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Lack of cortico-limbic coupling in bipolar disorder and schizophrenia during emotion regulation

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Bipolar disorder (BD) and schizophrenia (Sz) share dysfunction in prefrontal inhibitory brain systems, yet exhibit distinct forms of affective disturbance. We aimed to distinguish these disorders on the basis of differential activation in cortico-limbic pathways during voluntary emotion regulation. Patients with DSM-IV diagnosed Sz (12) or BD-I (13) and 15 healthy control (HC) participants performed a well-established emotion regulation task while undergoing functional magnetic resonance imaging. The task required participants to voluntarily upregulate or downregulate their subjective affect while viewing emotionally negative images or maintain their affective response as a comparison condition. In BD, abnormal overactivity (hyperactivation) occurred in the right ventrolateral prefrontal cortex (VLPFC) during up- and downregulation of negative affect, relative to HC. Among Sz, prefrontal hypoactivation of the right VLPFC occurred during downregulation (opposite to BD), whereas upregulation elicited hyperactivity in the right VLPFC similar to BD. Amygdala activity was significantly related to subjective negative affect in HC and BD, but not Sz. Furthermore, amygdala activity was inversely coupled with the activity in the left PFC during downregulation in HC ($r = -0.76$), while such coupling did not occur in BD or Sz. These preliminary results indicate that differential cortico-limbic activation can distinguish the clinical groups in line with affective disturbance: BD is characterized by ineffective cortical control over limbic regions during emotion regulation, while Sz is characterized by an apparent failure to engage cortical (hypofrontality) and limbic regions during downregulation.
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Introduction

It is increasingly accepted that schizophrenia (Sz) and bipolar disorder (BD) share some genetic vulnerability,[1] comparably high heritability estimates[2,3] and neuropsychological dysfunction in common cognitive domains.[4–6] Consistent with these common traits, the neuroanatomical basis of these disorders shares various abnormalities in prefrontal, limbic and paralimbic brain regions.[7,8] Recently, however, the importance of determining the functional impact of these brain abnormalities has been proposed as a priority to improve diagnostic validity and identify new treatment targets.[9] An important target may be the specific cortico-limbic pathways that underlie the distinct forms of overt emotional dysfunction associated with each disorder. That is, although BD is characterized by the disturbance of mood, reflected in manic and depressive states, overt manifestations of emotionality in Sz are often characterized by inappropriate or flat affect (that is, lack of context-appropriate emotional expressivity). In addition, unique differences in the ability to voluntarily regulate subjective affect have been associated with BD and Sz, in comparison to healthy adults. For example, people with Sz have difficulty upregulating positive emotions,[10] while BD patients have inefficient strategies to downregulate negative affect, in association with higher levels of depression and anxiety.[11] In the present study, we sought to distinguish these related disorders on the basis of brain activation during the voluntary regulation of negative affect, as a means of differentiating cortico-limbic function in each disorder.

Neuroimaging research of emotion regulation in healthy adults consistently implicates lateral prefrontal brain regions such as the dorso- and ventrolateral prefrontal cortex (DLPFC, VLPFC) in the voluntary regulation of negative emotion, as well as medial frontal and limbic cortex such as the anterior cingulate (ACC) and ventromedial PFC.[12–15] Moreover, the recruitment of these prefrontal regions, especially the ventromedial PFC, is inversely correlated with amygdala reactivity during emotion regulation.[14,16–18] Such data, along with considerable animal lesion and anatomical tracing studies,[19–24] substantiate a top-down (voluntary) circuit of emotion regulation in which prefrontal regions exert inhibitory control over subcortical amygdala pathways.[18,25] Within this system, the amygdala is critical for the generation and expression of negative emotions such as fear and anxiety, while regions such as the DLPFC and VLPFC are thought to regulate responses to emotional stimuli via direct projections from the ventromedial PFC to inhibitory GABAergic neurons in the amygdala.[17,20,22–25]

Neuroimaging studies implicate cortico-limbic dysfunction in BD and Sz.[26–28] For example, studies of threat-related face processing in Sz demonstrate decreased amygdala activity,[29–32] while studies involving passive viewing of affective

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images show hypofrontality shortly after viewing affective stimuli, relative to healthy controls (HC).[33] In contrast, BD patients demonstrate increased activation of subcortical limbic regions when viewing emotional stimuli alongside hypofrontality when inhibiting a motor response to emotion stimuli.[34–37] However, such studies do not examine the function of cortico-limbic circuits during voluntary emotion regulation, an adaptive ability that may be central to affective dysfunction in Sz and BD.[33,38,39] This is relevant because at least one recent study indicates the pattern of cortico-limbic function is quite different during affect regulation in non-clinical psychosis-prone individuals—with greater activation in VLPFC regions alongside a decoupled amygdala response.[40] Whether affect regulation confers similar VLPFC hyperactivity in psychotic individuals has yet to be examined.

We thus aimed to distinguish unique patterns of cortico-limbic activation during emotion regulation in BD and Sz, using an established paradigm designed to examine brain activity during voluntary up- and downregulation of negative affect.[41] During downregulation, we expected both clinical groups to demonstrate VLPFC hyperactivation, with greater amygdala activity in BD distinguishing the patient groups.[31,34,35,40] During upregulation, we expected Sz patients to demonstrate VLPFC hyperactivation alongside diminished amygdala activity,[31,33] with BD distinguished from Sz by hypofrontality alongside greater amygdala activation. We expected that coupling of activation in cortico-limbic regions during emotional regulation would be absent or reversed in both groups.[25,40]

Materials and methods

Participants. In all, 15 HC, 13 people with BD (bipolar-I disorder) and 12 people with Sz were included in the study after meeting the criteria for right-handedness, restricted head movement (<3 mm), no structural brain abnormalities, no history of head injuries and no recent drug abuse in the past year. Healthy participants also had no personal or family history of Sz or BD. Clinical participants were medicated, chronic outpatients recruited from psychiatric services at the Prince of Wales Hospital, the Sydney Bipolar Disorders Clinic at the Black Dog Institute and the Australian Schizophrenia Research Bank (ASRB). Only participants with a clinician-confirmed DSM-IV diagnosis of Sz or BD (based on all available medical information) were included in the study; the ASRB also provided confirmation of Sz diagnosis using the Diagnostic Interview for Psychosis (DIP) based on DSM-IV diagnostic criteria.[42,43] All clinical diagnoses were confirmed independently by a qualified clinical psychologist using the Mini International Neuropsychiatric Interview (MINI).[44] The MINI was also used to assess (hypo)mania, depression and anxiety in clinical participants, and to screen for these disorders in HC. All participants provided written informed consent according to the approval requirements of the Human Research Ethics Committees of the South East Sydney and Illawarra Area Health Service (Protocol 07/171) and the University of New South Wales (Protocol 07/167).

Materials. Premorbid IQ estimates were obtained using the National Adult Reading Test (NART).[45] Symptom severity ratings on the day of the MRI scan were provided by the Depression, Anxiety and Stress Scale (DASS)[46] and Positive and Negative Syndrome Scale (PANSS).[47] The Edinburgh handedness inventory[48] was used to measure handedness in each participant. The Internal State Scale (ISS) was used to measure mood state in BD.[49]

Emotion regulation task. The experimental task was adapted from previous studies of emotion regulation in healthy adults.[18,41] The stimulus set comprised 63 negative (for example, scenes of threat or suffering) and 12 neutral (for example, household and working scenes) images selected from the International Affect Picture System (IAPS).[50] The neutral images were assigned to the 'maintain' condition as filler trials to prevent habituation to negative images,[14,41] and were not included in the planned analysis. The negative images were randomly sorted into three different sets (21 in each set), and sets were counterbalanced across instruction conditions ('increase', 'decrease' and 'maintain'), such that there were three versions of the task administered equally across participant groups to avoid confounding instruction effects with any particular image sets.

Stimulus presentation and timing of all stimuli were automatically synchronized with the onset of each echoplanar images acquisition to ensure accurate event timing. The task was programmed and executed using Presentation software (Neurobehavioral Systems, Albany, CA, USA) on a Dell computer running Windows XP (Microsoft, Redmond, WA, USA). The participant viewed the task on a monitor placed at the rear of the MRI scanner, through a mirror positioned above the headcoil. A Lumina MRI-compatible two-button response pad (Cedrus, CA, USA) recorded each response.

Procedure. Prior to the scan, participants were given at least three practice trials under instruction to increase or decrease their subjective emotional response to each image through processes of cognitive reframing (including reappraisal and/or distancing techniques described previously by Oschner *et al*.[41]). Responses were not recorded during this practice and training continued until the participant successfully implemented the strategy.[41] Methods to 'increase' subjective affect were guided by instruction to, for example, imagine that they or a loved one were involved in the depicted situation, while attempts to 'decrease' subjective affect were guided with instructions to imagine that the situation was not real or that they were a detached observer. In contrast, for the 'maintain' condition, participants were instructed to maintain their initial subjective emotional response to each image, without alteration. During functional magnetic resonance imaging (fMRI) acquisition, each trial began with an instruction to 'increase', 'decrease' or 'maintain' for 2 s, followed by an image for 10 s. Following each image presentation, participants were asked to rate their level of subjective affect on a 7-point likert scale, (where $1 =$ no affect and $7 =$ strongest affect), by pressing the response button until the desired rating was highlighted (Supplementary Figure 1). The duration of fMRI scanning was 25 min.

fMRI acquisition. We acquired 760 whole-brain T2* weighted echoplanar images, with 28 axial slices in ascending order, 4.5 mm slice thickness with no gap. The repetition time (TR) was 2000 ms; echo time (TE) was 30 ms; flip angle, 90°; field of view (FOV): 250 mm using a Phillips Achieva 3T scanner at Neuroscience Research Australia in Sydney. A T1-weighted high resolution anatomical scan (MPRAGE) was acquired for each participant for registration and screening: TR 5.4 ms, TE 2.4 ms, FOV 256 mm, sagittal plane, 1 mm slice thickness, no gap, 180 slices.

fMRI data analysis. Functional images were realigned and slice time corrected using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Anatomical images were coregistered to the mean functional image and normalized to a standard template brain; functional images were normalized using parameters generated by anatomical image normalization and interpolated to $3 \times 3 \times 3\,mm^3$ voxels. Functional images were smoothed with a Gaussian filter (9 mm full width–half maximum). A high pass filter with a cutoff period of 128 s was applied to remove drifts within sessions.

Fixed effects for each participant were modeled at the first-level of analysis. The 10-s regulation periods in each condition (increase, decrease, maintain, neutral) were modeled as separate boxcar regressors, convolved with the canonical hemodynamic response function. A general linear model analysis in SPM8 was used to create contrast images representing differences between conditions for each participant. On the basis of prior work,[41] we defined specific contrasts of the 'increase' and 'decrease' conditions relative to the 'maintain' baseline condition to reveal the effect of emotion upregulation (increase > maintain) and downregulation (decrease > maintain) on neural activity in each participant, when viewing negative images. These contrast images from each participant were then analyzed in a second-level general linear model to determine group effects in the mean level of cortical activation. As we were interested in group differences in the extent of prefrontal cortical activation rather than differences in peak voxels, the threshold for statistical maps of group analyses was set at an uncorrected voxel-level $P<0.005$, and we report regions with a mean *t*-value that exceeds the FWER corrected cluster-level $P<0.05$. This implies mean activity in each region exceeded significance, rather than only a peak voxel within that region. Regions wherein mean activity exceeded the clusterwise threshold were automatically labeled using the WFU PickAtlas tool in SPM8,[51] and Brodmann area labels were confirmed according to the Talaraich atlas.[52]

Cortico-limbic coupling. We first determined whether amygdala activity was related to the level of negative affect in line with models of emotion generation and affect regulation. A standard anatomical mask defining the bilateral amygdala region was constructed using the PickAtlas tool,[51] and this aROI was used across participants. Average percent signal change in the aROI (beta weights averaged across all voxels as a proportion of global signal) were extracted using REX.[53] In this manner, the mean percent signal change in the amygdala was calculated in a non-biased manner for each individual, in each condition (increase, decrease, maintain and neutral). The association between amygdala activity and negative affect was estimated using the Pearson r correlation between the aROI values and mean subjective affect ratings for each group. To investigate cortico-limbic coupling, we calculated the difference in percent signal change in the amygdala aROI for each participant, in the downregulation contrast (decrease—maintain). These delta values were then entered as a covariate-of-interest in an analysis of cortical activation during downregulation for each group separately. Thus, each group's covariate analysis aimed to reveal cortical regions inversely correlated with amygdala deactivation (that is, cortico-limbic coupling[18]). In line with the main analysis described above, we controlled the cluster-level FWER at $P<0.05$. To compare common regions of cortico-limbic coupling between groups, we used the resulting significant cortical region from the healthy adult group as a functional ROI (fROI) in the other groups. There were no cortical regions with significant correlations with amygdala deactivation in either patient group, so no reverse comparison of aberrant cortico-limbic coupling (with the healthy adult group) was possible.

Covariates-of-interest. Separate covariate-of-interest analyses in SPM were conducted to test potential associations between neural activation and medication dosage, symptom severity and the behavioral measure of emotion regulation (that is, subjective affect ratings). Potential medication effects were tested by converting antipsychotic medication dosage to a chlorpromazine (CPZ) or imipramine (IMI) equivalent;[54,55] these values were included as covariates-of-interest in separate whole-brain tests of the upregulation and downregulation contrasts in each patient group. We also tested *post-hoc* correlations between medication dosage and BOLD signal in PFC regions for which significant group differences emerged in between-group comparisons of emotional up- and downregulation, as a further test of the possible effects of medication. To determine associations between symptoms and neuropathology, the positive and negative symptom scores from the PANSS were included as covariates-of-interest for within-subjects contrasts to determine activation in up- and downregulation conditions. These *post-hoc* analyses were restricted to regions of abnormal activity in the patient groups (relative to controls). Finally, to test whether the success of emotion regulation was linearly related to cortical activation, we included individual change scores (Δ) in subjective affect ratings during upregulation and downregulation. The average change (Δ) relative to the maintain condition were calculated for each participant and included as covariates-of-interest in separate whole-brain analyses of upregulation and downregulation in each group.

Results

Participant characteristics. Demographic data are summarized in Table 1. Significant group differences existed in age (Sz > HC, $t_{25}=2.71$, $P=0.01$) and years of education (HC > Sz, $t_{25}=3.65$, $P<0.01$). There were no significant group differences in adult reading scores (NART) (the largest

Table 1 Demographic means (s.e.m.)

	Healthy adults (15)	*Bipolar-I (13)*	*Schizophrenia (12)*
Age	35 (2)	41 (3)	44 (3)*
Females	9	5	4
Education	16 (1)	16 (1)	13 (1)*
Handedness	90 (4)	92 (5)	85 (5)
NART	114 (2)	118 (2)	109 (3)
Antipsychotic			
Amisulpride			2
Clozapine			5
Olanzapine		1	1
Palliperidone		1	
Quetiapine		2	1
Risperidone		1	4
Zuclopenthixol			3
CPZ (mg)		168 (106)	352 (58)
Antidepressant			
Citalopram		2	
Dosulepin		1	
Phenelzine		1	
Sertraline		2	1
IMI (mg)		132 (32)	
DASS			
Anxiety	2 (1)	12 (3)*	8 (2)*
Stress	6 (2)	18 (3)*	11 (3)
Depression	2 (1)	10 (3)*	8 (4)
PANSS			
Positive		10 (1)	19 (2)^
Negative		11 (1)	22 (2)^
General		25 (2)	32 (2)^

Abbreviations: CPZ, chlorpromazine equivalent dose; DASS, depression, anxiety and stress scale; IMI, imipramine equivalent dose; PANSS, positive and negative syndrome scale; WASI, Weschler abbreviated scale of intelligence; WTAR, Weschler test of adult reading.
*$P<0.05$ versus healthy adults, ^$P<0.05$ versus bipolar-I.

difference was BD > Sz, $t_{25}=1.45$, $P=0.08$). On average, BD patients reported significantly higher stress, anxiety and depression scores on the DASS than HC ($t_{26}=2.67$, 3.07 and 2.3, respectively, all $P<0.05$). Sz patients, on average, had significantly higher PANSS scores than people with BD ($t_{23}=4.25$, 4.69, 3.03, all $P<0.01$), and also significantly higher anxiety scores than HCs ($t_{25}=2.42$, $P=0.02$). Among clinical participants, nine of the Sz patients and five of the BD patients were being treated with atypical antipsychotic medication, and all BD patients were taking antidepressant medication. Scores on the ISS scale for BD participants were interpreted to estimate illness phase: six BD patients met criteria for euthymia (that is, activation score < 150, well-being score > 120) and five met criteria for hypomania (that is, activation score > 150, well-being score > 120); the mean (s.d.) activation and well-being scores for the entire BD group on the ISS were 167 (60) and 185 (133), respectively.

Ratings of subjective affect. Mean subjective negative affect ratings elicited by negative or neutral images in each condition are shown in Figure 1. A mixed design 3×4 ANOVA, with group (HC, Sz, BD) as the between-subject factor, and task condition (neutral, maintain, increase, decrease) as the within-subject factor, tested for differences between groups. There was a significant main effect of group ($F_{2,37}=9.31$, $P<0.01$), reflecting greater subjective affect ratings in both patient groups compared with HC across all

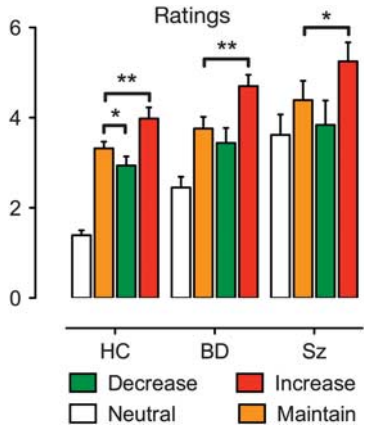

Figure 1 Mean subjective affect ratings. Healthy controls (HC), bipolar disorder (BD) and schizophrenia (Sz) rated emotionally negative pictures after instructions to increase, decrease or maintain the emotional response. Neutral pictures were rated only under instructions to maintain, as filler stimuli. Bars represent s.e.m.
*$P<0.05$; **$P<0.01$.

conditions. A *post-hoc* Dunnett's test (versus HC) confirmed the Sz group had significantly higher subjective affect ratings across conditions than HC ($F_{2,\ 37}=18.53$, $P<0.001$), while the BD group was not significantly greater than HC ($F_{2,\ 37}=2.15$, $P=0.69$). In addition, there was a main effect of condition ($F_{3,11}=70.82$, $P<0.01$), such that subjective affect was significantly greater for negative images than neutral images across groups. The group × condition interaction was also significant ($F_{6,\ 11}=2.57$, $P=0.02$); within-group paired *t*-tests between maintain and regulation conditions revealed that HC participants reported significant increases in subjective affect during upregulation, and significant decreases in subjective affect during downregulation of negative affect, compared with the maintain condition ($t_{14}=4.19$ and 2.31, respectively, both $P<0.05$). In BD and Sz, significant increases in subjective negative affect were reported for upregulation conditions, (t_{12} and $t_{11}=5.02$ and 2.94, respectively, both $P<0.05$), while observed reductions in subjective affect during downregulation approached statistical significance (BD $t_{12}=2.02$, $P=0.07$; Sz $t_{11}=1.89$, $P=0.09$).

SPM *t*-test of downregulation of negative affect (decrease > maintain)

Healthy controls. Downregulation of negative affect produced bilateral activation throughout the PFC, with the mean activity in the left VLPFC exceeding significance (BA45/BA47, shown in Figure 2). Significant activation also occurred in the left OFC (BA10, BA11), as well as the right DLPFC (BA46) and rostral ACC (BA32), consistent with an inhibitory role of these regions (on limbic centers of affect generation) during the cognitive control of emotion.[18,25,41] Supplementary Table 1 shows the list of significant within-group differences in the PFC for each group.

Bipolar disorder. During downregulation, large significant clusters of activation occurred bilaterally throughout the prefrontal cortex, with mean significant activity occurring in

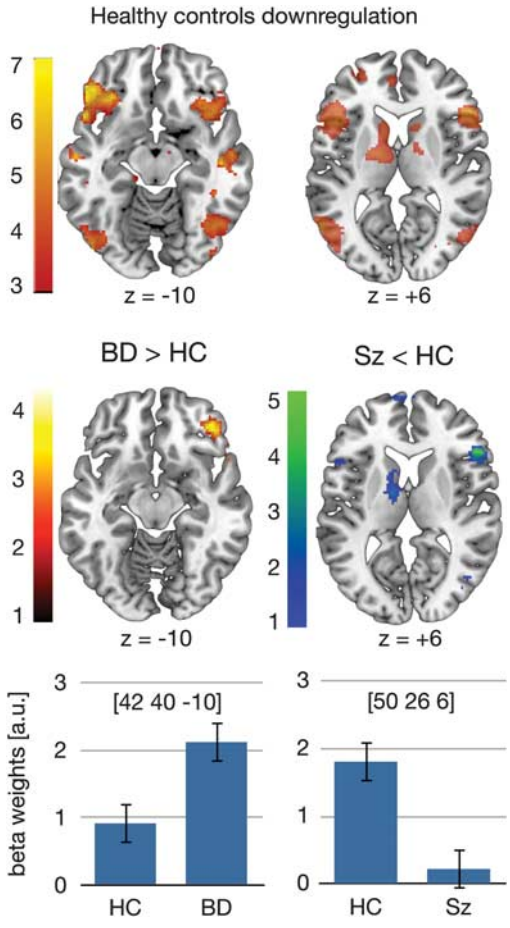

Figure 2 Activation during emotion downregulation in HC, and regions of relative hyperactivation in BD and hypoactivation in Sz. Color bars represents *t*-values ($P<0.005$). Bar charts show beta weights (s.e.m.) at peak voxels in BD and Sz (relative to HC), respectively.

the left VLPFC (BA47/45), as in healthy adults. Other regions with significant activation included the right VLPFC, OFC (BA47, BA11), as well as the DLPFC (BA46). Significant activity in the rostral ACC (BA32) as well as the adjacent BA9 region was also evident (Supplementary Table 1).

Schizophrenia. In contrast to the other two groups, no significant differential activity was revealed during emotion downregulation among people with Sz. Application of a more liberal threshold (voxel $P<0.05$, uncorrected) revealed clusters of activation in the middle occipital gyrus (bilateral) but no significant clusters in the PFC.

BD versus HC. Abnormal overactivity occurred in BD relative to HC, centered in the right VLPFC (BA47, Figure 2). Table 2 lists the complete set of regions of significant group differences in the PFC. Overactivation of the VLPFC in BD is consistent with the relatively large cluster of strong activity revealed in the same region by the within-group contrast for this group described above. Examination of the beta weights (in arbitrary units) at the peak voxel in the VLPFC confirmed the results were consistent with abnormal prefrontal hyperactivity, as predicted.

Sz versus HC. Less activation appeared in the right inferior frontal gyrus (IFG) (BA45), extending to the right VLPFC (BA47) in Sz relative to HC. Less activation also occurred in the left superior frontal lobe (BA8) and frontal pole (BA10) (Table 2). Examination of the beta weights at the peak voxel in BA45 confirmed activity was absent in Sz (Figure 2). The abnormal hypofrontality in the right IFG of Sz is consistent with the lack of differential activity during downregulation reported above for this group.

In light of substantial evidence that apparent hypoactivation occurs in Sz due to a higher baseline level of activity that reduces differential activity,[29,32] we also tested for significant differences between Sz and HC during the 'maintain' condition, to clarify the source of the hypoactivation revealed in the 'decrease > maintain' contrast. The ACC/medial frontal gyrus (BA32/10) was relatively overactive in Sz during the 'maintain' (that is, baseline) condition. However, there was no overlap between the ACC and hypoactive regions during downregulation among Sz.

BD versus Sz. During emotion downregulation, there were no regions significantly more active in people with Sz compared with BD participants. However, significantly greater bilateral activation occurred in BD throughout the prefrontal cortex, including the right VLPFC, the OFC and the DLPFC (BA46), compared to Sz. The right amygdala was also more active among BD compared to Sz (peak voxel: 20 −6 20, $t=3.18$, $P<0.005$), consistent with our prediction.

SPM *t*-test of upregulation of negative affect (increase > maintain)

Healthy controls. Significant unilateral activation occurred in the left IFG, including the left VLPFC (BA47) during upregulation, in an area contained within that activated for downregulation but more focal. Other regions significantly activated included the superior frontal lobe (BA8) and premotor cortex (BA6) (Supplementary Table 1).

Bipolar disorder. A largest cluster of significant activation occurred in the left PFC, extending from BA6 to BA47, while smaller distinct clusters also occurred in the ACC (BA32) as well as the right VLPFC (BA47) (Supplementary Table 1). Significant bilateral amygdala activation occurred during upregulation of negative emotion in people with BD (right amygdala peak voxel: 20 −6 −16, $t=5.12$, $P<0.005$, left amygdala peak voxel: −12 −6 −16, $t=6.30$, $P<0.005$), as might be expected in line with the greater levels of negative affect reported by this group.

Schizophrenia. A significant cluster of activation occurred in the left PFC in the lateral superior frontal lobe (BA6), extending to adjacent regions on the IFG (for example, BA44) during upregulation (Supplementary Table 1).

BD versus HC. Abnormal hyperactivity occurred in the right VLPFC (BA47), as well as the ACC (BA9, BA32) in BD (Table 2). Examination of the beta weights at the peak voxel in the right VLPFC confirmed hyperactivity in the BD during upregulation was due to positive activation in this group, rather than an absence of 'deactivation' (Supplementary

Table 2 Regions of group differences in the PFC

Downregulation: BD > HC,* k = *185,* t-*crit* = *2.79
Cluster 1: 186 voxels, peak at (40 42 −10), t = *4.82,* z = *1.52,* P = *0.045*

Label	*Voxels*	*Mean* T
Brodmann area 11	27	3.38
Brodmann area 47	25	3.29

Downregulation: HC > Sz,* k = *269,* t-*crit* = *2.79
Cluster 1: 506 voxels, peak at (50 26 6), t = *5.45,* z = *1.71,* P = *0.001*

Label	*Voxels*	*Mean* T
Brodmann area 45	76	3.77
Brodmann area 47	22	3.47
Brodmann area 46	8	3.39

Cluster 2: 478 voxels, peak at (−22 30 46), t = *5.20,* z = *2.58,* P = *0.002*

Label	*Voxels*	*Mean* T
Brodmann area 8	122	3.55
Brodmann area 9	5	3.03
Brodmann area 32	2	2.94

Cluster 3: 970 voxels, peak at (−46 2 −24), t = *4.83,* z = *1.56,* P < *0.001*

Label	*Voxels*	*Mean* T
Brodmann area 21	162	3.31
Brodmann area 38	101	3.26
Brodmann area 47	90	3.21

Cluster 4: 557 voxels, peak at (−12 64 22), t = *4.09,* z = *1.35,* P = *0.001*

Label	*Voxels*	*Mean* T
Brodmann area 10	154	3.10
Brodmann area 11	5	2.97
Brodmann area 9	4	3.13

Downregulation: BD > Sz,* k = *260,* t-*crit* = *2.81
Cluster 1: 777 voxels, peak at (50 28 6), t = *5.89,* z = *2.25,* P < *0.001*

Label	*Voxels*	*Mean* T
Brodmann area 45	64	3.83
Brodmann area 47	57	3.63
Brodmann area 46	15	3.10

Cluster 2: 317 voxels, peak at (26 24 −20), t = *4.22,* z = *1.53,* P = *0.023*

Label	*Voxels*	*Mean* T
Brodmann area 38	82	3.19
Brodmann area 47	37	3.35
Brodmann area 11	16	3.42

Upregulation: BD > HC,* k = *197,* t-*crit* = *2.79
Cluster 1: 170 voxels, peak at (46 14 −12), t = *4.26,* z = *1.60,* P = *0.039*

Label	*Voxels*	*Mean* T
Brodmann area 38	59	3.35
Brodmann area 47	48	3.08
Brodmann area 22	2	2.99

Cluster 2: 397 voxels, peak at (10 46 18), t = *4.11,* z = *2.62,* P = *.004*

Label	*Voxels*	*Mean* T
Brodmann area 9	64	3.25
Brodmann area 32	11	2.93
Brodmann area 10	8	3.00

Cluster 3: 221 voxels, peak at (40 40 −10), t = *4.05,* z = *2.11,* P = *.035*

Label	*Voxels*	*Mean* T
Brodmann area 47	19	3.29
Brodmann area 10	12	3.04
Brodmann area 11	7	2.96

Upregulation: Sz > HC,* k = *280,* t-*crit* = *2.79
Cluster 1: 298 voxels, peak at (40 42 −10), t = *4.40,* z = *2.80,* P = *0.036*

Label	*Voxels*	*Mean* T
Brodmann area 10	16	2.98
Brodmann area 47	12	3.46
Brodmann area 11	7	3.03

Cluster 2: 436 voxels, peak at (8 42 18), t = *4.25,* z = *1.98,* P = *0.004*

Label	*Voxels*	*Mean* T
Brodmann area 32	44	3.14
Brodmann area 9	25	3.36
Brodmann area 10	22	3.28

List of significant clusters and associated Brodmann regions with a mean *T*-value greater than the *t*-critical (clusterwise FWER $P<0.05$).

Figure 2). No regions were abnormally underactive in BD relative to HC.

Sz versus HC. During upregulation, Sz displayed abnormal hyperactivation in the right VLPFC (BA47) relative to HC, as well as hyperactivity in the right ACC (BA32, BA9) (Table 2). Supplementary Figure 2 shows the regions and amount of hyperactivity were remarkably similar to that observed among people with BD.

BD versus Sz. There were no significant group differences between BD and Sz during upregulation.

Cortico-limbic coupling. Mean percent signal change in the amygdala ROI during each condition and self-reported negative affect in each condition were significantly related in HC ($r=0.67$, $P<0.01$) and BD ($r=0.76$, $P<0.001$), but not Sz ($r=0.49$, $P=0.1$). Thus, negative affect was related to amygdala activity in HC and people with BD. For HC, amygdala activation during downregulation was negatively correlated with cortical activity in the left IFG of HCs, in a significant cluster overlapping BA46, BA47 and BA11, including the peak voxel of activity during downregulation (Figure 3). The negative correlation at this significant cluster in the IFG of HCs ($r=-0.76$, $P<0.001$) indicates cortico-limbic coupling consistent with prefrontal inhibition of limbic regions during emotion downregulation.[18,25] Among the patient groups, there were no significant correlations between the amygdala aROI and left cortical activation (fROI) ($r=+0.12$ and $+0.19$ for BD and Sz, respectively, both $P>0.05$) (Figure 3). Directly comparing the BD and Sz *r*-values with HC in this *post-hoc* (fROI) region confirmed cortico-limbic coupling was significantly weaker in each

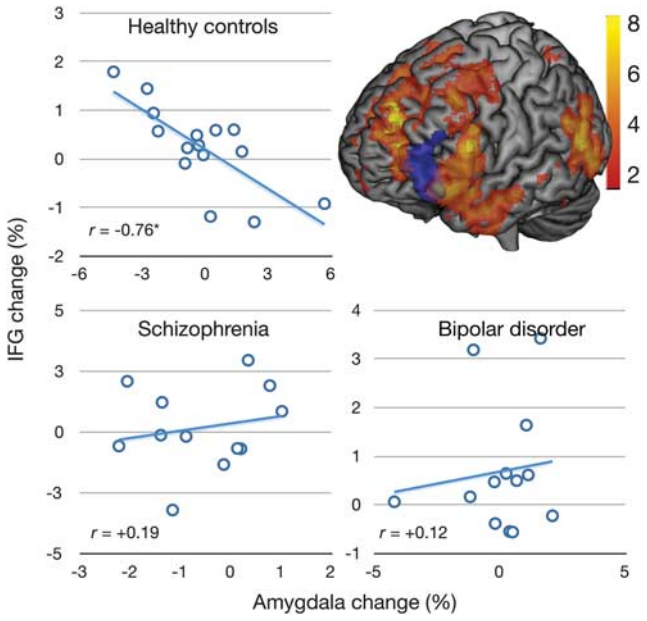

Figure 3 Scatterplots showing the correlation between left PFC activity and negative amygdala parameter estimates during downregulation in each group. Brain image shows cortical activation during downregulation alongside the region of correlation in the left IFG (cool) of healthy controls, $P<0.005$.

patient group (both $P<0.01$). A whole-brain analysis with amygdala deactivation in each of the patient groups also revealed no significant correlations occurred anywhere else in the cortex of these groups. Thus, evidence of cortico-limbic coupling during downregulation was not found in either a whole-brain or a fROI analysis of the patient groups.

We also tested whether activity in cortical regions was coupled with amygdala activation during emotion upregulation. Positive correlations with mean amygdala activation (aROI) from the increase > maintain contrast were tested; however, no significant correlations in the cortex occurred in any group.

Covariates-of-interest

Medication effects. There were no significant associations between CPZ or IMI and cortical activity during emotion regulation in Sz or BD groups, when medication dosage was included as a covariate in within-group analyses of up- and downregulation in clinical groups (voxel $P>0.005$). In addition, *post-hoc* analyses confirmed no significant correlations between medication dosage and brain activation in the VLPFC (as the main region of group differences) in emotion regulation (Supplementary Figure 4). However, a near-significant trend emerged for a positive association between CPZ and activity in the right VLPFC of Sz during downregulation ($r=0.51$, $P=0.09$); we note that this positive association cannot explain the group differences of hypoactivation of PFC regions in Sz during downregulation, relative to HC or BD groups (reported above), because any antipsychotic medication effects would have served to increase PFC activation in Sz, consistent with the desired therapeutic effects, but clearly in contrast to the effects reported here. In contrast, for the BD group during downregulation, IMI was not significantly correlated with hyperactivity in (the right) VLPFC ($r=-0.06$, $P=0.85$). During upregulation, medication dosages were not related to VLPFC activity in either BD (IMI and right VLPFC $r=-0.09$, $P=0.70$) or Sz (CPZ and right VLPFC $r=-0.13$, $P=0.69$).

Symptoms. There were significant correlations between symptoms and cortical activity in patients. In Sz, there was a strong correlation between negative symptoms and hyperactivity in the right ACC during the maintain condition ($r=0.78$, $P<0.005$), indicating the severity of negative symptoms increased with the neural response to negative images, and consistent with heightened processing of anxiety-provoking stimuli. Among people with BD, a significant negative correlation between positive symptoms and hyperactivity was revealed in the rACC during emotion upregulation ($r=-0.72$, $P<0.005$).

Subjective affect ratings. The amount of downregulation of subjective affect was linearly related to change in the left IFG (BA46/10) among individuals in the HC group ($r=-0.83$, $P<0.005$). This region overlapped the same region coupled with amygdala activity (Supplementary Figure 3). Percent signal change in this left cortical region increased with greater decreases in subjective affect during downregulation, as expected if this region has a functional role in inhibition of negative affect. However, no significant relationship in the same cortical region (fROI) existed among patient groups. Upregulation of subjective affect was not linearly related to changes in prefrontal cortex activity in any group.

Discussion

We examined cortico-limbic brain function during voluntary regulation of negative emotion in Sz, BD and HC groups, using an established task known to activate prefrontal cortical regions concomitant with changes in amygdala activity during regulation of subjective affect. Consistent with previous reports in healthy individuals,[12–15] downregulation of negative affect elicited VLPFC activity in healthy participants, and moreover, a region of the left IFG was inversely correlated with amygdala activation during emotional regulation of negative affect (cortico-limbic coupling). Among BD patients, we found bilateral prefrontal activity to be evoked by both emotional upregulation and downregulation conditions, with between-group comparisons revealing abnormal hyperactivation in the right VLPFC during both up- and downregulation conditions (as well as amygdala hyperactivity during downregulation), relative to controls and Sz. In contrast, Sz participants displayed relative hypoactivation of prefrontal regions during attempts to downregulate negative affect, while attempts to upregulate negative affect produced abnormal hyperactivity in the VLPFC. Thus, BD was distinguished by hyperfrontal activity during both up- and downregulation of subjective emotion, and this activation was not coupled with amygdala activity.[40] By contrast, Sz was uniquely hypofrontal during downregulation of negative affect, with little or no limbic activity across emotion regulation conditions. Collectively, these results confirm unique patterns of cortico-limbic activation in Sz and BD during both down- and upregulation of negative affect: in contrast to our hypotheses (that distinctions

in PFC activation would be most apparent during upregulation), PFC activation during downregulation differentiated the two groups.

Investigation of the inverse association between the amygdala and prefrontal cortices revealed the novel finding that people with BD and Sz had significantly less cortico-limbic coupling than healthy adults. The cortical region most strongly associated with amygdala activity in healthy adults occurred in the left IFG. Testing correlations in the same region as patients may have introduced a bias towards a null result in these independent groups. However, we also tested for significant correlations in each patient group using a voxel-wise approach, and both the whole-brain and ROI analysis failed to reveal any significant cortico-limbic coupling in patients. Other studies have shown that among healthy adults, the amygdala is downregulated by lateral parts of the IFG via connections with the ventromedial PFC.[25] The latter region is directly connected to the amygdala and actively participates in inhibition of amygdala function.[24] Thus, contemporary models of emotion regulation suggest limbic centers of emotion generation are tightly regulated by top-down inhibitory control from the PFC. With respect to this model, the apparent lack of cortico-limbic coupling in BD and Sz indicates the putative inhibitory connections are absent or dysfunctional in these diseases. Furthermore, the strong relationship between amygdala activity and affect ratings in BD ($r = 0.76$) suggests the absence of top-down inhibitory control over the amygdala may manifest as greater limbic and emotional reactivity. By contrast, in Sz there was no evidence of association between amygdala activity and subject affect, so the absence of top-down control of limbic function may be epiphenomenal to flat affect in Sz. Furthermore, the high levels of negative affect in people with Sz are paradoxical in the absence of amygdala reactivity. However, we did find significant hyperactivity in the rostral ACC and medial frontal gyrus during maintenance of negative affect in Sz: this region has been associated with self-monitoring of negative affect,[41,56] and suggests heightened contextual processing of anxiety-provoking stimuli occurred. Thus, overactivity in this region may be responsible for the high levels of reported negative affect in Sz, despite overt affective blunting and lack of amygdala reactivity.

With regard to the subjective emotional experience during each condition, only healthy participants' self-reported affect decreased significantly during downregulation, while a similar pattern in Sz and BD did not reach conventional levels of significance. Although the (non-significant) decrease in negative affect during downregulation in both clinical groups suggests the task was attempted as instructed, the small sample size may have prevented sufficient power to detect within-group differences. Nevertheless, we note the decrease in negative affect was linearly related to the amount of activity in the left IFG in healthy adults, consistent with other evidence of a critical role for this left lateralized region in the voluntary regulation of affect.[18,25] This suggests that reliable down-regulation of subjective affect might not have been achieved by clinical participants precisely because of dysfunction in the IFG, or it's functional connectivity with the amygdala.

As in other neuroimaging studies of psychiatric illness, medication dose may be an important confound among our groups. As detailed in Table 1, less than half the people with BD and all of those with Sz were being treated with antipsychotics. However, a correlation analysis including the CPZ equivalent dose among people with Sz did not reveal any significant effect of medication during upregulation. Furthermore, a linear effect of antipsychotic treatment alone cannot explain the opposite group differences relative to healthy adults, which we obtained during emotion downregulation (Figure 2). Another limitation of our study may have been the low n, especially in the Sz group, which potentially reduced statistical power. However, we found the smallest significant effect size in the Sz group (Supplementary Table 1, $z = 1.01$), indicating power was not substantially reduced in the smallest sample size. Nevertheless, due to the low n in all groups, the present results must be considered as preliminary.

In summary, this preliminary study demonstrates differential fronto-limbic activity in BD and Sz during efforts to regulate negative affect, relative to HCs, and in direct comparison to each other. The results for healthy adults are consistent with many other animal and human studies that demonstrate an inhibitory influence of the prefrontal cortex on subcortical limbic regions that generate negative affect. However, the opposite effect of emotional downregulation on cortical and limbic activation in BD and Sz (hyperactivity in BD, hypoactivity in Sz) demonstrate these disorders can be distinguished on the basis of functional neuroanatomy during subjective emotion regulation. Furthermore, the dysregulated affect in BD may be due to an absence of normal cortico-limbic coupling, despite the presence of PFC hyperactivity during voluntary efforts to regulate emotion. In contrast, lack of activity in the PFC and amygdala during downregulation in Sz, as well as lack of limbic activity during upregulation was consistent with predominant flat affect in this group. Thus, the unique functional neuroanatomy demonstrated in these groups during affect regulation is in line with the characteristic emotional dysfunction of each disorder, and may contribute to future biologically based diagnostic criteria for these conditions.

Conflict of interest

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)