional interrelationships among these dorsal and ventral regions during emotion regulation, finding that the inferior frontal gyrus is strongly interconnected with the dorsolateral prefrontal cortex (dlPFC), while the ventromedial prefrontal cortex serves as the primary conduit through which prefrontal regions directly modulate amygdala activity (Morawetz et al., 2016; Steward et al., 2021).

Obsessive-compulsive disorder (OCD) is a psychiatric disorder that affects 1–3% of the population and is characterized by the presence of distressing and recurring thoughts, urges, or images (obsessions), followed by mental or physical repetitive behaviors (compulsions) (American Psychiatric Association, 2013). When confronted with

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disease-relevant stimuli patients with OCD experience negative emotions such as anxiety, fear, guilt, or disgust (Schienle et al., 2005; van den Heuvel et al., 2004), and increased brain activity in ventral frontal and limbic regions such as the orbitofrontal cortex (OFC), the rostral anterior cingulate cortex (rACC) and the amygdala (Picó-Pérez et al., 2020; Thorsen et al., 2018). Previous studies have shown that patients with OCD present decreased emotion regulation abilities, with difficulties in engaging in cognitive reappraisal strategies (Goldberg et al., 2016). Thus, it has been hypothesized that the exaggerated emotional reactivity in OCD is related to emotion regulation impairments (Mataix-Cols and van den Heuvel, 2006; Milad and Rauch, 2012; Paul et al., 2016). Indeed, one of the components of cognitive-behavior therapy (CBT) (a first-line treatment for OCD; Franklin and Foa, 2011), consists of teaching patients emotion regulation strategies to help them cognitively reappraise negative symptom-eliciting situations as non-threatening.

From a neurobiological perspective, a dysfunctional interaction between dorsal and ventral networks is hypothesized to be responsible for the impaired emotional processing and regulation found in several psychiatric disorders (Hu et al., 2014; Phillips et al., 2003; Picó-Pérez et al., 2017). Particularly in OCD, previous structural and functional neuroimaging studies have shown alterations in brain areas associated with these circuitries (de Wit et al., 2014; Ferreira et al., 2020b; Menzies et al., 2008; Thorsen et al., 2018), with some of these functional deficits normalizing after symptom improvement (Huyser et al., 2010; Vriend et al., 2013). These findings support the hypothesis that emotion regulation deficits in OCD may be related to altered dorsal control functioning and/or hyperactivation in the ventral system. Thus, the rebalancing of these networks by means of cognitive reappraisal training could be expected to improve patients' symptomatology (Fink et al., 2018).

Despite this evidence, the neural correlates of effortful emotion regulation in OCD using fMRI have only been explored in one previous dataset. In the first publication from this dataset, the authors compared OCD patients and matched controls in an fMRI cognitive reappraisal task, where they had to regulate the distress provoked by general fear and OCD-related pictures (de Wit et al., 2015). They found that OCD patients showed increased amygdala activation during emotional processing, while emotion regulation–related activation was lower in the left dlPFC and parietal cortex while viewing fear-related pictures, and higher in the dorsomedial prefrontal cortex (dmPFC) while viewing OCD-related pictures. Furthermore, patients showed lower functional connectivity between the dmPFC and bilateral amygdala during the regulation of fear-related pictures, suggesting that OCD patients show frontolimbic and frontoparietal dysfunction during emotional processing and regulation. Although promising, these findings await replication, and further studies are needed before firm conclusions can be drawn.

Thus, in this study we aimed to compare patients with OCD and matched controls while they performed an fMRI negative emotion regulation task using cognitive reappraisal strategies. To this end, both activation and connectivity analyses were performed. We hypothesized that OCD patients would be less successful in regulating their emotions compared with controls, and this would be accompanied at the neurobiological level with a decreased recruitment of dorsal regions and an increased activation in ventral regions. Moreover, connectivity differences between groups were also expected in regions from the dorsal and ventral systems.

2. Methods

2.1. Participants

Thirty-four OCD patients were recruited from the Psychiatry Service of Hospital de Braga in Braga, Portugal. Thirty-one healthy controls (HC) were recruited from the community matching the OCD group by sex/gender, age and education. In order to be included, participants had to be adults (18 years old or older) and not have any incompatibilities to perform an MRI scan (such as metallic implants, etc.). OCD patients had to be diagnosed with OCD according to the Diagnostic and Statistical Manual of Mental Disorders criteria (DSM-5; American Psychiatric Association, 2013), regardless of the magnitude of the main symptom and treatment status. Patients were excluded if they had other current psychiatric diagnoses (Axis I or Axis II disorders), or current or past presence of major neurological or medical conditions. HC were excluded if they had current or history of any psychiatric or neurological disorder. After excluding 4 patients and 2 controls due to MRI artifacts or not performing the task properly, our final sample was composed of 30 patients and 29 controls. Their sociodemographic information can be found in Table 1. All participants gave informed consent before starting the study procedures. This study was conducted according to the Declaration of Helsinki and received approval of the Ethics Committee of the University of Minho (CEICVS 057/2019) and of Hospital de Braga (Braga, Portugal; 111_2019).

2.2. Behavioral scales

Before going into the scanner, participants completed scales measuring OCD symptomatology and emotion regulation. The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Castro-Rodrigues et al., 2018; Goodman et al., 1989) was used to measure symptom severity in OCD patients. This scale is composed by 10 items and is divided in two subscales, separately measuring severity of obsessions and compulsions.

Table 1
Demographic and clinical characteristics of the sample.

	OCD (N = 30)	HC (N = 29)	Statistic (p-value)
Age, Mean (*SD*)	28.97 (11.14)	29.35 (12.14)	U = 421.50 (0.844)
Sex/gender, *N* females (%)	17 (56.67)	15 (51.72)	$\chi^2(1)$ = 0.15 (0.703)
Years of education, Mean (*SD*)	13.37 (3.57)	13.86 (3.89)	U = 482.50 (0.47)
Age of onset, Mean (*SD*)	17.00 (7.77)	–	–
Medication, *N* (%)			
SSRI	16 (53.33)	–	–
Tricyclic	2 (6.67)	–	–
SSRI + Tricyclic	5 (16.67)	–	–
SSRI + AP	1 (3.33)	–	–
Unmedicated	2 (6.67)	–	–
Naïve	4 (13.33)	–	–
Y-BOCS Compulsions	13.90 (2.23)	–	–
Y-BOCS Obsessions	12.10 (3.08)	–	–
Y-BOCS Total	26.00 (4.81)	–	–
OCI-R Washing	4.03 (3.50)	1.66 (2.02)	U = 244.50 (**0.006***)
OCI-R Checking	5.52 (3.78)	2.10 (2.01)	U = 189.50 (< **0.001***)
OCI-R Ordering	5.72 (3.87)	3.79 (2.53)	$t(56)$ = −2.25 (**0.028***)
OCI-R Hoarding	3.41 (3.33)	3.28 (2.85)	U = 423.50 (0.969)
OCI-R Obsessing	7.14 (3.60)	2.35 (2.62)	U = 119.00 (< **0.001***)
OCI-R Neutralizing	4.21 (3.87)	1.90 (1.97)	U = 295.50 (**0.049***)
OCI-R Total	29.79 (16.70)	15.21 (10.35)	$t(56)$ = −4.00 (< **0.001***)
ERQ Reappraisal	25.97 (8.19)	29.21 (7.82)	$t(57)$ = 1.55 (0.126)
ERQ Suppression	14.57 (4.51)	14.83 (5.84)	$t(57)$ = 0.19 (0.85)
Reactivity	2.01 (1.48)	2.52 (0.94)	U = 506.50 (0.182)
Success	0.30 (1.00)	0.83 (0.85)	$t(55)$ = 2.15 (**0.036***)

Total N = 58 for the OCI-R subscales, and N = 57 for the ratings (Reactivity and Success variables). Abbreviations: HC, healthy controls; OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitors; AP, antipsychotics; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; OCI-R, Obsessive-Compulsive Inventory-Revised; ERQ, Emotion Regulation Questionnaire.

The Obsessive-Compulsive Inventory – Revised (OCI-R) (Foa et al., 2002; Huppert et al., 2007) is an inventory of 18 items measuring six dimensions of OCD symptoms (washing, checking, ordering, obsessing, hoarding, and neutralizing), and was applied to both patients and controls. Finally, all participants completed the Emotion Regulation Questionnaire (ERQ) (Gross and John, 2003; Vaz et al., 2008), which assesses habitual use of two emotion regulation strategies: cognitive reappraisal and expressive suppression.

2.3. fMRI cognitive reappraisal task

We used the fMRI cognitive reappraisal task described by Steward et al. (2016), which was an adapted version of the original task by Phan et al. (2005). This task consists of presenting neutral or negative images that participants have to (1) Observe (to passively observe neutral pictures); (2) Maintain (to actively pay attention to the emotions elicited by negative emotional pictures, sustaining them over time); or (3) Regulate (to reappraise the emotions induced by negative emotional pictures). Before entering into the scanner, participants were given reappraisal examples using both distancing and reinterpretation techniques. Then, after the MRI session, we interviewed the participants to confirm that they were performing the task properly. Specifically, we asked them which type of emotion regulation strategies they applied (reinterpretation, distancing, or others), and whether they changed regulation strategies during the task.

We used 24 stimuli from the International Affective Picture System (IAPS; Lang et al., 2005): eight neutral pictures (e.g. household objects), which were presented in the Observe condition, and 16 highly unpleasant, arousing pictures (e.g. mutilations) in the Maintain and Regulate conditions. Specifically, it consisted of 12 blocks: four blocks for each condition. Instructions (Observe, Maintain or Regulate) were pseudo-randomized throughout the task to avoid the induction of sustained mood states. Each block began with the instructive prompt (Observe, Maintain or Regulate) presented in the middle of the screen for 4 s. After the prompt, participants viewed two different pictures of equal valence for 10 s each. After the presentation of the second picture of each block, 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'). To minimize carryover effects, a fixation cross was shown for 10 s after each block.

PsychoPy3 software (v1.90.1, University of Nottingham; Peirce, 2007) and an MRI-compatible angled mirror system were used to display task's instructions and visual stimuli. We used an MRI-compatible response pad (Lumina–Cedrus Corporation, USA) to record in-scanner ratings.

2.4. Image acquisition and preprocessing

We used a Siemens Verio 3T scanner (Siemens, Erlangen, Germany) with a 32-channel head antenna. The scanning session included as an anatomical acquisition one sagittal Magnetization-Prepared Rapid Acquisition with Gradient Echo (MPRAGE, TR/TE=2420/4.12 ms, FA=9°, 1 mm^3 isometric voxel size, Field-of-View=176 × 256 × 256 mm^3). Next, participants performed the cognitive reappraisal task, acquired using a multi-band Echo Planar Imaging sequence, CMRR EPI 2D (R2016A, Center for Magnetic Resonance Research, University of Minnesota, Minnesota, USA) sensitive to fluctuations in the Blood Oxygenation Dependent Level contrast and with the parameters: TR/TE=1000/27 ms, FA=62°, 2 mm^3 isometric voxel size, 64 axial slices over a matrix of 200 × 200 mm^2. This acquisition lasted for 7.8 min.

Images were preprocessed using fMRIPrep (Esteban et al., 2019). This software performs an optimized preprocessing pipeline for functional and structural data, and further information can be found in the Supplementary Material.

2.5. Statistical analyses

2.5.1. Behavioral data analyses

Statistical analyses were conducted using JASP software (version 0.16.1.0; JASP Team, University of Amsterdam, the Netherlands). *P* values under 0.05 were considered statistically significant. Groups were compared on continuous variables using independent-sample *t*-tests or Mann-Whitney tests, depending on the Shapiro-Wilk's test of normality. Sex/gender distribution between groups was analyzed using a chi-squared test. We used a 2 × 3 repeated-measures ANOVA to compare the in-scanner ratings of each condition (Observe, Maintain and Regulate) between both groups. Post-hoc tests with Holm correction were used to check the differences between every two conditions. Moreover, participants' self-reported success in lowering their in-scanner negative emotion intensity was calculated by subtracting Regulate ratings from Maintain ratings (Success = Maintain - Regulate), while participants' reactivity during emotional processing was computed as Reactivity = Maintain – Observe, and these variables were compared between the groups.

2.5.2. fMRI task activation analysis

First-level (single-subject) analyses were performed using the statistical parametric mapping software (SPM12; https://www.fil.ion.ucl.ac.uk/spm/), and we defined two contrasts of interest: Maintain>Observe, to identify activations related to the induced negative emotions, and Regulate>Maintain, to detect activations associated with cognitive reappraisal. Conditions were modeled for the 20 s that the images were on the screen and did not include instruction and rating periods. The BOLD response at each voxel was convolved with the SPM12 canonical hemodynamic response function using a 128 s high-pass filter. The mean corticospinal fluid (CSF) and white-matter (WM) signals were used as covariates, as well as variables related to movement computed during fMRIprep preprocessing (the first 6 aCompCor components, framewise displacement and DVARS). Two-sample *t*-tests were used at the second-level to compare the groups in our contrasts of interest. Data were analyzed at the whole-brain level, and the SPM12 cluster thresholding correction was used, requiring an uncorrected *p* voxel of 0.001, and a family-wise error (FWE) corrected *p* cluster of 0.05.

2.5.3. Psychophysiological interactions analysis

We conducted psychophysiological interactions (PPI) analysis using SPM12 to investigate the connectivity between brain regions stimulated by the task. The PPI seeds were chosen based on previous literature on emotional processing and OCD. Specifically, the regions identified in Picó-Pérez et al. (2020) meta-analysis as having increased activation during emotional processing in OCD patients were used. These regions comprised: a right anterior insula/amygdala/putamen cluster, the left angular gyrus, the left amygdala/ventral putamen, the left precentral gyrus, the medial prefrontal cortex (mPFC), and the left thalamus (see Fig. 1 and Supplementary Table 1 for further information).

Thus, we explored the impact of the two contrasts of interest (the 'psychological' factor) on the strength of time-course correlations between these six seeds and all the other regions of the brain (the 'physiological' factor). Functional connectivity maps were estimated for each seed and each contrast by means of whole-brain linear regression analyses. A high-pass filter set at 128 s was used to remove low-frequency drifts of less than approximately 0.008 Hz. Contrast images were generated for each subject by estimating the regression coefficient between the seed time series and each brain voxel signal. Resulting images were then included in a two-sample *t*-test model for each of the contrasts (second-level) to assess for between-group effects. The same significance thresholding as in the task activation analysis was used.

2.5.4. Brain-behavior correlations

Eigenvariates from regions showing between-group activation or connectivity differences were extracted, and correlations between

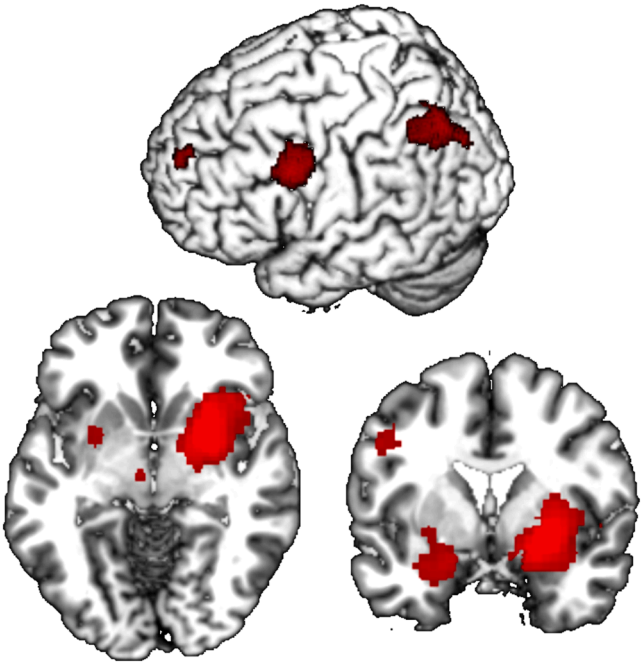

Fig. 1. Regions used as seeds for the PPI analysis: right anterior insula, left angular gyrus, left amygdala, left precentral gyrus, medial prefrontal cortex, and left thalamus. Image adapted from Fig. 2 in Picó-Pérez et al. (2020), reproduced with permission from the authors.

neuroimaging measures and behavioral scales (emotion regulation and OCD symptoms) were assessed using JASP. Correlations were tested for the full sample, as well as for each group separately, and Pearson or Spearman correlations were used depending on the normality of the data. The presence of outliers was also tested and these were removed from the correlation analysis.

3. Results

3.1. Sociodemographic and clinical characterization

Both groups were comparable in terms of age, education years and sex/gender (Table 1). Clinical information of the OCD group (age of onset, symptom severity, and medication status) is also shown in Table 1.

3.2. Behavioral results

3.2.1. In-scanner behavioral measures

The assumption of sphericity from our 2 × 3 repeated-measures ANOVA was violated, so the Huynh-Feldt test was used. There was a significant main effect of condition ($F(1.783, 98.067) = 112.728$, $p < .001$), and post-hoc tests showed that Maintain differed from Observe, indicating successful negative emotion induction during this condition for both groups ($t = -14.423$, $p_{holm} < 0.001$), and that Regulate differed from Maintain, indicating successful emotion regulation ($t = 3.597$, $p_{holm} < 0.001$) (Fig. 2). There was no main effect of group ($F(1, 55) = 0.155$, $p = .695$), nor interaction effect between condition and group ($F(1.783, 98.067) = 1.877$, $p = .163$). On the other hand, the Success variable was significantly different between groups ($t(55) = 2.15$, $p = .036$), with HC showing more successful regulation.

3.2.2. Outside-scanner behavioral measures

There were no significant between-group differences on the ERQ subscales. Instead, patients scored significantly higher in all OCI-R subscales, except for OCI-R Hoarding (Table 1).

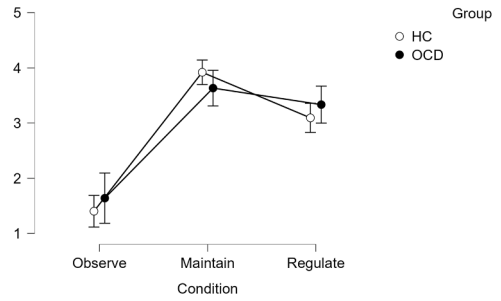

Fig. 2. In-scanner negative emotion intensity ratings. Mean (95% Confidence Interval) in-scanner negative emotion ratings elicited during each condition (Observe, Maintain and Regulate) for each group (1 being 'neutral' and 5 being 'extremely negative'). HC, healthy controls; OCD, obsessive-compulsive disorder.

3.3. fMRI task activation results

There were no significant between-group whole-brain activation differences for Maintain>Observe or Regulate>Maintain.

3.4. PPI results

3.4.1. Group differences in Maintain>Observe

The connectivity between the left angular gyrus seed and the left ventrolateral prefrontal cortex (vlPFC) was significantly higher in HC in comparison to OCD patients (Table 2, Fig. 3). There were no other regions of significantly different connectivity at the whole-brain level for any of the other seeds.

3.4.2. Group differences in Regulate>Maintain

Compared to HC, patients showed significantly increased connectivity between the left angular gyrus and the vlPFC (Table 2, Fig. 3). For this contrast, there were also no other regions of significantly different connectivity at the whole-brain level for any of the other seeds.

3.5. Brain-behavior correlations

After the removal of two outliers, there was a significant correlation between the left angular gyrus – left vlPFC connectivity during Maintain>Observe and the variables Success (Pearson's $r(54) = 0.292$, $p = .031$), OCI-R Washing (Spearman's $rho(55) = -0.331$, $p = .013$), and OCI-R Obsessing (Spearman's $rho(55) = -0.351$, $p = .008$). Moreover, there was a significant correlation between the left angular gyrus – left vlPFC connectivity during Regulate>Maintain and OCI-R Obsessing (Spearman's $rho(55) = 0.357$, $p = .007$). Importantly, these correlations were no longer significant when explored for each group separately. On the other hand, specifically for the OCD group, the connectivity between these regions during regulation was negatively correlated with Y-BOCS Compulsions (Pearson's $r(28) = -0.461$, $p = .012$) and Y-BOCS Total (Pearson's $r(28) = -0.391$, $p = .036$). Plots of the correlations can be found in Supplementary Fig. 1.

4. Discussion

In this study, we aimed to explore the neural correlates of emotion regulation in OCD patients compared to controls, using an fMRI cognitive reappraisal task. Patients with OCD seem to be less successful than controls at lowering the emotional impact of negative images, but this was not accompanied by differences in brain activations. On the other hand, our PPI analysis showed that HC had increased frontoparietal connectivity when experiencing negative emotions in comparison to OCD patients, while this pattern was reversed when having to regulate emotions (increased connectivity in patients). Finally, frontoparietal connectivity during emotional processing and regulation was correlated

Table 2
Psychophysiological interaction analysis results.

Contrast	Seed	Region	MNI coordinates	Ke	*t*-value	p_{FWE}
Maintain>Observe						
HC>OCD	Left angular gyrus	Left vlPFC	−18, 56, 2	413	4.48	.008
Regulate>Maintain						
OCD>HC	Left angular gyrus	Left vlPFC	−50, 40, −4	330	4.33	.037

Findings are significant at the whole-brain level $p < .05$ FWE-cluster corrected. Abbreviations: HC, healthy controls; OCD, obsessive-compulsive disorder; vlPFC, ventrolateral prefrontal cortex; MNI, Montreal Neurological Institute; Ke, cluster extent in voxels.

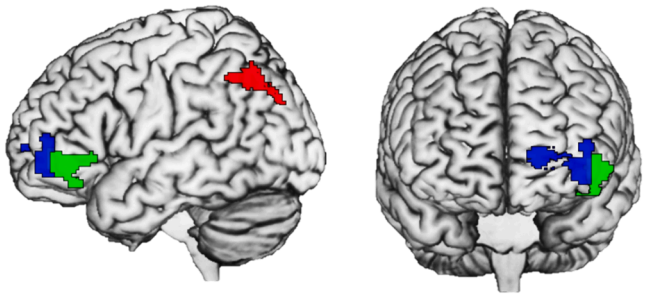

Fig. 3. PPI results. Differential between-group connectivity between the left angular gyrus seed (red) and the left ventrolateral prefrontal cortex for the Maintain>Observe contrast (blue, HC>OCD) and the Regulate>Maintain contrast (green, OCD>HC).

with measures of emotion regulation success and with obsessive-compulsive symptomatology.

At the behavioral level, there were no significant differences between groups in the in-scanner ratings when using a 2 × 3 repeated-measures ANOVA. This is in accordance with previous systematic reviews and meta-analyses in psychiatric samples (Picó-Pérez et al., 2017; Zilverstand et al., 2017), which suggest that this could be reflecting the limitations of intra-scanner behavioral assessments, social desirability effects or impaired self-awareness of emotional experience. Nonetheless, groups significantly differed in the Success variable, with OCD patients showing less successful regulation. Thus, even if the pattern of ratings across all conditions was relatively similar in both groups (see Fig. 2), differences can still be found when focusing only on Maintain and Regulate conditions. Surprisingly, the groups did not differ in their ERQ scores, contrarily to previous reports showing that OCD patients make higher use of suppression and lower use of reappraisal compared to HC (de Wit et al., 2015; Picó-Pérez et al., 2018). A number of factors could be influencing this, including cultural differences between the populations, and sociodemographic and clinical characteristics of the samples. In any case, our current findings provide limited evidence for cognitive reappraisal deficits in patients with OCD. It could well be that these deficits become more obvious when patients are faced with stimuli that are relevant for their symptomatology (as in symptom provocation tasks), while their reappraisal ability remains relatively preserved when faced with general negative stimuli.

This modest difference in emotion regulation success is accompanied by a lack of significant differences in brain activation, which goes against the findings from de Wit et al. (2015). One difference between both studies is that they used fear images and OCD-related stimuli while we used general negative images (not symptom specific, and including but not limited to fear stimuli). This could partially explain our negative findings, in line with the interpretation provided above regarding the in-scanner ratings. It is important to note, though, that de Wit et al. (2015) found differential activations not only for the OCD stimuli condition, but also for fear stimuli. Moreover, most of our patients were under medication while in de Wit et al. (2015) unmedicated patients were included, which poses a relevant difference considering that SSRIs seem to reduce limbic activation during emotional processing (Arce et al., 2008; Maron et al., 2016). Another important difference is that we used a whole-brain approach in all our analyses, while in this previous study they used regions of interest (ROI). Thus, considering that we are exploring an effect that is probably subtle and depends on other factors besides diagnosis status (relevance of the stimuli, specific clinical features of the patients, cultural differences regarding emotion regulation use, etc.), our approach could have been too conservative to capture significant differences corrected for multiple comparisons at the whole-brain level. Previous meta-analyses on emotional processing in OCD (Picó-Pérez et al., 2020; Thorsen et al., 2018) also found significant activation differences between patients and controls in several frontal and limbic regions, but again in these meta-analyses a broad range of tasks were included, and most of them were symptom provocation tasks. These tasks typically include OCD-relevant and neutral visual stimuli to induce maximal and minimal OCD symptoms, and thus, are more prone to elicit differential activations. More generally, recent studies have highlighted the lack of power and poor reliability of task fMRI (Elliott et al., 2020; Kennedy et al., 2022), which could also explain this inconsistency across findings.

Nonetheless, using PPI analysis, we found connectivity differences in the left frontoparietal network, more specifically between the left angular gyrus seed and the left vlPFC. These regions are involved in cognitive control, selective attention and working memory (Aron et al., 2014; Pessoa et al., 2003), and, in the context of reappraisal, may be used to direct attention to relevant stimulus features and hold in mind reappraisal goals as well as the content of one's reappraisal (Ochsner and Gross, 2014). When participants were asked to freely experience their emotions, patients with OCD presented a decreased connectivity between these regions compared to HC, while this connectivity was increased in patients when they were asked to regulate their emotions. A possible interpretation for this could be that this network is intrinsically more connected in HC, providing an automatic regulation when faced with negative emotions, while patients would lack (or exert to a lower extent) this automatic regulation. Then, when asked to perform effortful regulation, patients would compensate for their deficits in automatic regulation by overrecruiting the frontoparietal network. A previous study looking at cognitive regulation of craving for food also found increased frontoparietal connectivity in OCD patients compared to HC, and the authors interpreted that this deficit in the cognitive regulation of internal states could be associated with inflexible behavior during reward processing (Ferreira et al., 2020a). In any case, our interpretation needs to be further corroborated in future work, since previous resting-state studies have shown both increased as well as decreased frontoparietal connectivity in OCD patients compared to controls (Gürsel et al., 2020; Liu et al., 2022; Stern et al., 2012), making it difficult to draw any firm conclusions.

Finally, when looking at brain-behavior correlations, we found that higher frontoparietal connectivity during emotional processing was positively correlated with emotion regulation success, and negatively correlated with obsessive-compulsive symptomatology (namely, the washing and obsessing subscales of the OCI-R). On the other hand, increased connectivity during emotion regulation was positively associated with OCD symptoms (OCI-R obsessing subscale), and particularly in OCD patients, it was negatively associated with Y-BOCS symptom severity. This provides a link between brain connectivity, emotion

regulation ability, and OCD symptoms, giving support to the idea that obsessive-compulsive symptomatology might be mediated or influenced by emotion regulation capacity, which is represented at the brain level by frontoparietal connectivity. Importantly, although the negative association with the Y-BOCS could seem counterintuitive at first (since OCD patients present higher connectivity than controls), this supports the interpretation of a successful compensatory increased connectivity, with those patients showing the highest levels of connectivity being the ones with the lowest levels of symptom severity. Moreover, previous studies have found that patients with lower insight (which is typically associated to higher symptom severity; Bellino et al., 2005) have more difficulty recognizing their emotions, especially negative emotions (Daros et al., 2014; Manarte et al., 2021). Thus, the patients with higher severity in our sample might present such a bias in emotion recognition that prevents frontoparietal compensatory connectivity and emotion regulation to come into play. On the other hand, we did not find any significant correlations between brain data and the ERQ, contrarily to what was found in Picó-Pérez et al. (2018). It is important to note that this previous study used resting-state instead of task data, and perhaps intrinsic connectivity at rest represents a better correlate of habitual emotion regulation behavior (as is measured by the ERQ), while task-fMRI data is associated with concurrent emotion regulation success. Future studies could explore the association between both imaging modalities (resting-state and emotion regulation task data) as well as with different behavioral measures in order to clarify this issue.

As a final consideration, our lack of fMRI task activation differences together with the significant connectivity differences in the frontoparietal network could seem inconsistent or contradictory at first. Instead, we believe this emphasizes the importance of performing different neuroimaging analyses, such as activation and connectivity analyses (or task and resting-state analyses, as abovementioned), since they provide different types of information, and specific alterations might only be captured with some neuroimaging modalities and analytical methods and not others.

This study is not without limitations. First, because of the inherent design of the task, the experimenter cannot be completely sure about participants' commitment and performance when they are asked to experience and to regulate emotions. To try to overcome this limitation, we asked participants after the MRI session which type of emotion regulation strategies they used, and excluded those participants that did not perform the task properly. In this line, for future studies it might be of interest to acquire objective psychophysiological measures such as heart-rate variability, which would allow for a more robust verification of emotion regulation performance. Moreover, the cross-sectional design precludes a more in-depth interpretation regarding the causal association between frontoparietal connectivity, emotion regulation ability, and obsessive-compulsive symptoms. Studies focusing on at-risk population could help disentangle the direction of effects. Also, a comparison between patients with OCD and patients with other psychiatric disorders with known deficits in emotion regulation (e.g. depression, anxiety) could also prove useful in this regard. Finally, most patients were under medication and we did not explore differences between patients according to their main symptom category (i.e. washing, checking, etc.). Clinical sources of variability such as these could partially explain our lack of more robust results, since it could be that one particular clinical profile (e.g. naïve patients with mainly washing symptoms) is more susceptible to emotion regulation deficits than others. Thus, it could also be of interest for future studies with big enough datasets (such as those from neuroimaging consortia) to explore the influence of these different sources of clinical variability.

In conclusion, patients with OCD seem to be less successful than HC at regulating negative emotions when performing an fMRI cognitive reappraisal task. Contrarily to our hypothesis, there were no significant differences between groups regarding brain activation. On the other hand, OCD patients showed decreased left frontoparietal connectivity when experiencing emotions, while this connectivity was increased when regulating emotions. Moreover, frontoparietal connectivity was associated with emotion regulation success during the task and with obsessive-compulsive symptomatology, pointing towards their altered connectivity as a potential compensatory mechanism.

CRediT authorship contribution statement

Maria Picó-Pérez: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Renato Barbosa:** Formal analysis, Investigation, Data curation, Writing – original draft. **Beatriz Couto:** Conceptualization, Investigation, Data curation. **Inês Castro:** Investigation, Data curation. **Ricardo Magalhães:** Conceptualization, Methodology, Writing – review & editing. **Nuno Sousa:** Conceptualization, Resources, Writing – review & editing, Funding acquisition. **Sónia Ferreira:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Pedro Morgado:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

PM has received in the past 3 years grants, CME-related honoraria, or consulting fees from Angelini, AstraZeneca, Bial, Biogen, Conselho Económico e Social, DGS-Portugal, FCT, FLAD, Janssen-Cilag, Gulbenkian Foundation, Lundbeck, Springer Healthcare, Tecnimede, Viatris, and 2CA-Braga outside of this study. The remaining authors reported no biomedical financial interests or potential conflicts of interest.

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Supplementary materials

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