INTRODUCTION

Bipolar disorder (BD) is one of the main psychiatric health burdens. A prominent feature of BD is its emotional symptomatology, cycling between grandiose mood (mania/hypomania) and depression. The emotional symptomatology in BD patients (e.g., emotional liability) has been suggested to be related to problems in effortful emotion regulation (ER). The most adaptive strategy of effortful ER has been suggested to be cognitive reappraisal compared to other regulation strategies (e.g., suppression). Reappraisal involves forming a reconceptualization of the situation to decrease emotional intensity. Behavioral evidence has shown that BD patients report more effort to achieve reappraisal, and are less successful in reappraisal compared to healthy individuals, although not consistently. Interestingly, better reappraisal ability has been shown to predict fewer depressive symptoms over time in BD. Therefore, cognitive reappraisal might be an essential process underlying the key symptoms of BD, and understanding the neural mechanism of

OBJECTIVES

Sufficient prefrontal top-down control of limbic affective areas, especially the amygdala, is essential for successful effortful emotion regulation (ER). Difficulties in effortful ER have been seen in patients with bipolar disorder (BD), which could be suggestive of a disturbed prefrontal-amygdala regulation circuit. The aim of this study was to investigate whether BD patients show abnormal effective connectivity from the prefrontal areas to the amygdala during effortful ER (reappraisal).

METHODS

Forty participants (23 BD patients and 17 healthy controls [HC]) performed an ER task during functional magnetic resonance imaging. Using dynamic causal modeling, we investigated effective connectivity from the dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC) to the amygdala, as well as connectivity between the DLPFC and VLPFC during reappraisal.

RESULTS

Both BD patients and HC showed decreased negative affect ratings following reappraisal compared to attending negative pictures ($P < .001$). There were no group differences ($P = .10$). There was a differential modulatory effect of reappraisal on the connectivity from the DLPFC to amygdala between BD patients and HC ($P = .04$), with BD patients showing a weaker modulatory effect on this connectivity compared to HC. There were no other group differences.

CONCLUSION

The disturbance in BD patients in effective connectivity from the DLPFC to the amygdala while reappraising is indicative of insufficient prefrontal control. This impairment should be studied further in relation to cycling frequency and polarity of switches in BD patients.

KEYWORDS

amygdala, bipolar disorder, dynamic causal modeling, effective connectivity, emotion regulation, prefrontal cortex
reappraisal in BD might provide insights into how to improve ER in this disorder. It has been strongly suggested that sufficient top-down control from the prefrontal cortex (PFC) to limbic affective areas (eg, amygdala) is essential for successful effortful ER. Therefore, it might be proposed that BD patients show disturbances in the PFC-limbic ER circuit.

During reappraisal in healthy individuals, the dorsolateral PFC (DLPFC) and ventrolateral PFC (VLPFC) have been found to be the most consistently activated prefrontal areas, while the amygdala has been shown to be the only area to decrease in activation while reappraising. Negative associations between the activation of the VLPFC and the amygdala have been found during reappraisal in healthy individuals, although one study has also reported increased correlational functional connectivity between the DLPFC and amygdala. In BD patients, only a few studies have investigated the PFC-amygdala relationship and have shown reduced negative, or even absent correlational functional connectivity between the VLPFC and amygdala compared to healthy individuals during reappraisal. These studies all investigated correlational functional connectivity, but a causal communication from the PFC to limbic affective areas has been strongly suggested for successful ER. Therefore, it is of importance to investigate the causal or directional influences of connectivity, which could be done with, for example, dynamic causal modeling (DCM). DCM could provide inferences about how neuronal activity of one area causes changes in another area, and how these dynamics are modulated by experimental manipulations. To the best of our knowledge, no study has yet investigated the causal communication (effective connectivity) from the PFC to limbic affective areas during reappraisal in BD patients.

Based on the results of correlational functional connectivity during reappraisal in BD and the suggestion of causal communication within the PFC-limbic circuit related to ER, we hypothesized that the lateral PFC has reduced influence on the limbic areas during reappraisal in BD patients, indicated by less connectivity between these areas. Furthermore, Morawetz et al. have shown that reappraising modulates the bidirectional connectivity between the DLPFC and VLPFC in healthy individuals, indicating that also connectivity within the PFC might contribute to reappraisal. Specifically, given that the DLPFC is involved in maintaining the reappraisal goal and contents in working memory, these authors speculated that the observed positive DLPFC-VLPFC effective connectivity may be involved in relaying this information from the DLPFC to the VLPFC for reappraisal selection. After reappraisal is finished, this process is supposed to be inhibited, represented by the observed negative effective connectivity from the VLPFC to the DLPFC. Therefore, we also tested effective connectivity between the DLPFC and VLPFC during reappraisal in BD patients.

In this study, for the first time, we investigated effective connectivity from the DLPFC and VLPFC to the amygdala and between the DLPFC and VLPFC during reappraisal in BD patients and controls, using DCM. We expected less modulatory effect of reappraisal on the connectivity from the PFC to the amygdala in BD patients. Furthermore, effective connectivity within the PFC was explored.

## 2 MATERIALS AND METHODS

### 2.1 Participants

Twenty-three BD patients with past psychotic symptoms were recruited from mental health care institutions in the north of the Netherlands. The diagnosis of BD was confirmed by the Mini International Neuropsychiatric Interview-Plus. Inclusion criteria for BD were: (i) no change in medication 1 week before scanning; (ii) did not undergo electroconvulsive therapy 1 year prior to scanning; (iii) no psychiatric disorders other than BD and no comorbidity of other disorders that may affect the central nervous system (eg, substance use disorder). Because the BD patients were originally recruited to investigate illness insight, all BD patients were additionally required to have a history of psychotic symptoms during their episodes, but a comorbid diagnosis of psychotic disorder was excluded. Moreover, 17 healthy controls (HC) were included, who had no past or current psychiatric disorders (confirmed by the MINI-Plus). All participants had to be magnetic resonance imaging (MRI)-compatible (eg, no metal implants or pregnancy) and to have no somatic/neurological disorders that may influence the central nervous system.

This study was approved by the medical ethical committee of the University Medical Center Groningen, according to the Declaration of Helsinki (2008). All participants provided written informed consent.

### 2.2 Clinical assessment and measures

The current state of depression and mania was measured with the Quick Inventory of Depressive Symptomatology (QIDS) and Young Mania Rating Scale (YMRS), respectively. The current severity of psychotic symptoms was assessed with the Positive and Negative Syndrome Scale (PANSS). Moreover, participants completed the Emotion Regulation Questionnaire (ERQ), assessing their daily life preference of ER strategies.

### 2.3 Emotion regulation task

Participants were instructed to perform an ER task during scanning (see Figure S1 and the Method S1 for a full description of the task and image acquisition). Briefly, stimuli were selected from the International Affective Picture System. Following a viewing phase, a regulating phase was presented including the conditions reappraising (reconceptualization of the presented negative picture to decrease the emotional intensity) and attending (feeling the emotion elicited by the picture without altering it). During attending, participants were presented with either a negative (attending-negative) or neutral (attending-neutral) picture. Subsequently, participants were asked to rate their intensity of negative feeling on a four-point scale (1 = not negative; 4 = extremely negative). Notably, there were two other regulation conditions: suppressing and increasing. Because these conditions were not of interest to us, we excluded these from the effective connectivity analyses (although modeled in the general linear model [GLM]). The whole experiment was designed in two runs, with the anatomical scan between as a rest period.
2.4 | Data analysis of demographic and behavioral data

An independent-samples t test and chi-square test were conducted where appropriate to compare BD patients with HC on age, sex, level of education, intelligence, QIDS score, and ERQ score. To compare the task rating scores, a repeated-measures analysis of variance (ANOVA) was conducted. The threshold was set at $P < 0.05$ for all analyses.

2.5 | Functional magnetic resonance imaging (fMRI) data analysis

2.5.1 | First-level analyses

fMRI data were analyzed using the statistical parametric mapping (SPM12b, v.5970; www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 7.13.0.564 (R2011b; the Math Works Inc., Natick, MA, USA). See Method S2 for a full description of pre-processing and first-level analyses. Briefly, first-level models were created within the GLM framework, with the following contrasts defined per participant: (i) reappraising > attending-negative, to identify the PFC clusters (DLPFC and VLPFC) related to top-down reappraisal; (ii) viewing-negative > fixation, to identify activation in the amygdala involved in basic emotional processing; (iii) attending-negative > reappraising, for investigating areas showing decreased activation while reappraising; (iv) attending-negative > attending-neutral, to identify task activation during basic attending of negative information.

2.5.2 | General linear model analyses

The contrasts reappraising > attending-negative, attending-negative > reappraising, and attending-negative > attending-neutral were entered in three one-sample t test models to test for the main task effects in all participants (DCM sample). For testing group differences, three independent-samples t tests were performed, with group as the independent variable. For group comparisons, separate region of interest (ROI) masks were created for the contrasts reappraising > attending-negative and attending-negative > reappraising by drawing a 20-mm-radius sphere around the cluster center coordinates of the corresponding contrast reported in the most recent meta-analysis on reappraisal.5 These two ROI masks were combined into one mask for the comparison on attending-negative > attending-neutral. The threshold for the main task effects and group comparisons was set to $P < .05$ family-wise error (FWE) corrected on cluster level, with an initial threshold of $P < .001$ uncorrected. Of note, a more liberal threshold was chosen for defining the center of the volumes of interest (VOIs) for subsequent effective connectivity analyses (see section ‘Selection of volumes of interest’), in order to include as many participants as possible; as such, each included participant would have sufficient activation in the three VOIs to extract the time course.

2.5.3 | Effective connectivity

DCM22 is a commonly used method to investigate effective connectivity (Figure S2 describes our DCM steps). Briefly, DCM models are built between ROIs or so-called volumes of interest (VOIs) to simulate the underlying neural dynamics. These models consist of several coefficients to describe causal interactions on a neural level: (i) task-independent connectivities between VOIs (intrinsic connectivity; parameter $A$); (ii) modulatory effects of experimental manipulations on the intrinsic connectivity between VOIs (modulatory effects; parameter $B$); (iii) direct influence of experimental condition(s) on the neural states of VOIs (driving input; parameter $C$). By defining different locations of driving inputs, locations of modulatory effects and intrinsic connectivities, a model space (all created DCM models) is created. Bayesian inferences are used to select the most plausible model(s) from the model space, without having the alpha inflation problem.

2.5.4 | Selection of volumes of interest

The selection of VOIs was carried out in three steps: (i) defining guiding coordinates on the group level; (ii) defining VOI center per participant; (iii) selecting the VOI per participant by drawing a sphere around the VOI center.

First, guiding coordinates were defined at the group level. Based on the most recent meta-analysis on reappraisal,17 the three regions involved the most during reappraisal were selected as ROIs: the left DLPFC, left VLPFC, and left amygdala. Anatomical masks were created for these regions based on the Automated Anatomical Labeling (AAL) library in the WFU Pick Atlas toolbox29 (DLPFC = left middle frontal gyrus and lateral superior frontal gyrus; VLPFC = left triangular and opercular part of the inferior frontal gyrus). The guiding coordinates of the DLPFC, VLPFC and amygdala were the peak coordinates within these masks of the main task effects in all participants. For these main task effects, two second-level one-sample t test models were built: one for determining the activation during reappraising > attending-negative to define the peak coordinates in the DLPFC and VLPFC; one for viewing-negative > fixation to define the peak coordinate of the amygdala. A threshold was set of $P < .05$ (uncorrected, $k \geq 5$, selected guided coordinates in Table S1).

Second, the VOI center per participant was defined as the individual’s first-level peak coordinate from the corresponding first-level contrast of interest, within 20 mm of the guiding coordinate and within the corresponding anatomical mask. The threshold was set at $P < .10$ uncorrected, $k \geq 5$.

Third, for each participant, the VOI was defined as a sphere with a 6 mm radius around the VOI center, consistent with previous literature.23 VOI voxels outside the corresponding anatomical mask were excluded. The first eigenvariate of this VOI was extracted per participant. Participants with no/insufficient voxels in the VOI ($k < 5$) were excluded from further analyses ($n = 3$).
2.5.5 | DCM model space

For the DCM model structure, we defined bidirectional intrinsic connections between the amygdala and VLPFC, and between the DLPFC and VLPFC, based on previous anatomical and animal studies. Therefore, given that most connections are bidirectional, we tested two possibilities of DLPFC-amygdala intrinsic connections: no or bidirectional connections. The conditions reappraising, attending-negative and attending-neutral were included as driving inputs. Although we included attending-neutral as a driving input to increase the explained variance, given our primary interest in effortful ER, we did not explore it thereafter. These driving inputs were hypothesized to enter the model via the prefrontal areas. Without hypotheses on the driving inputs locations, three variations were tested: DLPFC, VLPFC, and DLPFC and VLPFC. Furthermore, we were particularly interested in the modulatory effects of reappraising on the connections. Given previous ER models, we tested whether reappraising affected the connectivity from the DLPFC/VLPFC to the amygdala, and the effective connectivity between the DLPFC and the VLPFC. Altogether, there were 96 DCM models (bilinear and stochastic) per participant: 3 (driving input locations) × 16 (modulation locations) × 2 (scanning runs) (Figure 1).

2.5.6 | Bayesian model selection and Bayesian model averaging

Models with similar model features were grouped in families. We first divided all models in three families based on driving input location (family#1, DLPFC; family#2, DLPFC and ventrolateral prefrontal cortex [VLPFC]; family#3, VLPFC). We further divided each family in two subfamilies: with or without DLPFC-amygdala connection. Red dots indicate the hypothesized connectivity modulated by reappraisal tested in the particular model of the subfamily. Model variations in (B) and (C) can also be made for family#1 and family#3, leading to 3 × 16 × 2 = 96 models per subject in total. (D) Bayesian model selection (BMS) reveals that family#2 (driving inputs at both the DLPFC and VLPFC) has the highest exceedance probability for both BD patients (family#2 = .9998, family#1 and family#3 = 0) and HC (family#2 = .9998, family#1 and family#3 = 0). Within family#2, BMS demonstrates that the winning family is subfamily#2.2 (with DLPFC-amygdala connection) for both BD patients and HC (HC, exceedance P = .9998; BD patients, exceedance P = .9995) compared to subfamily#2.1 (without DLPFC-amygdala connections; HC, exceedance probability = 0; BD patients, exceedance probability = 0).
After model selection via BMS, connectivity parameters were computed. Because there was no robust winning model (see DCM results) based on the fact that the EP was comparable and approximately 50%, we conducted Bayesian model averaging (BMA) to calculate connectivity parameters on an averaged model composed of the models of the winning subfamily. The contribution of each model to the average model was weighted based on the model evidence (ie, the probability of the DCM model explaining the observed data), and connectivity parameters were averaged over runs. Accordingly, for each participant, intrinsic connectivity (parameter A, representing connectivities between VOIs without being modulated by reappraising) and modulatory strength of reappraising (B/A, representing the modulatory effect [parameter B] relative to the intrinsic connectivity as a sensitive index for the degree of modulation due to reappraisal) were obtained.

DCM parameters were analyzed with spss (v.22.0; IBM, Armonk, NY, USA). For the parameters A and B/A, one-sample t tests were conducted in HC to provide connectivity information during reappraisal in unaffected individuals, and independent-samples t tests were performed to estimate whether BD patients deviated from HC. Because we a priori expected BD patients to have less control from the PFC to amygdala,10,14-16,21 meaning smaller B/A values, we planned one-tailed comparisons to test for differences in modulatory strength (B/A) between BD patients and HC on connectivity from the DLPFC/VLPFC to the amygdala, using a threshold of $P < .05$ (one-tailed). For these two connections, correction for multiple comparisons was not applied due to the limited number of comparisons ($k = 2$). For the other tests (A and B/A in HC; group comparisons on A and B/A for the DLPFC-VLPFC connections), a false discovery rate (FDR) correction for multiple comparisons was applied with a threshold of $P < .05$ (two-tailed). To rule out the influence of depression severity on the comparison between BD patients and HC, sensitivity analyses were performed by excluding the depressed BD patients ($n = 2$).

We did not investigate correlations between the DCM parameters and any behavioral measures (eg, rating scores during the task and ERQ score) or emotional symptomatology (eg, QIDS score and YMRS score), for two reasons. First, due to the limited sample size, a null result of the correlation analysis might be a false negative result. Second, most of the BD patients in our study were euthymic, with an average QIDS score of 5.07 (score range of the median 20%-80% was from 2 to 7) and an average YMRS score of 1.40 (score range of the median 20%-80% was from 0 to 3), implying a narrow range of severity level of depression and mania for performing correlation analyses. It would be interesting for future studies to test this.

3 | RESULTS

3.1 | Sample description and behavioral results

Six BD patients and two HC were excluded because of excessive head movements (>3 mm/3° in any direction), incomplete imaging data or missing E-prime log-files. Due to insufficient activation in VOIs(s), two BD patients and one HC were excluded (these subjects were included for defining guiding coordinates). In total, we included 15 BD patients (13 with BD-I and two with BD-II) and 14 HC in the final analyses.

Table 1 shows the medication information and demographics of the final sample (Table S2 shows data for all participants). BD patients were comparable to HC on age, sex, level of education, intelligence, and ERQ score. There was a higher level of depression severity in BD patients than in HC, with two BD patients having a moderate level of depression (QIDS scores > 10; www.ids-qids.org).

Concerning the behavioral performance (Figure S3), there was a main effect of condition ($F(2,54) = 102.08, P < .001, \eta_p^2 = 0.79$). Post hoc t tests demonstrated differences between the conditions, with the lowest subjective negative ratings for attending-neutral, the highest for attending-negative and intermediate for reappraising (attending-negative > reappraising > attending-neutral; all $P < .001$). There was no main effect of group ($F(1,27) = 2.94, P = .10, \eta_p^2 = 0.098$), nor a group x condition interaction ($F(2,54) = .36, P = .67, \eta_p^2 = 0.01$).

3.2 | GLM results

During reappraising > attending-negative, there were activations in the VLPFC, insula, middle temporal gyrus, superior temporal gyrus, dorsomedial PFC (DMPFC), mid-cingulate cortex, caudate, thalamus, supplementary motor area, parahippocampal gyrus, posterior cingulate cortex, precuneus and cerebellum (Table S3). There were no activations during attending-negative > reappraising. Attending-negative > attending-neutral showed activation in the middle occipital gyrus, cuneus, fusiform gyrus, and the inferior parietal lobule/angular gyrus (Table S4). Moreover, there were no group differences between BD patients and HC on these contrasts.

3.3 | DCM results

BMS revealed that the winning family had the driving input location at the DLPFC and VLPFC (family#2) for both HC and BD patients (Figure 1D). Furthermore, within family#2, for both groups the EP of the subfamily with DLPFC-amygdala connections (subfamily#2.2) was superior to that of the subfamily without DLPFC-amygdala connections (subfamily#2.1) (Figure 1D). Within this winning subfamily#2.2, there was no obvious winning model (Figure S4), since all EPs in HC were < 60%. In HC, two models had comparable EPs (model#4 and model#7), while BD patients had a different second best model (model#6). Therefore, to compare the groups we calculated the weighted averaged connectivity parameters over the models of the winning subfamily, using BMA (Table 2).

Regarding the intrinsic connectivity (parameter A) in HC, there was a positive intrinsic connectivity on all connections (all FDR corrected $P < .001$). BD patients did not differ from HC on all intrinsic connections (Table 2).

Concerning modulatory strength of reappraising (B/A), there were no significant effects in HC (all FDR corrected $P > .10$). Planned comparisons showed that BD patients had a weaker modulatory effect on the connectivity from the DLPFC to the amygdala compared to HC (Table 2 and Figure 2; $P = .04$, Cohen’s $d = .68$). Specifically,
reappraising changed and reversed the intrinsic connectivity from the DLPFC to amygdala in HC, resulting in a negative DLPFC-amygdala effective connectivity (visual inspection), while in BD patients this effect was not present (Figure 2B). There were no group differences in modulatory effect of reappraising on the connectivity from the VLPFC to the amygdala (Table 2; \( P = .30 \), Cohen’s \( d = 0.20 \)) or on the DLPFC-VLPFC
connections (Table 2; DLPFC-VLPFC connection, \( P_{FDR} = .29 \), Cohen’s \( d = 0.56 \); VLPFC-DLPFC connection, \( P_{FDR} = .30 \), Cohen’s \( d = 0.48 \)). After excluding two depressed BD patients, there was no group difference in depression severity (\( t = 1.69 \), \( P = .10 \), Cohen’s \( d = 0.65 \)). Excluding these patients from the DCM analysis showed that the group comparison of modulatory effect of reappraising on the DLPFC-amygdala effective connectivity became trend-wise significant (\( P = .07 \) [one tailed], Cohen’s \( d = 0.59 \)). For the remaining analyses, similar results were obtained (all FDR-corrected \( P > .05 \)).

4 | DISCUSSION

This study provided, to our knowledge, the first evidence of effective connectivity from the PFC to the amygdala during reappraisal in patients with BD compared to HC. Importantly, BD patients showed a weaker modulatory effect of reappraising on the connectivity from the DLPFC to the amygdala compared to HC. This disturbed DLPFC-amygdala effective connectivity in BD patients likely reflects impairments in effortful ER, although our behavioral data did not show this.

4.1 | Group comparisons on modulatory effect of reappraising

We showed that BD patients had weaker connectivity from the DLPFC to the amygdala while reappraising compared to HC. The DLPFC is associated with cognitive control\(^{37}\) and reappraising\(^{17,38,39}\), mostly by reducing activation of the amygdala\(^{4,14,16,40}\), an area essential for emotional processing.\(^{15}\) Our behavioral data showed that reappraising decreased the elicited negative emotional feeling, suggesting more control over the negative emotion. BD patients often report more difficulty in reappraising\(^{8}\), and diminished reappraisal success compared to HC.\(^{8-10}\) Therefore, we propose that the disturbed DLPFC-amygdala effective connectivity in BD patients indicates inadequate prefrontal control during reappraisal, which may be associated with regulation inefficiency as often seen in BD. Furthermore, the inadequate influence of the DLPFC on the amygdala in BD patients might be associated with the heightened sensitivity to emotional stimuli commonly observed.\(^{3}\) Given our predominantly euthymic BD patients, this disturbed DLPFC control over the amygdala might be associated with vulnerability for depressive or manic episodes. That we did not observe behavioral differences might be explained by the following possibilities. First, BD patients have been shown to be able to perform reappraisal under instruction, although less efficiently compared to controls.\(^{9}\) It could be that BD patients retain the ability to perform the reappraisal task as instructed, while they show differences on the neural level. Second, there has been evidence suggesting that disturbances in functional connectivity may precede measurable changes in behavior.\(^{41}\) Therefore, the differences in brain connectivity in BD compared to HC might indicate that they already have difficulties in reaching the same level of performance. It might also mean that these BD patients may show a future behavioral difference. Third, the lack of behavioral differences might also suggest that our behavioral measure is not the optimal measure to detect

<p>| TABLE 2 | Connectivity parameters for bipolar disorder (BD) patients and healthy controls (HC) |
|---------------------------------|---------------------------------|-----------------|-----------------|-------------|-----------------|-----------------|---------|</p>
<table>
<thead>
<tr>
<th></th>
<th>BD Mean</th>
<th>SD</th>
<th>HC Mean</th>
<th>SD</th>
<th>( t^a )</th>
<th>( P^a )</th>
<th>( P_{FDR}^a )</th>
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<tr>
<td>Intrinsic connectivity (A)</td>
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<td></td>
<td></td>
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<td>VLPFC to amygdala</td>
<td>0.029</td>
<td>0.025</td>
<td>0.049</td>
<td>0.032</td>
<td>-1.964</td>
<td>.06</td>
<td>.60</td>
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<td>0.019</td>
<td>0.017</td>
<td>0.010</td>
<td>-1.958</td>
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<td>.31</td>
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<tr>
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<td>0.020</td>
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<td>0.037</td>
<td>0.027</td>
<td>-1.814</td>
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<td>.20</td>
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<td>DLPFC to VLPFC</td>
<td>0.048</td>
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<td>0.070</td>
<td>0.051</td>
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<td>.18</td>
<td>.29</td>
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<tr>
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<td>0.016</td>
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<td>DLPFC to amygdala</td>
<td>0.630</td>
<td>2.832</td>
<td>-1.208</td>
<td>2.542</td>
<td>1.834</td>
<td>.04(^b)</td>
<td>-</td>
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<tr>
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<td>2.048</td>
<td>1.631</td>
<td>6.195</td>
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<td>.30(^b)</td>
<td>-</td>
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<td>0.736</td>
<td>-1.231</td>
<td>.24</td>
<td>.30</td>
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</table>

DLPFC, dorsolateral prefrontal cortex; SD, standard deviation; VLPFC, ventrolateral prefrontal cortex.

\( ^a P < .05 \).

\( ^b \) Comparisons between BD patients and HC.

\( ^{\text{One-tailed P-value.}} \)
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A subtle behavioral difference between BD patients and HC. Therefore, a longitudinal study in a bigger sample would be interesting to conduct in the future. Taking these findings together, we propose that a weaker modulatory effect of reappraising on the DLPFC-amygdala effective connectivity in BD patients might be an important mechanism underlying their difficulties in reappraisal and contributing to their emotional instability, which needs further investigation in relation to the polarity of switching and cycling frequency in new BD samples.

BD patients did not differ from HC in effective connectivity from the VLPFC to the amygdala, and between the DLPFC and VLPFC. VLPFC activation has often been observed during reappraisal. It has been suggested that the VLPFC is not involved in cognitive control of emotion per se, but in detecting needs to regulate emotion, playing an intermediate role between top-down control from the DLPFC and bottom-up emotional processing by the amygdala during reappraisal. Therefore, it might be proposed that there is a direct route of cognitive control on emotional processing from the DLPFC to the amygdala and an indirect route between the DLPFC and amygdala via the VLPFC. Our results suggest that indirect control of emotion (via the VLPFC) is preserved in BD patients, while direct control via the DLPFC appears to be disturbed. This might additionally explain why we did not find behavioral differences for BD patients.

4.2 | Modulatory effects of reappraising in HC

In HC, we observed no modulatory effects of reappraising on the DLPFC-VLPFC effective connectivity, which is in contrast to Morawetz et al., who have shown bidirectional negative modulatory effects of reappraising on the DLPFC-VLPFC connections (leading to a negative VLPFC-DLPFC connectivity and a positive DLPFC-VLPFC connectivity). Important differences in DCM model structures might explain this discrepancy. Specifically, we tested all the possibilities of modulatory effects of reappraising on the DLPFC-VLPFC connections, while Morawetz et al. predefined that at least one DLPFC-VLPFC connection would be modulated while reappraising. Notably, with DCM analyses, the superiority of one DCM model/family is relative to other included models/families, rather than absolute superiority. Therefore, investigating all possible modulatory effects on the DLPFC-VLPFC connections, like we did, will provide more objective information. Moreover, our DCM models included the amygdala. Given that reappraising aims to reduce activity in affective areas to decrease negative affect, and a meta-analysis has revealed that the amygdala is the only area modulated by reappraising, the amygdala seems a crucial area to include in DCM models investigating reappraisal. However, Morawetz et al. did not, and so important causal information might have been missed. This reasoning leads us to believe that our study provides more informative evidence on the mechanisms underlying reappraising. Our results suggest that modulatory effects of reappraising on the indirect route between the DLPFC and VLPFC might help, but are not necessary for successful ER.

Moreover, modulatory effects of reappraisal on the DLPFC/VLPFC-amygdala connections in HC did not reach statistical significance. It might be speculated that the insufficient power issue of this study is related to non-significant findings of modulatory effects of reappraisal in HC, but the power was sufficient to detect group differences, especially when BD patients and HC had a tendency for modulation in different directions (i.e., Figure 2B; HC, around zero or towards positive; BD, towards negative). Further replication is encouraged.

4.3 | Group differences in brain activation

In line with previous suggestions of prefrontal involvement being essential for reappraising, we showed heightened prefrontal
activation during reappraising (compared to attending-negative) in HC and BD patients. No prefrontal involvement was shown during attending conditions, where participants were asked to not regulate their emotion, indicating that prefrontal activation was specific for reappraising. This suggests that our task manipulations were valid. BD patients showed no differences in activation while reappraising compared to HC. Previous studies have shown mixed results in BD patients, including heightened, lower and no differences in activation. Various differences between these studies could account for these mixed results; for example, differences in the patient sample size (n = 13, 15, 19, 22 and 30), the length of the regulation phase (4 s-10 s), the paradigm used (eg, early- vs late-cueing paradigm) and statistical thresholds. It remains unclear how these differences might contribute to these mixed results specifically.

4.4 | Limitations

Some limitations need to be mentioned. First, most BD patients were taking medication. No studies to date have tested medication effects on effective connectivity. However, it has been reported that medication has no or ameliorative effects on brain activation and functional connectivity. Therefore, it might be hypothesized that the observed differences in effective connectivity between BD patients and HC may also have been reduced instead of being induced by medication. Second, not all BD patients were euthymic, with two BD patients showing a moderate level of depression. Excluding these two depressed BD patients gave comparable results. However, it remains unknown whether the current results are generalizable to BD patients during other mood states (eg, depression and mania), given the different disturbances in ER circuits observed in depression vs euthymia. The group difference in modulatory effects of reappraising on DLPFC-amygdala effective connectivity became trend-wise after excluding depressed BD patients, which might be due to a drop in power and/or driving effects of depression. Third, our sample size was moderate, although comparable to the sample sizes in previous functional connectivity studies of reappraisal in BD patients (BD patients, n = 13, 22 and 30; HC, n = 15, 22 and 26). However, we observed a medium to strong effect size of the group difference in modulatory effects of reappraisal between BD patients and HC. Furthermore, Thirion et al. have reported that a sample size of n = 15 results in a kappa value around 0.6, which indicates moderate power for reproducibility (kappa statistic = 0.41-0.60). This indicates sufficient group differences in our study that should not be ignored. This is also in line with the suggestion of Friston that findings from small sample studies are more likely to be replicated compared to studies with larger samples, and should be reported. Finally, this study only used negative pictures. Differential modulatory effects of reappraisal on positive and negative stimuli have been found. Therefore, future studies are encouraged to include both negative and positive stimuli, to understand the disturbances in both positive and negative emotional processing and regulation.

5 | CONCLUSION

In conclusion, our finding of weaker modulatory effect of reappraisal on the DLPFC-amygdala effective connectivity in BD patients compared to HC indicates disturbed direct cognitive control over negative emotions, while indirect control via the VLPFC was intact. Future studies of effective connectivity during effortful ER should investigate state and trait effects further and link these abnormalities to symptomatology such as the polarity of episodes and cycling frequency in BD patients.

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DISCLOSURES

The authors have no conflicts of interest to declare.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

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